Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Clinical Trial of Apatinib Mesylate Tablets as Second-Line Treatment in Patients with Advanced Hepatocellular Carcinoma
Clinical trial registration number: NCT02329860
Version Date: 10 Mar., 2017

A Randomized, Double-Blind, Parallel-Controlled, Multi-Center, Phase III Clinical Study Evaluating Apatinib Mesylate Tablets as Second-Line Treatment in Patients with Advanced Hepatocellular Carcinoma

Study Protocol

Protocol No.: APTN-III-HCC

Version No.: 1.4

Version Date: 10 Mar., 2017

Principal Investigator: [redacted]

Clinical Study Site: [redacted]

Sponsors: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Shanghai Hengrui Pharmaceutical Co., Ltd.

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Principal Investigator:	[redacted]
Telephone:	[redacted]
Fax:	[redacted]
Address:	[redacted]
Sponsor:	**Jiangsu Hengrui Pharmaceuticals Co., Ltd.** **Shanghai Hengrui Pharmaceutical Co., Ltd.**
Medical Director:	[redacted]
Telephone:	[redacted]
Fax:	[redacted]
Address:	[redacted]
Statistical Unit:	**Department of Epidemiology and Health Statistics, Nanjing Medical University**
Source Data Retention:	[redacted]
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Version Date:	10 Mar., 2017

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Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Shanghai Hengrui Pharmaceutical Co., Ltd.

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PROTOCOL SYNOPSIS

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Protocol No.		APTN-III-HCC
Sponsors		Jiangsu Hengrui Pharmaceuticals Co., Ltd. Shanghai Hengrui Pharmaceutical Co., Ltd.
Nature		Phase III clinical trial for IND application
Study Population		Patients with advanced HCC refractory to systemic treatment
Study Objective		To observe and evaluate the efficacy and safety of apatinib mesylate tablet as second-line treatment in patients with advanced HCC
Study Endpoints	Primary endpoint	Overall survival (OS)
	Secondary endpoints	**Efficacy endpoints:** Progression free survival (PFS); 3-, 6-, and 12-month PFS rates; Time to progression (TTP); Objective response rate (ORR); Disease control rate (DCR); The percentage of evaluable patients with stable disease (SD) of ≥ 4 weeks (confirmed SD); 6- and 12-month mortalities; Quality of life score; **Safety endpoints:** Vital signs, laboratory measurements, adverse events (AEs), serious adverse events (SAEs), treatment-related AEs and SAEs, and AEs of special interest (e.g., hypertension, proteinuria, and hand-and-foot syndrome [palmar-plantar erythrodysesthesia syndrome]); Judged as per NCI-CTCAE V4.0 criteria
Study Design		A randomized, double-blind, placebo-controlled, multi-center phase III clinical trial; Subjects will be stratified and randomized based on the ECOG PS (0 or 1), the past medication of sorafenib, and the presence of vascular invasion and/or extrahepatic metastasis
Planned Enrollment		A total of 360 subjects are planned to be enrolled, including 240 subjects in the apatinib group and 120 subjects in the placebo group. According to the resolution of scientific committee, additional subjects will be enrolled, i.e., 390 subjects in total.
Screening Criteria		**Clinical Diagnostic Criteria:** "Guideline on Diagnosis and Treatment for Primary Liver Cancer" (2011 Edition) states: The clinical diagnosis of HCC can be confirmed when the following conditions (1) + (2)a or conditions (1) + (2)b + (3) are met: (1) With evidence of cirrhosis and HBV and/or HCV infection (positive HBV and/or HCV antigen);

(2) Typical imaging features of HCC: Multidetector CT scan and/or dynamic contrast-enhanced MRI showing hepatic space-occupying lesions with arterial hypervascularity and venous or delayed phase washout;

a One of the two imaging examinations (CT and MRI) showing the above features of liver cancer for those with lesions ≥ 2 cm in diameter;

b Both CT and MRI imaging examinations showing the above features of liver cancer for those with lesions of 1-2 cm in diameter, so as to enhance the specificity of the diagnosis;

(3) Serum AFP ≥ 400 μg/L for 1 month or ≥ 200 μg/L for 2 months, and when the increase in AFP level due to other reasons can be excluded, including pregnancy, germline embryogenic tumor, active liver disease and secondary liver cancer.

Inclusion Criteria:

1. Age: ≥ 18 years old;
2. Patients strictly meeting the clinical diagnostic criteria in "Guideline on Diagnosis and Treatment for Primary Liver Cancer" (2011 Edition) or with histologically or cytologically confirmed recurrent/metastatic HCC, unsuitable for palliative surgery or radiation therapy, with at least one measurable lesion (must be ≥ 10 mm in longest diameter by spiral CT or ≥ 15mm in shortest diameter for enlarged lymph nodes, as per RECIST 1.1, as shown in Annex 1);
3. Patients with HCC refractory or intolerant to systematic chemotherapy (with oxaliplatin, alone or in a therapeutic combination) and/or molecular targeted therapy with sorafenib;

Note: Definition of treatment failure: disease progression during treatment or relapse after treatment is completed (must have received ≥ 1 cycle of systemic chemotherapy with oxaliplatin (or plus other drugs) or ≥ 14 days of molecular targeted therapy with sorafenib);

Definition of intolerability: Grade ≥ IV hematological toxicity or Grade ≥ III non-hematological toxicity or Grade ≥ II major organ injury such as the heart, liver, or kidneys during treatment.

4. The interval between the last systemic treatment failure (with treatment discontinued) and the enrollment (time of signing the informed consent form) was ≥ 2 weeks, and the adverse event(s) had basically returned to normal (NCI-CTCAE ≤ Grade I);
5. Child-Pugh score: Class A or Class B (≤ 7); the Child-Pugh scoring system is shown in Appendix 2;
6. BCLC staging: B-C ("Barcelona Clinic Liver Cancer (BCLC) Staging System, 2010" is shown in Appendix 3);
7. ECOG PS of 0–1 within 1 week before enrollment, as shown in Appendix 4;
8. Expected survival ≥ 12 weeks;
9. HBV DNA < 2000 IU/mL (10^4 copies/mL);
10. Major organs must function normally, meeting the following criteria:

(1) Hematology: (without blood transfusion, G-CSF, or medication within 14 days prior to screening)

a. HB ≥ 90 g/L;

b. ANC ≥ 1.5×10^9/L;

c. PLT ≥ 80×10^9/L;

(2) Biochemistry: (no ALB transfusion within 14 days)

a. ALB ≥ 29 g/L;

b. ALT and AST < 5 × ULN;

c. TBIL ≤ 1.5 × ULN;

d. Creatinine ≤ 1.5 × ULN;

(Only one of the two items, albumin or bilirubin, has a Child-Pugh score of 2)

11. Women of childbearing potential must have a negative pregnancy test (serum or urine) within 7 days prior to enrollment, and be willing to take appropriate contraceptive measures during the trial and within 8 weeks after the last dose of the investigational drug. Male subjects should either undergo surgical sterilization, or agree to take appropriate contraceptive measures during the trial and within 8 weeks after the last dose of the investigational drug;
12. Subjects must participate voluntarily, sign the informed consent form, have good compliance and corporate with follow-up visits.

Exclusion Criteria:

1. Patients who have received any local treatment within 4 weeks prior to participating in this study (including but not limited to surgery, radiation, hepatic artery embolization, TACE, hepatic arterial infusion, radiofrequency ablation, cryoablation, or percutaneous ethanol injection);
2. Patients with known intrahepatic cholangiocarcinoma, mixed hepatocellular carcinoma and fibrolamellar hepatocellular carcinoma; other uncured malignancies currently or within the past 5 years, except for cured skin basal cell carcinoma or cervical carcinoma in situ;
3. Patients planning to receive liver transplant (except for patients who have undergone liver transplant);
4. Patients with symptomatic ascites requiring therapeutic paracentesis or drainage, or with a Child-Pugh score > 2;
5. Patients with hypertension which cannot be controlled to the normal range by antihypertensives (systolic pressure > 140 mmHg, diastolic pressure > 90 mmHg);
6. Patients with Grade II or greater myocardial ischemia or myocardial infarction, uncontrolled arrhythmias (QTc interval ≥ 450 ms in males and ≥ 470 ms in females);
7. Patients with NYHA (see Appendix 5) Class III-IV cardiac insufficiency or LVEF (left ventricular ejection fraction) < 50% by echocardiography;
8. Presence of multiple factors affecting oral medications (such as inability to swallow, chronic diarrhea, and intestinal obstruction, which significantly affect drug administration and absorption);
9. Patients with a history of gastrointestinal bleeding within the past 6 months or a high risk of bleeding such as esophageal varices with bleeding risk, active ulcers, and fecal occult blood ≥ (++); in the case of fecal occult blood (+), a gastroscopy is required;
10. Abdominal fistula, gastrointestinal perforation or abdominal abscess within 28 days prior to the study;
11. Abnormal coagulation function (INR > 1.5 or prothrombin time (PT) > ULN + 4 s), bleeding tendency or receiving thrombolytics or anticoagulant therapy;
12. Patients with central nervous system metastases or known brain metastases;
13. Patients with previous or current objective evidence of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-induced pneumonitis, and severe lung function impairment;
14. Urine protein ≥ ++ or 24-h urine protein > 1.0 g as indicated by urinalysis;

	15. Had received treatment with a potent CYP3A4 inhibitor within 7 days prior to study participation, or had received treatment with a potent CYP3A4 inducer within 12 days prior to study participation; 16. Pregnant or lactating women; patients of child-bearing potential unwilling or unable to take effective contraceptive measures; 17. Patients with a known history of mental illness or psychotropic substance abuse; 18. Patients with bone metastasis who had received a palliative radiotherapy in an area of > 5% of bone marrow area within 4 weeks prior to the participation in this study. **Termination Criteria:** 1. Subject withdraws informed consent and requests to withdraw from the study; 2. Medical imaging examinations show disease progression; 3. Subjects showing unacceptable toxicity after dose modification; 4. Other reasons for which the investigator considers a withdrawal necessary; 5. Study termination by the sponsor for the sake of safety.
Investigational Drugs and Method of Administration	Treatment group: Apatinib is given via oral administration after meals (the dosing time on each day should remain the same whenever possible) at an initial dose of 750 mg/day, once a day, 3 tablets per dose, in 28-day cycles. The dose can be adjusted based on the toxic reactions of the subjects as per protocol (first dose reduction: 500 mg/day, q.d.; second dose reduction: 250 mg/day, q.d.). If the toxic side effects are completely resolved after dose reduction, the dose can be resumed to the previous dose level; however, if the dose is reduced again, it should not be resumed again according to the protocol. Placebo group: Placebo is given via oral administration after meals (the dosing time on each day should remain the same whenever possible) at an initial dose of 750 mg/day, once a day, 3 tablets per dose, in 28-day cycles. The dose can be adjusted based on the toxic reactions of the subjects as per protocol (first dose reduction: 500 mg/day, q.d.; second dose reduction: 250 mg/day, q.d.);
Study Period	November 2013-March 2018
Statistical Methods	In this trial, placebo is used as a control and a superiority test is performed between the two groups. All statistical analyses will be performed using SAS. All statistical analyses are performed using two-tailed tests. $P \leq 0.05$ is considered statistically significant, and 95% confidence is used for confidence intervals. **Pre-set subgroup analysis:** Subgroups will be pre-defined based on the following factors for a confirmatory subgroup analysis in this study: age ≤ 65 years or > 65 years; ECOG PS 0 or 1; with or without vascular invasion; with or without extrahepatic metastases; with or without vascular invasion and extrahepatic metastases; positive or negative HBV; and with or without past history of sorafenib treatment. The baseline data is analyzed based on the full analysis set (FAS). All efficacy endpoints are analyzed based on the FAS and the per protocol set (PPS). The analysis of primary efficacy endpoint OS is carried out mainly in the FAS, but the PPS is used for the final analysis. The safety analysis is carried out based on the safety analysis set (SS). The measurement data obtained from various treatment groups during various visits will be statistically described by mean ± standard deviation or median (minimum, maximum). For comparison with baseline values of the screening period, paired t-tests are used to compare pre and post intra-group differences. Changes occurring in each group before and after treatment should be

	compared by the analysis of variance (ANOVA) or rank sum test. The frequency data obtained from various treatment groups during various visits will be statistically described by frequency (proportions). Changes occurring in each group before and after treatment should be compared by χ^2 test (exact test) or nonparametric test. ● Dropout analysis: Descriptive analysis is mainly used. If necessary, the total dropout rate of each group and the comparison of dropout due to AEs will be tested by χ^2 test or Fisher's exact test. ● Balance analysis of baseline values: ANOVA or χ^2 test is used to compare demographic data and other baseline values to evaluate the balance of various groups. ● Efficacy analysis: For the comparison of 3-, 6-, and 12-month PFS rates, objective response rate (ORR), disease control rate (DCR), the percentage of patients with stable disease (SD) of ≥ 4 weeks (confirmed SD in particular), and 6- and 12-month mortalities, CMH-χ^2 tests with and without central stratification are used to compare the efficacy between the two groups. In addition, the 95% confidence interval of the difference between the two groups is also calculated. Based on the product limit method and the actual condition of the data, 25%, 50% (median) and 75% of PFS and TTP, as well as PFS and OS at different time points after the start of treatment, are calculated and the endpoints are compared between the two groups using the Log-Rank test. ● Safety analysis: Descriptive statistical analysis will be mainly used. The AEs and SAEs, treatment-related AEs and SAEs, and AEs and SAEs of special interest (e.g., hypertension, proteinuria, and hand-and-foot syndrome) are listed and summarized. If necessary, the incidence and severity of AEs and SAEs between different groups are compared using Fisher's exact test.
Pre-Set Point for Efficacy Analysis	Date of the 312th death (≥ 80% of the subjects have died) based on the full analysis set
Version No.	1.4

SCHEDULE OF ACTIVITIES

Treatment Cycle / Visit / Test Items	Screening Period	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	Withdrawal	28 Days after Withdrawal		Follow-up 1	Follow-up 2
	V1 (-3W)	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	Vn	Vn+1	V100	V101	V201
Date of Visit	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	√
Demographics	√																		
Tumor History	√																		
Surgical History of Primary Lesions	√																		
History of Local Ablation	√																		
History of Intervention	√																		
History of Radiotherapy	√																		
History of Systemic Treatment	√																		
Past Medical History	√																		
History of Drug Allergy	√																		
Chest X-Ray[a]	√																		
Hepatitis B/Hepatitis C Markers and HBV-DNA	√																		
Serum AFP[b]	√				√			√											
Vital Signs	√		√		√	√	√	√	√	√	√	√	√	√	√	√			
Physical Examination	√		√		√	√	√	√	√	√	√	√	√	√	√	√			
ECOG Performance Status Score	√		√		√	√	√	√	√	√	√	√	√	√	√	√			
Hematology	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√			
Blood Biochemistry	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√			
Urinalysis[c]	√	√	√	√	√	√	√	√	√	√	√	√	√	√					

Treatment Cycle / Visit / Test Items	Screening Period	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	Withdrawal	28 Days after Withdrawal		Follow-up 1	Follow-up 2
	V1 (-3W)	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	Vn	Vn+1	V100	V101	V201
Coagulation Function	√		√		√	√	√	√	√	√	√	√	√	√					
Pregnancy Test[d]	√																		
Stool Routine[e]	√																		
Echocardiography[f]	√																		
ECG[g]	√		√		√	√		√		√		√		√					
Quality of Life Score[h]	√				√	√		√		√		√		√	√				
Child-Pugh Score	√																		
Imaging Evaluation-Target Lesion[i]	√				√	√		√		√		√		√	√			√	
Imaging Evaluation-Non-target Lesion[i]	√				√	√		√		√		√		√	√			√	
Imaging Evaluation-New Lesion[i]					√	√		√		√		√		√	√			√	
Inclusion and Exclusion Criteria	√																		
Enrollment Assessment	√																		
Drug Return and Dispensing			√		√	√	√	√	√	√	√	√	√	√	√				
Blood Pressure Record			√		√	√	√	√	√	√	√	√	√	√	√				
Drug Interruption Form																	√		
Dose Modification Form																	√		
Additional Examinations																	√		
Concomitant Medication																	√		
Adverse Event																	√		
Serious Adverse Event																	√		

Treatment Cycle / Visit / Test Items	Screening Period	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	Withdrawal	28 Days after Withdrawal		Follow-up 1	Follow-up 2
	V1 (-3W)	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	Vn	Vn+1	V100	V101	V201
Summary of Study																	√		
Survival Follow-Up																			√

Note: (1) The results of ECOG PS, hematology, urinalysis, blood biochemistry, coagulation function, quality of life score, and ECG must be collected within 1 week before randomization.

(2) a: Chest X-ray: If the chest CT has been performed during the screening period, chest X-ray is not required.

(3) b: Serum AFP: Only detected at the end of Cycle 2 and Cycle 5; not strictly required after Cycle 5.

(4) c: Urinalysis: Not required for female subjects during their menstrual period.

(5) d: Pregnancy test: Additional pregnancy tests can be carried out during the treatment period if necessary.

(6) e: Stool routine (occult blood): In the case of fecal occult blood (+) during the screening period, a gastroscopy is required; and additional fecal occult blood tests can be carried out during the treatment period if necessary.

(7) f: Echocardiography: Must be performed during the screening period. For clinically significant ECG abnormalities observed during the study period, an additional echocardiography examination is required.

(8) g: ECG: The QTc interval must be indicated for 3 times, with about 5 min apart. ECG examination shall be carried out before drug administration during the screening period and then always after drug administration in each visit. For clinically significant ECG abnormalities, an additional echocardiography examination is required; if there are symptoms such as precordial pain and palpitations, the myocardial zymogram (creatine kinase, lactate dehydrogenase) should be tested immediately. The examination should be carried out every two cycles after Cycle 3.

(9) h: Quality of life score: Must be measured before the efficacy evaluation; and measured every two cycles after Cycle 3.

(10) i: Imaging examination: Screening period: including CT or MRI of the chest and abdomen. Brain CT/MRI is required for clinically suspected metastases to the central nervous system. A bone scan is required for clinically suspected bone metastasis. Treatment period: The examination should be carried out in Cycles 2 and 3, and then every two cycles after Cycle 3.

(11) i: Efficacy evaluation: The first efficacy evaluation is carried out at the end of Cycle 2; efficacy confirmation is carried out at 4 weeks after the first efficacy evaluation (i.e., at the end of Cycle 3), Afterwards, the efficacy evaluation is carried out every two cycles;

For subjects who withdraw from the study due to unacceptable toxicity, the efficacy evaluation should be conducted upon withdrawal if the efficacy evaluation is not carried out within 4 weeks before withdrawal. Thereafter, the imaging examination is performed every 2 cycles until progressive disease.

(12) Follow-up 1 (can be repeated for V101): The subjects who withdraw from the study due to unacceptable toxicity should be followed-up for tumor progression until the tumor progression is confirmed by imaging or the start of new anti-tumor treatment.

(13) Follow-up 2 (can be repeated for V201): Survival follow-up, visit number from 201, 202, 203…

REGULATIONS FOR DOSE MODIFICATION

NCI Toxicity Grade	Regulations for Dose Modification	Regulations for Toxicity Recovery upon Re-Administration after Treatment Discontinuation	Regulations for Toxicity Recovery at the Beginning of Next Cycle
Grade I Hematological Toxicity	Maintain original dose	After treatment discontinuation during treatment cycle, hematological toxicity must recover to Grade ≤ II before treatment can be resumed	At the beginning of the next cycle of administration, hematological toxicity must recover to Grade ≤ II before treatment can be started
Grade II Hematological Toxicity	Maintain original dose		
Grade III Hematological Toxicity	Interrupt treatment and give symptomatic treatment until toxicity returns to Grade ≤ II, and then resume treatment at the original dose level		
Grade IV Hematological Toxicity	Interrupt treatment and give symptomatic treatment until toxicity returns to Grade ≤ II, and then resume treatment at the next lower dose level; upon complete recovery of toxicity, dose may be re-adjusted to the previous level to continue treatment; if a Grade IV hematological toxicity occurs again after such re-adjustment, dose should be reduced accordingly and no further adjustments shall be allowed		
Grade I Non-Hematological Toxicity	Maintain original dose	After treatment discontinuation during treatment cycle, non-hematological toxicity must recover to Grade ≤ I before treatment can be resumed	At the beginning of next cycle, non-hematological toxicity must recover to Grade ≤ I before treatment can be started
Grade II Non-Hematological Toxicity	Give symptomatic treatment and continue study administration at the same time, if toxicity returns to Grade ≤ I after one week, continue dosing; if the toxicity does not recover or even worsens, interrupt treatment until toxicity returns to Grade ≤ I, and then resume treatment at the original dose level		
Grade III Non-Hematological Toxicity	Interrupt treatment and give symptomatic treatment until toxicity returns to Grade ≤ I, and then resume treatment at the original dose level, and reduce by 1 dose level for the next cycle; investigator may decide accordingly for certain patients based on the specific conditions without waiting for the next cycle; upon complete recovery of toxicity, dose may be re-adjusted to the previous level to continue treatment; if a Grade III non-hematological toxicity occurs again after such re-adjustment, dose should be reduced accordingly and no further adjustments shall be allowed		

NCI Toxicity Grade	Regulations for Dose Modification	Regulations for Toxicity Recovery upon Re-Administration after Treatment Discontinuation	Regulations for Toxicity Recovery at the Beginning of Next Cycle
Grade IV Non-Hematological Toxicity	Interrupt treatment and give symptomatic treatment until toxicity returns to Grade ≤ I, and then resume treatment at the next lower dose level for at least 1 cycle; upon complete recovery of toxicity, dose may be re-adjusted to the previous level to continue treatment; if a Grade IV non-hematological toxicity occurs again after such re-adjustment, dose should be reduced accordingly and no further adjustments shall be allowed (if a life-threatening adverse reaction, such as Grade IV renal impairment, neurotoxicity, cardiotoxicity, or hepatotoxicity occurs, discontinue the treatment and withdraw)		

ABBREVIATIONS AND DEFINITIONS

The following abbreviations and special terms are used in this study protocol

Abbreviations and Special Terms	Definitions
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse event
AFP	Alpha-Fetoprotein
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
B-Scan	B-mode ultrasound
Ca	Calcium
Cl	Chlorine
Cr	Creatinine
CR	Complete response
CT	Computed tomography
DCR	Disease control rate
DLT	Dose-limiting toxicity
DRQ	Data ready queue
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
Fbg	Fibrinogen
GCP	Good Clinical Practice
FAS	Full analysis set
Glu	Glucose
Hb	Hemoglobin
HCC	Hepatocellular carcinoma
HFS	Hand-foot-skin reaction
HMG-CoA	β-Hydroxy β-methylglutaryl-coenzyme A
ITT	Intention to treat
K	Potassium
LD50	Median lethal dose
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
Na	Sodium
NCI-CTC	National Cancer Institute Common Toxicity Criteria
OB	Occult blood
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PDGFR	Platelet derived growth factor receptor
PFS	Progression free survival

Abbreviations and Special Terms	Definitions
PI	Principal investigator
PLT	Platelet
PR	Partial response
PRO	Protein
PPS	Per-protocol set
PT	Prothrombin time
q.d.	Quaque die
QoL	Quality of life
RBC	Red blood cell
RC	Red color sign
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
RTKs	Receptor tyrosine kinase
γ-GT	γ-glutamyltransferase
SAE	Serious adverse event
SAS	Safety analysis set
SD	Stable disease
TT	Thrombin time
TTP	Time to progression
ULN	Upper limit of normal
URIC	Uric acid
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell

Apatinib mesylate tablet is a novel drug developed and filed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. and Shanghai Hengrui Pharmaceutical Co., Ltd. The product (strength of 0.2 g) has been approved for phase I clinical trial by National Medical Products Administration (NMPA) in Apr. 2007 (approval no. 2007L00837), and for phase II/III clinical trials in May 2009 (approval no. 2009L03464). Having completed the technical review of the means of production at dosage strength of 0.25 g in Feb. 2014, the Center for Drug Evaluation (CDE) reissued clinical trial approval for strength of 0.25 g in Jun. 2014 (approval no. 2014L00877).

At present, the National Clinical Research Center in the 81st Hospital of the Chinese People's Liberation Army (Nanjing) is leading the nationwide multi-center phase III clinical trial of apatinib mesylate tablets as second-line treatment in patients with advanced hepatocellular carcinoma, in accordance with the "Provisions for Drug Registration" and "Good Clinical Practice" (GCP). To this end, this study protocol has been formulated.

1 BACKGROUND

1.1 Epidemiology and Current Treatment of Hepatocellular Carcinoma

Primary hepatocellular carcinoma ranked fifth among common malignant tumors in the world in 2008, with about 748,300 new cases, accounting for 6% of all new cancer cases. Due to the poor prognosis of this disease, it is responsible for up to 695,900 deaths per year, hence making it the third leading cause of cancer deaths[1]. China is a high-risk area for liver cancer, accounting for about 55% of the world's liver cancer incidences, and about 50% of deaths[2], which is second only to lung cancer in cancer-related deaths. Liver cancer is more prevalent in men than in women, with male-to-female ratio of 2-5:1, and is most common in the age group of 35-45 years. A higher proportion of male patients has been observed in areas with higher incidence.

Hepatocellular carcinoma (HCC) is the most common type of primary hepatocellular carcinoma, accounting for 90% of all primary hepatocellular carcinomas[3]. The most important risk factors for HCC are hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, water contamination (blue-green algae toxins), alcoholism, and aflatoxin. HCC occurs mostly in patients with hepatitis and liver cirrhosis, at approximately 10-20 years after primary hepatic damage.

Most early-stage liver cancers are asymptomatic, and majority of the patients have reached a locally advanced stage or distant metastasis at the time of diagnosis. Currently, there are no standard treatments for advanced HCC, and mounting challenges stand in the way of clinical therapies. The survival times of patients with advanced HCC in China fall within the range of 3–6 months, and the longest survival time among patients worldwide is not more than 1 year[2]. This is largely attributed to the lack of effective systemic treatment for HCC patients. Due to its resistance to conventional chemotherapy, HCC is usually treated through surgical

operations (hepatectomy, liver transplantation, and palliative treatment), non-surgical approaches (locoregional treatment, arterial chemoembolization, chemotherapy, radiotherapy, biological therapy, and molecular targeted therapy), and other therapies (including participation in clinical studies).

1.2 Developments in Targeted Therapies for HCC

1.2.1 VEGF/VEGFR signaling pathway and angiogenesis of hepatocellular carcinoma

Therapies targeting receptor tyrosine kinases (RTKs) are currently the focus of research in the treatment of malignant tumors. Today, it is well known that angiogenesis represents a crucial step in the development and progression of malignant tumors. Tumor angiogenesis is thought to provide nourishment for the tumor and eliminate metabolites, thus allowing tumor cells to be transferred to other parts of the body through the new blood vessels. Therefore, tumor cell growth can be suppressed and the occurrence of metastasis can be reduced through the effective inhibition of angiogenesis. As such, this has become a promising new strategy for cancer treatment. Tumor angiogenesis is mainly dependent on the regulation of vascular growth factors and vascular growth inhibitors. Growth factor receptors include: epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR), etc., which play important roles in tumor angiogenesis, tumor nourishment, elimination of metabolites, distant metastasis, signaling in tumor cells, as well as the transmission of signals regulating cell growth, cell differentiation, cell adhesion, cell migration, and apoptosis. Among which, the most important growth factor is vascular endothelial growth factor (VEGF). The binding of VEGF to VEGF receptor (VEGFR) can induce VEGFR-mediated downstream signaling, ultimately leading to tumor angiogenesis.

HCC is a typical hypervascular tumor. Its occurrence, development, metastasis, and invasion are all closely related to angiogenesis. In the pathogenesis of HCC, several of the aforementioned RTKs are up-regulated, causing disease progression and providing a key target for pharmacological treatment. At present, there are 3 known members of the VEGFR family, namely VEGFR-1 (flt-1), VEGFR-2 (KDR/flk-1), and VEGFR-3 (flt-4), all of which belong to the family of RTKs. Among them, VEGFR-1 has the highest binding affinity to VEGF, 10 times that of VEGFR-2, while VEGFR-2 plays a major role in VEGF-regulated angiogenesis. In HCC patients, VEGF binds to two major receptors, VEGFR-1 (flt-1) and VEGFR-2 (KDR/flk-1)[4]. VEGFR-1 and VEGFR-2 have distributions of 87% and 53% on human hepatocellular carcinoma tumor-derived endothelial cells, respectively[5], and are also expressed on hepatocellular carcinoma cells. Both VEGFR-1 and VEGFR-2 consist of 7 immunoglobulin-like extracellular domains, a transmembrane domain, and an intracellular domain with a tyrosine kinase insert, with VEGFR-2 being the most crucial one. Expression of VEGFR-1 and VEGFR-2 is closely related to the formation of hepatic precancerous lesions, i.e., liver cirrhosis, and VEGFR-2 is closely related to the differentiation and prognosis of liver cancer. Both VEGFR-1 and VEGFR-2 antibodies cause dose-dependent

inhibition of angiogenesis in HCC models, which verifies the relationship between VEGFR and HCC, as well as provides a theoretical basis for the development of VEGFR as a target for HCC treatment.

1.2.2 Research developments in targeted therapies for HCC

In Dec. 2007, sorafenib became the first FDA-approved drug for the treatment of HCC, based on its remarkable benefits in terms of survival as demonstrated in the SHARP trial[6], in which PFS was increased by 73% (5.5 vs. 2.8 months), and OS was increased by 44% (10.7 vs. 7.9 months) when compared with placebo. This kicked off the new era of targeted therapy for patients with HCC. In 2008, sorafenib was approved for the treatment of HCC in China, hence offering a new treatment option to numerous liver cancer patients in China. However, the application of sorafenib treatment remains limited due to its high cost (approx. RMB 50,000 per patient per month).

Furthermore, several multi-kinase inhibitors that are being developed have suffered setbacks in head-to-head comparisons with sorafenib:

The phase III clinical trial of sunitinib (Pfizer) in patients with advanced liver cancer was terminated prematurely in Apr. 2010 due to the failure of sunitinib to improve survival in comparison to sorafenib, and the incidence of serious adverse events was higher in the sunitinib group than in the sorafenib group [7].

The multi-kinase inhibitor ABT-869 (Linifanib) developed by Abbott had also failed to demonstrate any advantages over sorafenib. As such, the phase III clinical trial of ABT-869 was terminated based on the recommendation of the independent data monitoring committee (IDMC).

A study involving 731 patients showed that Roche's Tarceva (erlotinib), an epidermal growth factor receptor tyrosine kinase inhibitor, had also failed to provide additional benefits, as compared with sorafenib.

Brivanib is a tyrosine kinase inhibitor targeting VEGF receptor and basic fibroblast growth factor (bFGF, FGF-2) receptor. The phase II trial of brivanib in patients with unresectable, locally advanced or distant metastatic liver cancer[8] showed that 6-month PFS reached 18.2%, median PFS was 2.7 months, and median survival was 10 months, with relatively mild side effects, mainly including weariness, hypertension, and diarrhea. However, brivanib failed in the comparison with sorafenib in the phase III non-inferiority clinical trial, because the overall survival for brivanib treatment was deemed unsatisfactory.

In summary, sorafenib remains the most superior targeted drug in terms of overall efficacy and safety in the treatment of HCC. In addition, the studies on Eli Lilly's ramucirumab (IMC-1121B) and bevacizumab in combination with chemotherapy are ongoing.

Eli Lilly's ramucirumab (IMC-1121B) is a human monoclonal antibody (IgG1) against VEGFR2, which can bind to expressed VEGFR and block the VEGF/VEGFR signaling pathway, thereby inhibiting vascular endothelial cell mitosis and producing anti-angiogenic effects [9]. A randomized, double-blind, multi-center phase III clinical study of ramucirumab is currently ongoing.

Anti-VEGF antibody: With its high affinity to VEGFR, anti-VEGF monoclonal antibody (mAb) can block VEGFR, thereby preventing the binding of VEGF to its receptor to inhibit VEGF activity. Bevacizumab is a recombinant humanized monoclonal antibody targeting VEGF-A. A phase II clinical trial of bevacizumab in combination with capecitabine and oxaliplatin in patients with unresectable and untransplantable HCC showed an efficacy of up to 20%, indicating that bevacizumab in combination with chemotherapy is a safe treatment regimen. Further research is required for the understanding of the therapeutic value of bevacizumab in HCC patients [10].

Dovitinib is an oral small molecule tyrosine kinase inhibitor targeting FGFR, VEGFR, and PDGFR. Huynh et al. [11] found that dovetinib is able to inhibit the proliferation and migration of HCC cells in mouse xenograft HCC model. The phase II clinical study of dovitinib in HCC patients is currently undergoing.

1.3 Development Background of Apatinib

Apatinib is a small molecule VEGFR tyrosine kinase inhibitor developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. with independent intellectual property rights. The chemical name of apatinib is N-[4-(cyanocyclopentyl)phenyl][2-[(4-pyridylmethyl)amino](3-pyridyl)] formamide mesylate. Apatinib has a molecular formula of $C_{25}H_{27}N_5O_3S$, and molecular weight of 493.58 (mesylate). Apatinib exerts its anti-angiogenic effect mainly by inhibiting VEGFR. Preclinical studies have shown that it's superior to PTK787 in anti-tumor effect. Phase II studies in HCC patients have preliminarily validated the efficacy and safety of apatinib in treatment of advanced HCC. The objective of this phase III study is to confirm the efficacy and safety of apatinib in treatment of advanced HCC.

1.4 Results of Preclinical Studies of Apatinib

1.4.1 Metabolism study of apatinib in animals

Results of PK studies in beagle dogs showed that: After a single intravenous dose of apatinib mesylate (i.v.bolus) at 5 mg/kg, maximum plasma concentrations (C_{max}) of apatinib were 6058 ng/mL (male) and 3523 ng/mL (female), areas under plasma concentration-time curve ($AUC_{0\rightarrow 24h}$) were 12599 ng/mL·h (male) and 9106 ng/mL·h (female), elimination half-lives ($T_{1/2}$) were 2.15 h (male) and 3.22 h (female), elimination rate constants (Kel) were 0.328 h^{-1} (male) and 0.216 h^{-1} (female), mean residence times (MRT) were 3.08 h (male) and 3.81 h (female), plasma clearance rates (CL) were 0.385 L/h/kg (male) and 0.515 L/h/kg (female), apparent volumes of distribution (Vd) were 1.19 L/kg (male) and 1.94 L/kg (female).

After a single oral dose of apatinib mesylate at 5, 15, and 30 mg/kg, linear correlation was not observed in C_{max} and $AUC_{0\rightarrow 24h}$ in male beagle dogs; however female beagle dogs exhibited linear correlation in C_{max} (formula: y = 65.217x + 38.411, R2 = 0.9894) and $AUC_{0\rightarrow 24h}$ (formula: y = 451.29x - 547.16, R2 = 0.9939). Mean residence times (*MRT*) were 4.132 h (male) and 4.327 h (female), and oral bioavailabilities (F) were 9.24% (male) and 15.42% (female).

1.4.2 Preclinical efficacy studies of apatinib

In vitro: The inhibitory effects of apatinib on the growth of various in vitro tumor cells such as colon cancer, lung cancer, gastric cancer, renal cell carcinoma, and leukemia were evaluated using SRB or MTT assays. Results showed that IC_{50} was greater than 20 μM in all tumor cell lines above, far higher than the concentration required to inhibit the activity of tyrosine kinase receptors such as VEGFR, suggesting that apatinib has no cytotoxic effect.
In vivo: Apatinib has significant anti-tumor effects on a variety of human tumors such as colon cancer, lung cancer, and gastric cancer xenografts in nude mice. Efficacy: Apatinib exerts obvious synergistic effects on traditional cytotoxic drugs such as oxaliplatin, 5-Fu, docetaxel, and doxorubicin, with a comparable efficacy to ZD6474 and AMG706, but more effective than PTK787.

Anti-tumor mechanism: Apatinib effectively inhibits VEGFR2 at very low concentrations, and is able to inhibit kinases such as PDGFR, c-Kit, and c-Src at higher concentrations. Refer to Table 1 for details. The effect of apatinib on VEGFR2 is 13.7-fold higher than PTK787; apatinib also inhibits KDR-mediated downstream signaling. Apatinib also inhibits the growth of KDR/NIH3T3 cell lines with high-expression of VEGF, inhibits VEGF-induced proliferation, migration, and lumen formation of HUVEC cells, and inhibits the germination of microvessels on rat arterial rings. The anti-angiogenic effect of apatinib in vitro is stronger or equivalent to that of the control compound PTK787.

Table 1. Effects of apatinib on KTRs

Kinase	Apatinib (IC_{50} ± SD nM)	PTK787 (IC_{50} ± SD nM)
VEGFR2	2.43 ± 1.30	33.30 ± 14.45
Flt1	70.08 ± 29.36	84.69 ± 20.74
PDGFRβ	537.31 ± 190.46	416.51 ± 143.73
c-Kit	420.31 ± 40.37	606.11 ± 77.93
EGFR	> 1000	> 1000
ErbB2	> 1000	> 1000
PGRFR1	> 1000	> 1000
c-Src	348.53 ± 194.42	> 1000

1.4.3 Toxicity studies of apatinib in animals

1.4.3.1 Acute toxicity study in animals

(1) Mice: Forty ICR mice were randomly assigned to 2 groups, 20 per group (half females and half males), including a 5 g/kg treatment group and a solvent control group. After a single dose by oral gavage, the immediate reactions of mice were observed for 14 days, during which the toxicities and deaths were recorded. Apart from slow increase in body weight in the treatment group, no significant clinical toxicity and death occurred during the observation period. Gross anatomical examination was carried out in all mice on D15, and no drug-related changes were observed.

(2) Rats: Eighty SD rats were randomly assigned to 4 groups, 20 per group (half females and half males), including two treatment groups (2 and 5 g/kg) and two corresponding solvent control groups. After a single dose by oral gavage, the immediate reactions of mice were observed for 14 days, during which the toxicities and deaths were recorded. During the observation period, the mortalities in female rats and male rats in the 5 g/kg group were 50% and 20%, respectively; in the 2 g/kg group, death was found in 1 female rat (mortality of 10%), but no death was observed in male rats. Symptoms of toxicity, such as loose hair, reduced activity, listlessness, and slow weight gain, were observed in rats in the treatment groups post-administration; weight loss was observed in dead and moribund rats. The following observations were noted in 1 moribund female rat in the 5 g/kg group: Bilateral adrenal enlargement, yellow plaques in the right kidney, abnormal blood biochemical indicators, as well as abnormal hepatic and renal functions (> 3-fold elevation in ALT, AST, and BUN levels); histopathological examination showed scattered spotty necrosis of hepatocytes, adrenal hemorrhage, thymic atrophy, and reduced lymphocyte levels in the germinal center in the white pulp of spleen. No significant abnormalities were observed during gross anatomical examination in other deaths and rats dissected on D14.

(3) Beagle dogs: Six beagle dogs around the age of 6 months (three per gender), weighing about 7 kg each, were included in the acute toxicity study to determine the approximate lethal dose in beagle dogs after oral administration. Single oral doses were administered in 50% escalation. Females received doses at 1050, 1575, and 2363 mg/kg, while males received doses at 1575, 2363, and 3545 mg/kg (1 dog per dose level). Decreased activity, limb weakness, gait instability, and slight weight loss were observed in female beagle dogs post-administration. Five-fold increase in BUN levels (17.3 mmol/L) was observed in dogs which received 2363 mg/kg. Male dogs started to vomit (2 times and drug in vomit) at approx. 2–4 h. Decreased activity, weakness in hind or all limbs, and reduced food intake were also observed in male dogs.The severity of toxicity increased with increasing dose. Significant toxicities were observed but no deaths occurred.

1.4.3.2 Long-term toxicity study in animals

(1) Rats: SD rats received apatinib by oral gavage for 13 weeks, followed by a 4-week recovery period for observation. Rats were assigned to four groups: 3 treatment groups (5, 15, and 50 mg/(kg·d)), and 1 solvent control group, with each group consisting of 14 per gender. Results showed that: 5 mg/(kg·d) group: No drug-related changes were observed throughout the course of the study. 15 mg/(kg·d) group: Male rats showed mild increase in ALT levels during the dosing period, which resolved after discontinuation. 50 mg/(kg·d) group: During the dosing period, both male and female rats showed slow weight gain, decreased food intake, weight loss, as well as mild increases in hepatic function indicators (ALT, AST, ALP); no abnormalities in relevant ions, relevant enzymes, and estrogen in serum were observed; no drug-related changes were observed in histopathological examination of the liver and other organs; in addition, 3 female rats in this group died during the fasting period prior to anatomical examination, which may be related to weight loss, marasmus, malnutrition, and fasting post-dose; female rats in this group also showed broken incisors (11/14, 78.6%), slight decrease in tibia bone density (mainly caused by decrease in trabecular bone density), which were resolved after discontinuation apart from partial changes in bones; histopathological results showed that through gross observation of each organ, statistical analysis of organ weights and coefficients, and histological examination, incisor changes were observed in treatment groups compared with control group, mainly manifested as broken incisor, and in severe cases, a complete loss, partially of which were resolved after 4 weeks of recovery. Apart from some commonly seen spontaneous lesions, no drug-related pathological changes were observed in all treatment groups.

(2) Beagle dogs: Twenty-four beagle dogs around the age of 6 months (12 per gender), weighing about 7 kg each, were randomized into 4 groups, with 6 dogs per group (3 male dogs and 3 female dogs) and were given oral doses of apatinib for 13 weeks. This study included 4 groups, i.e., 3 treatment groups (3, 10, and 30 mg/(kg·d)), and 1 control group. Results showed that the behavioral responses, body weight, and food intake of dogs in each dose group were similar to those in the control group. Hematology, blood biochemistry, electrocardiogram (ECG), and bone density test results showed that various indicators were similar between the treatment and control groups, and all results were within the normal range, indicating generally normal hepatic and renal functions. During the dosing period, the skin around the noses and mouths of dogs in the 30 mg/(kg·d) group appeared pale, and histopathological examination revealed thinner epidermis on the nose; while no abnormality was noted in the control group.

1.5 Results of Clinical Studies of Apatinib

1.5.1 Phase I tolerance test of apatinib

According to the modified Fibonacci method, the designed doses of apatinib were 250 mg, 500 mg, 750 mg, 850 mg, and 1000 mg. According to the experimental design, the Grade IV hematological toxicity and/or Grade ≥ III non-hematological toxicity occurring in the first course of treatment (28 days) were determined as dose limiting toxicities (DLTs). A total of 18 subjects could be used for tolerability evaluation, with 3 subjects in each dose group (6 subjects in the 850 mg dose group).

DLT was observed in the 1000 mg dose group of apatinib, characterized by Grade III hypertension (2 out of 3 patients) and Grade III hand-foot-skin reaction (1 patient). All had recovered following dose discontinuation and were controlled through dose reduction. In the additional 850 mg dose group, none of the 6 patients showed DLT. For further safety considerations, the observation time of the 850 mg group was extended to 2 cycles and DLT was still not present, so the 850 mg dose was identified as the maximum tolerated dose (MTD).

The main adverse events in the first cycle of the tolerability study included: hand-foot-skin reactions (2 cases of Grade I in the 500 mg/day group; 2 cases of Grade I and 1 case of Grade II in the 750 mg/day group; 1 case of Grade I and 2 cases of Grade II in the 850 mg/day group; 1 case of Grade III in the 1000 mg/day group; 9 cases in total, 47.4%); hypertension (1 case of Grade I in the 250 mg/day group; 1 case of Grade II in the 850 mg/day group; 1 case of Grade II in the 1000 mg/day group; 9 cases in total, 47.4%); white blood cell decreased (1 case of Grade II in the 500 mg/day group; 2 cases of Grade II and 1 case of Grade I in the 750 mg/day group; 3 cases of Grade I and 1 case of Grade II in the 850 mg/day group; 1 case of Grade II in the 1000 mg/day group; 6 cases in total, 31.6%); oral mucositis (1 case in Grade I in the 250 mg/day group; 1 case of Grade I and 1 case of Grade II in the 750 mg/day group; 1 case of Grade I and 1 case of Grade II in the 1000 mg/day group; 5 cases in total, 26.3%); pyrexia (2 cases of Grade II in the 250 mg/day group; 1 case of Grade II in the 500 mg/day group; 1 case of Grade I in the 850 mg/day group; 4 cases in total, 21.1%); platelet count decreased (1 case of Grade II in the 500 mg/day group; 1 case of Grade II in the 750 mg/day group; 1 case of Grade II in the 750 mg/day group; 1 case of Grade II in the 1000 mg/day group; 3 cases in total, 15.8%); asthenia (2 cases of Grade II in the 850 mg/day group; 1 case of Grade II in the 1000 mg/day group; 3 cases in total, 15.8%); bilirubin increased (1 case of Grade I in the 750 mg/day group; 1 case of Grade I in the 850 mg/day group; 2 cases in total, 10.5%); headache (1 case of Grade I in the 1000 mg/day group, 1 case of Grade II in the 850 mg/day group; 2 cases in total, 10.5%); abdominal pain (1 case of Grade II in the 500 mg/day group, 1 case of Grade I in the 750 mg/day group; 2 cases in total, 10.5%); low back pain (1 case of Grade II in the 750 mg/day group, 1 case of Grade I in the 1000 mg/day group; 2 cases in total, 10.5%); esophagitis (1 case of Grade II in the

500 mg/day group; 1 case of Grade I in the 750 mg/day group; 2 cases in total, 10.5%); nausea (1 case of Grade II in the 750 mg/day group; 1 case in total, 5.3%); tongue pain (1 case of Grade I in the 1000 mg/day group; 1 case in total, 5.3%); anterior chest pain (1 case of Grade II in the 500 mg/day group; 1 case in total, 5.3%); chest pain (1 case of Grade II in the 500 mg/day; 1 case in total, 5.3%); transaminases increased (1 case of Grade II in the 850 mg/day group; 1 case in total, 5.3%); pruritus (1 case of Grade I in the 500 mg/day group, 5.3%); epigastric discomfort (1 case of Grade I in the 850 mg/day group, 5.3%); hoarseness (1 case of Grade I in the 850 mg/day group; 1 case in total, 5.3%); stomach discomfort (1 case of Grade II in the 850 mg/day group, 5.3%); chest tightness, cough (1 case of Grade I in the 850 mg/day group; 1 case in total, 5.3%); proteinuria (1 case of Grade I in the 850 mg/day group, 5.3%); sinus bradycardia (1 case of Grade I in the 500 mg/day group, 5.3%); lung abscess (1 case of Grade I in the 850 mg/day group; 1 case in total, 5.3%); constipation (1 case of Grade I in the 250 mg/day group, 5.3%); intestinal obstruction (1 case of Grade I in the 250 mg/day group I, 5.3%).

Adverse events mentioned above that were definitely unrelated or unlikely related to apatinib included pruritus, esophagitis, lung abscess, abdominal pain, constipation, and intestinal obstruction. Primary treatment-related adverse drug reactions included hand-foot-skin reactions, white blood cell count decreased, hypertension, fever, bilirubin increased, oesophagitis, dermal toxicity, thrombocytopenia, nausea, asthenia, headache, transaminases increased, oral mucositis, epigastric discomfort, tongue pain, hoarseness, stomach discomfort, chest tightness and cough, proteinuria, and sinus bradycardia. In 850 mg and lower dose groups, hematological toxicities were of Grade I–III, including white blood cell count decreased and thrombocytopenia, while other non-hematological toxicities were of Grade I–II, which could recover to normal after symptomatic treatment.

1.5.2 Phase I clinical pharmacodynamic (PD) observation of apatinib

From May 2007 to December 2008, a phase I clinical study of apatinib was conducted at Fudan University Shanghai Cancer Center, including 3 studies, i.e., a tolerability study, a pharmacokinetic study, and a phase I supplement clinical study. This study enrolled a total of 81 subjects with advanced solid tumors who were refractory to standard treatment or had no effective standard treatment. Nine of the subjects were not evaluated, and 3 others were only administered with a low dose of 250 mg/day. A total of 69 subjects received apatinib treatment at doses of 500–1000 mg/day (only 3 subjects received 1000 mg/day), and a total of 56 patients were evaluated. Refer to Table 2 for a summary of tumor types of the 69 subjects and efficacy in the 56 evaluable subjects:

Table 2. Efficacy of apatinib in the treatment of different solid tumors

	Gastric Cancer	Colorectal Cancer	Lung Cancer	Breast Cancer	Nasopharyngeal Cancer	Renal Carcinoma	Esophageal Cancer	Hepatocellular Carcinoma	Small Intestinal Stromal Tumor	Neurilemmoma Malignant of Left Iliac Fossa
Not Evaluable	1	7	1	1	1	0	1	1	0	0
CR	0	0	0	0	0	0	0	0	0	0
PR	2	2	0	0	0	1	0	0	1	0
SD	5	15	3	4	1	0	4	1	0	0
PD	1	7	1	2	0	0	0	0	0	1
Death Without Evaluation	3	1	0	0	0	0	0	0	0	0
Objective Response Rate	18.1%	8%	0	0	0	100%	0	0	100%	0
Disease Control Rate	63.6%	68%	75%	66.7%	100%	100%	100%	100%	100%	0
Total	12	32	5	7	2	1	5	2	1	1

Result analysis:

A total of 69 subjects with various types of solid tumors were included in statistical analysis, and 13 were deemed unevaluable for efficacy. Of the 69 subjects included in the statistics, 16 subjects were given 500 mg, 37 subjects were given 750 mg, 13 subjects were given 850 mg, and 3 subjects were given 1000 mg.

Analysis of ORR showed that 1 evaluable case was found for each of renal carcinoma and small intestinal stromal tumor, with both achieving PR. 11 and 25 evaluable patients were included for the gastric cancer and colorectal cancer respectively, and higher response rates of 18.1% and 8%, respectively, were achieved.

Based on the analysis of DCR, 1 each of evaluable patient for nasopharyngeal cancer, HCC, and GIST were observed, and all had achieved SD. Due to the small sample size, the efficacy should be assessed with caution. There were 4, 4, and 6 evaluable patients for esophageal cancer, lung cancer, and breast cancer, respectively, with DCRs of 100%, 75%, and 66.7%.

1.5.3 Phase I clinical pharmacokinetic study of apatinib

The single-dose study involved oral administration at 3 dose levels of 500, 750 and 850 mg to subjects with cancer, including 7 male subjects and 5 female subjects in low-dose group, 6 male subjects and 3 female subjects in medium-dose group, and 6 male subjects and 6 female subjects in high-dose group. In this study, drugs were administered within 0.5 h after meals, and blood and urine samples were collected at multiple time points within 48 h. Results showed that M1 was a major metabolite of apatinib in humans, with $AUC_{M1}/AUC_{apatinib}$ of 1.15-5.06, as well as 48-h cumulative excretion in urine, $Cum.Ae_{M1}/Cum.Ae_{apatinib}$ of 24.5-353. $T_{1/2}$ values of apatinib and M1 were 8.93 ± 0.81 h and 12.5 ± 1.666 h, respectively. At the same dose level, large inter-individual variability was seen in apatinib and M1 exposure (AUC and C_{max}); significant gender difference was observed in the high-dose group ($P < 0.05$), in which, AUC in females was 1.96 times higher than that in males, and C_{max} was

3.57 times higher than that in males. The levels of apatinib and M1 exposure in male and female subjects were non-linearly but positively correlated to oral doses.

The food-effect study mainly compared the differences in absorption of a single oral dose of apatinib given at 1 h before meals and 0.5 h after meals. The concentrations of M1 were also examined. Blood and urine samples were collected at multiple time points within 48 h. Results showed that there was no significant difference in T_{max} and C_{max} of apatinib in the blood of male and female subjects with respect to the order of eating and drug administration ($P > 0.05$). In addition, the AUC, $T_{1/2}$ and Cum.Ae of apatinib, as well as relevant pharmacokinetic parameters of M1 were not affected by the order of eating and drug administration ($P > 0.05$).

Due to the relatively long half-life of M1 ($T_{1/2}$: 12.9 ± 1.85 h), the repeated-dose trial mainly focused on M1 accumulation in vivo, and changes in apatinib ($T_{1/2}$: 9.24 ± 1.40 h) concentrations were observed concurrently during the trial. The drugs were administered once a day for 4 weeks during the trial, and blood and urine samples were collected at multiple time points within 24 h on Days 1, 14, and 28 after the start of the trial. Results showed that: Although M1 and apatinib had relatively long half-lives, no significant accumulations of M1 and apatinib were observed in subjects on D14 vs. D1 ($P > 0.05$). However, a significant increase in M1 exposure was noted in male subjects on D28 vs. D1 ($P < 0.05$). Apatinib: AUC (1d), AUC (14d), and AUC (28d) were 9260 ± 4308, 7256 ± 4709, and 21930 ± 20098 ng·h/mL, respectively; C_{max} (1d), C_{max} (14d), and C_{max} (28d) were 1285 ± 776, 693 ± 430, and 1602 ± 1755 ng/mL, respectively. M1: AUC (1d), AUC (14d), and AUC (28d) were 13846 ± 7061, 10899 ± 6702, and 39784 ± 21900 ng·h/mL, respectively; C_{max} (1d), C_{max} (D14d), and C_{max} (28d) were 1193 ± 673, 908 ± 597, and 1728 ± 1233 ng/mL, respectively. There was no significant accumulation of apatinib and M1 based on the cumulative levels of urinary and renal excretion ($P > 0.05$). Cum.Ae (1d), Cum.Ae (14d), and Cum.Ae (28d) of M1 were 30281 ± 8141, 34537 ± 15867, and 33466 ± 17737 μg, respectively.

1.5.4 Study on the effect of apatinib on serum VEGF

The phase I clinical PK/PD study of apatinib enrolled 10 subjects who completed 0-28 days of VEGF testing. The results are shown in Table 3:

Table 3. Changes in plasma VEGF at different time points in 10 subjects

Subject	Day 0	Day 14	Day 28
1	1627	323	3962
2	822	1144	497
3	244	524	312
4	240	419	475
5	280	797	920

Subject	Day 0	Day 14	Day 28
6	518	2000	1841
7	1105	1728	1630
8	162	467	761
9	417	761	826
10	266	477	512
Mean	568	864	1174
Standard Deviation	477	581	1101

As shown in Table 3, significant increase in VEGF levels was observed in 8 patients due to apatinib; 1 patient experienced an increase on D14, followed by a decline on D28; in addition, 1 patient reported abnormally elevated VEGF levels pre-dose, which decreased first and then increased post-dose. In general, progressive increases in serum VEGF levels were observed in 10 patients with various advanced solid tumors post-dose. Serum concentration was 568 ± 477 ng/mL on D1 pre-dose, 864 ± 581 ng/mL on D14 post-dose, and 1174 ± 1101 ng/mL on D28 post-dose. No statistically significant difference in serum VEGF levels was observed pre- and post-dose. This may be related to the small sample size.

1.5.5 Results of phase II clinical trial of apatinib in patients with gastric cancer

This is a randomized, double-blind, double-dummy, parallel controlled, multi-center phase II clinical trial.

A total of 141 subjects completed the trial, including 48 in the placebo group, 47 in the 850 mg q.d. group, and 46 in the 425 mg b.i.d. group.

Primary endpoint: PFS; secondary endpoints: ORR, DCR, OS, and safety.

mPFS values of the 850 mg q.d. group, 425 mg b.i.d. group, and placebo group were 110, 96, and 42 days, respectively. mOS values of the 850 mg q.d. group, 425 mg b.i.d. group, and placebo group were 145, 128, and 75 days, respectively. DCR values of the 850 mg q.d. group, 425 mg b.i.d. group, and placebo group were 51.06%, 34.78%, and 10.42%, respectively. ORR values of the 850 mg q.d. group, 425 mg b.i.d. group, and placebo group were 6.38%, 13.04%, and 0%, respectively.

AEs in the placebo, 850 mg q.d., and 425 mg b.i.d. groups were reported by 36, 42, and 44 subjects, with incidences of 75%, 89.36%, and 95.65%, respectively; severe AEs (NCI CTC Grade III–IV) occurred in 18, 30, and 48 subjects, with incidences of 37.5%, 48.94%, and 73.91%, respectively. The incidence of AE was higher in both 850 mg q.d. and 425 mg b.i.d. groups as compared with the placebo group, and the incidence in the 425 mg b.i.d. group was higher than that in the 850 mg q.d. group.

1.5.6 Results of phase III clinical trial of apatinib in patients with gastric cancer

This is a randomized, double-blind, parallel-controlled, nation-wide multi-center phase III clinical trial to validate the efficacy and safety of apatinib in patients with advanced gastric cancer.

In this trial, 267 randomized patients who received at least one dose were included in FAS analysis, including 176 patients in the treatment group and 91 patients in the control group.

In the FAS, endpoint events were observed in 146 (82.95%) subjects in the treatment group and 78 (85.71%) subjects in the control group, with an incidence > 80% in both groups, indicating that the statistical model is reliable.

Analysis showed that as of 23 May, 2013, without taking the influence of crossover design into consideration, median OS (mOS) values were 6.5 and 4.7 months in the treatment and control groups, respectively. The mOS in the treatment group was 1.8 months longer than the control group, $P = 0.0149$. The HR of treatment group to control group was 0.709 and the 95% CI was (0.537, 0.937), with P = 0.0156. The above results demonstrated that apatinib provided significant survival benefits when compared with placebo.

All the 267 subjects in this trial were included in the SS for analysis. Results showed that:

The incidences of AEs in the treatment and control groups were 98.30% v.s 90.11%, $P = 0.0038$; the incidences of Grade ≥ II AEs were 88.07% v.s 67.03%, $P = 0.0001$; the incidences of Grade III–IV AEs were 60.23% v.s 41.76%, $P = 0.0045$.

The incidence of ADRs in the treatment and control groups were 92.05% v.s 71.43%, P = 0.0000; the incidence of Grade ≥ II ADRs were 80.68% v.s 45.05%; the incidences of Grade III–IV ADRs were 51.70% v.s 24.18%, $P = 0.0000$.

The incidence of SAEs in the treatment and control groups were 15.34% v.s 16.48%, P = 0.8598; the incidence of serious ADRs were 6.25% v.s 6.59%, $P = 1.0000$.

1.5.7 Results of phase II clinical trial of apatinib in patients with HCC

A randomized, open-label, multi-center phase II clinical trial evaluating apatinib mesylate tablets in advanced HCC was initiated in Jul. 2010 by the 81st Hospital of the Chinese People's Liberation Army and other sites.

The trial involved two treatment groups: 850 mg and 750 mg groups. Primary endpoint: TTP; secondary endpoints: OS, ORR, DCR, AFP, QoL, and safety.

Simon's two-stage design for the clinical study of anti-tumor drugs is used. Sample size is determined based on disease control rate (DCR). It was assumed that patients receiving the best supportive care for this indication could achieve DCR of 30%. Patients in the apatinib group achieved DCR of 50%, indicating that apatinib is superior to the best supportive care in terms of DCR. Based on the optimal design criteria, with $\alpha = 0.05$ and $\beta = 0.2$, and using

NCSS & PASS, 15 patients were enrolled in each group in the first stage. If 5 patients reach DCR, the sample size would be expanded to 46 patients. If 15 of the 46 patients reach DCR, subsequent studies could be carried out at this dose. Taking dropout factors into consideration, a total of 36 subjects were enrolled in the first stage, and sample size was expanded to 117 in the second stage, i.e., 81 subjects were enrolled (including 51 in the 850 mg group and 30 in the 750 mg group).

As of Jun. 2013, the results are as follows:

The phase II clinical trial of apatinib mesylate tablet in patients with advanced HCC had an actual enrollment of 121 subjects, including 70 in the 850 mg group and 51 in the 750 mg group.

Efficacy results showed that in the FAS (ITT population), mTTP values in the 850 mg and 750 mg groups were 4.2 and 3.3 months, and mOS values were 9.7 and 9.8 months, respectively. ORRs were 8.6% and 0.0%, and DCRs were 48.6% and 37.3%, respectively.

Table 4. Inter-group comparison of efficacy results (FAS)

Group	mTTP (month)	mOS (month)	ORR (%)	DCR (%)
850 mg	4.2	9.7	8.6	48.6
750 mg	3.3	9.8	0.0	37.3

Safety results showed that the incidences of AEs in the 850 mg and 750 mg groups were 98.6% and 94.1%, respectively; the incidences of severe AEs (NCI CTCAE Grade III–V) were 67.1% and 72.6%, respectively. The incidences of ADRs in the 850 mg and 750 mg groups were 95.7% and 90.2%, respectively; the incidences of severe ADRs (NCI CTCAE Grade III–V) were 58.6% and 58.8%, respectively. The incidences of SAEs were 18.6% and 23.5%, respectively; and the incidences of serious ADRs were 4.3% and 5.9%, respectively.

Table 5. Comparison of the incidences of AEs and ADRs between the two groups (SS)

	Group	Yes	No	Total	Incidence (%)	Inter-Group Comparison *P*
Adverse Events (n)	850 mg group	69	1	70	98.57	0.3090
	750 mg group	48	3	51	94.12	
Grade III–V Adverse Events (n)	850 mg group	47	23	70	67.14	0.5551
	750 mg group	37	14	51	72.55	
Adverse Drug Reactions (n)	850 mg group	67	3	70	95.71	0.2790
	750 mg group	46	5	51	90.20	
Grade III–V Adverse Drug Reactions (n)	850 mg group	41	29	70	58.57	1.0000
	750 mg group	30	21	51	58.82	

	Group	Yes	No	Total	Incidence (%)	Inter-Group Comparison *P*
Serious Adverse Events	850 mg group	13	57	70	18.57	0.5060
(n)	750 mg group	12	39	51	23.53	
Serious Adverse Drug Reactions	850 mg group	3	67	70	4.29	0.6960
(n)	750 mg group	3	48	51	5.88	

Common adverse events (incidence ≥ 10%) mainly included: transaminases increased, hypertension, proteinuria, hand-and-foot syndrome, etc., most of which were mild to moderate, and all were controllable. Refer to Table 6 for details:

Table 6. Common AEs (incidence ≥ 10%) in both groups

Adverse Events	Group	Total	Adverse Events n (%)	Grade III–V Adverse Events n (%)
Transaminases Increased	850 mg	70	44 (62.9)	8 (11.4)
	750 mg	51	25 (49.0)	7 (13.7)
Bilirubin Increased	850 mg	70	44 (62.9)	8 (11.4)
	750 mg	51	24 (47.1)	8 (15.7)
Hypertension	850 mg	70	36 (51.4)	3 (4.3)
	750 mg	51	25 (49.0)	7 (13.7)
Proteinuria	850 mg	70	33 (47.1)	1 (1.4)
	750 mg	51	24 (47.1)	2 (3.9)
Gamma-Glutamyltransferase Increased	850 mg	70	30 (42.9)	13 (18.6)
	750 mg	51	6 (31.4)	5 (9.8)
Hand-and-Foot Syndrome	850 mg	70	29 (41.4)	4 (5.7)
	750 mg	51	15 (29.4)	4 (7.8)
Platelet Count Decreased	850 mg	70	27 (38.6)	6 (8.6)
	750 mg	51	23 (45.1)	7 (13.7)
White Blood Cell Count Decreased	850 mg	70	21 (30.0)	3 (4.3)
	750 mg	51	17 (33.3)	2 (3.9)
Lactate Dehydrogenase Increased	850 mg	70	19 (27.1)	2 (2.9)
	750 mg	51	6 (11.8)	2 (3.9)
Neutrophil Count Decreased	850 mg	70	18 (25.7)	4 (5.7)
	750 mg	51	16 (31.4)	3 (5.9)
Abdominal Pain	850 mg	70	18 (25.7)	4 (5.7)
	750 mg	51	7 (13.7)	0 (0.0)
Asthenia	850 mg	70	17 (24.3)	3 (4.3)
	750 mg	51	9 (17.7)	2 (3.9)

The 850 mg and 750 mg groups had comparable efficacy. In terms of safety, the types and incidence of AEs and ADRs observed in both groups were also similar.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

To observe and evaluate the efficacy and safety of apatinib mesylate tablet as second-line treatment in patients with advanced HCC.

2.2 Primary Endpoints

- Overall survival (OS)

  Defined as the time from randomization to death from any cause.

2.3 Secondary Endpoints

- Progression free survival (PFS)

  Defined as the time from randomization to the occurrence of progressive disease (PD) or death, whichever occurs first.
- 3-, 6-, and 12-month PFS rates

  Defined as the proportions of evaluable patients without disease progression from the start of the trial to 3, 6, and 12 months.
- Time to progression (TTP)

  Defined as the time from randomization to radiographic disease progression.
- Objective response rate (ORR)

  Defined as the proportion of evaluable subjects who have a tumor response assessed by RESIST 1.1, including complete response (CR) and partial response (PR).
- Disease control rate (DCR)

  Defined as the proportion of evaluable subjects who have disease control assessed by RESIST 1.1, including CR, PR and stable disease (SD) (≥4 weeks）.

Evaluable subjects are defined as all subjects who have received at least 2 cycles (8 weeks) of apatinib treatment and have received a tumor evaluation after 2 treatment cycles (8 weeks). If the efficacy reaches CR, PR or SD, the subject must be reexamined 4 weeks after the first evaluation.

- The percentage of evaluable patients with stable disease (SD) of ≥ 4 weeks (confirmed SD in particular)
- 6- and 12-month mortalities
- Quality of life score (EORTC QLQ-C30 and HCC-18);

- Drug safety: Vital signs, laboratory measurements, AEs, SAEs, treatment-related AEs and SAEs, and AEs of special interest (e.g., hypertension, proteinuria, and hand-and-foot syndrome [palmar-plantar erythrodysesthesia syndrome]); judged as per NCI-CTCAE V4.0.

3 SELECTION AND WITHDRAWAL OF SUBJECTS

3.1 Clinical Diagnostic Criteria

"Guideline on Diagnosis and Treatment for Primary Liver Cancer" (2011 Edition) states:

The clinical diagnosis of HCC can be confirmed when the following conditions (1) + (2)a or conditions (1) + (2)b + (3) are met:

(1) With evidence of cirrhosis and HBV and/or HCV infection (positive HBV and/or HCV antigen);

(2) Typical imaging features of HCC: Multidetector CT scan and/or dynamic contrast-enhanced MRI showing hepatic space-occupying lesions with arterial hypervascularity and venous or delayed phase washout;

a One of the two imaging examinations (CT and MRI) showing the above features of liver cancer for those with lesions ≥ 2 cm in diameter;

b Both CT and MRI imaging examinations showing the above features of liver cancer for those with lesions of 1-2 cm in diameter, so as to enhance the specificity of the diagnosis;

(3) Serum AFP ≥ 400 μg/L for 1 month or ≥ 200 μg/L for 2 months, and when the increase in AFP level due to other reasons can be excluded, including pregnancy, germline embryogenic tumor, active liver disease and secondary liver cancer.

3.2 Inclusion Criteria

Inclusion criteria:

1. Age: ≥ 18 years old;

2. Patients strictly meeting the clinical diagnostic criteria in "Guideline on Diagnosis and Treatment for Primary Liver Cancer" (2011 Edition) or with histologically or cytologically confirmed recurrent/metastatic HCC, unsuitable for palliative surgery or radiation therapy, with at least one measurable lesion (must be ≥ 10 mm in longest diameter by spiral CT or ≥ 15 mm in shortest diameter for enlarged lymph nodes, as per RECIST 1.1, as shown in Annex 1);

3. Patients with HCC refractory or intolerant to systematic chemotherapy (with oxaliplatin, alone or in a therapeutic combination) and/or molecular targeted therapy with sorafenib;

Note: Definition of treatment failure: disease progression during treatment or relapse after treatment is completed (must have received ≥ 1 cycle of systemic chemotherapy with oxaliplatin (or plus other drugs) or ≥ 14 days of molecular targeted therapy with sorafenib);

Definition of intolerability: Grade ≥ IV hematological toxicity or Grade ≥ III non-hematological toxicity or Grade ≥ II major organ injury such as the heart, liver, or kidneys during treatment.

4. The interval between the last systemic treatment failure (with treatment discontinued) and the enrollment (time of signing the informed consent form) was ≥ 2 weeks, and the adverse event(s) had basically returned to normal (NCI-CTCAE ≤ Grade I);

5. Child-Pugh score: Class A or Class B (≤ 7); the Child-Pugh scoring system is shown in Appendix 2;

6. BCLC staging: B-C (the "Barcelona Clinic Liver Cancer (BCLC) Staging System, 2010" is shown in Appendix 3);

7. ECOG PS of 0–1 within 1 week before enrollment, as shown in Appendix 4;

8. Expected survival ≥ 12 weeks;

9. HBV DNA < 2000 IU/mL (10^4 copies/mL);

10. Major organs must function normally, meeting the following criteria:

(1) Hematology: (without blood transfusion, G-CSF, or medication within 14 days prior to screening)

d. HB ≥ 90 g/L;

e. ANC ≥ 1.5×10^9/L;

f. PLT ≥ 80×10^9/L;

(2) Biochemistry: (no ALB transfusion within 14 days)

e. ALB ≥ 29 g/L;

f. ALT and AST < 5 × ULN;

g. TBIL ≤ 1.5 × ULN;

h. Creatinine ≤ 1.5 × ULN;

(Only one of the two items, albumin or bilirubin, has a Child-Pugh score of 2)

11. Women of childbearing potential must have a negative pregnancy test (serum or urine) within 7 days prior to enrollment, and be willing to take appropriate contraceptive measures during the trial and within 8 weeks after the last dose of the investigational drug. Male subjects should either undergo surgical sterilization, or agree to take

appropriate contraceptive measures during the trial and within 8 weeks after the last dose of the investigational drug;

12. Subjects must participate voluntarily, sign the informed consent form, have good compliance and corporate with follow-up visits.

3.3 Exclusion Criteria:

1. Patients who have received any local treatment within 4 weeks prior to participating in this study (including but not limited to surgery, radiation, hepatic artery embolization, TACE, hepatic arterial infusion, radiofrequency ablation, cryoablation, or percutaneous ethanol injection);
2. Patients with known intrahepatic cholangiocarcinoma, mixed hepatocellular carcinoma and fibrolamellar hepatocellular carcinoma; other uncured malignancies currently or within the past 5 years, except for cured skin basal cell carcinoma or cervical carcinoma in situ;
3. Patients planning to receive liver transplant (except for patients who have undergone liver transplant);
4. Patients with symptomatic ascites requiring therapeutic paracentesis or drainage, or with a Child-Pugh score > 2;
5. Patients with hypertension which cannot be controlled to the normal range by antihypertensives (systolic pressure > 140 mmHg, diastolic pressure > 90 mmHg);
6. Patients with Grade II or greater myocardial ischemia or myocardial infarction, uncontrolled arrhythmias (QTc interval ≥ 450 ms in males and ≥ 470 ms in females);
7. Patients with NYHA (see Appendix 5) Class III-IV cardiac insufficiency or LVEF (left ventricular ejection fraction) < 50% by echocardiography;
8. Presence of multiple factors affecting oral medications (such as inability to swallow, chronic diarrhea, and intestinal obstruction, which significantly affect drug administration and absorption);
9. Patients with a history of gastrointestinal bleeding within the past 6 months or a high risk of bleeding such as esophageal varices with bleeding risk, active ulcers, and fecal occult blood ≥ (++); in the case of fecal occult blood (+), a gastroscopy is required;
10. Abdominal fistula, gastrointestinal perforation or abdominal abscess within 28 days prior to the study;
11. Abnormal coagulation function (INR > 1.5 or prothrombin time (PT) > ULN + 4 s), bleeding tendency or receiving thrombolytics or anticoagulant therapy;
12. Patients with central nervous system metastases or known brain metastases;

13. Patients with previous or current objective evidence of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-induced pneumonitis, and severe lung function impairment;
14. Urine protein ≥ ++ or 24 h urine protein > 1.0 g as indicated by urinalysis;
15. Had received treatment with a potent CYP3A4 inhibitor within 7 days prior to study participation, or had received treatment with a potent CYP3A4 inducer within 12 days prior to study participation;
16. Pregnant or lactating women; patients of child-bearing potential unwilling or unable to take effective contraceptive measures;
17. Patients with a known history of mental illness or psychotropic substance abuse;
18. Patients with bone metastasis who had received a palliative radiotherapy in an area of > 5% of bone marrow area within 4 weeks prior to the participation in this study.

3.4 Termination Criteria

1. Subject withdraws informed consent and requests to withdraw from the study;
2. Medical imaging examinations show disease progression;
3. Subjects showing unacceptable toxicity even after dose modification;
4. Other reasons for which the investigator considers a withdrawal necessary;
5. Study termination by the sponsor for the sake of safety.

3.5 Randomization Criteria

Randomization should only be performed after the patients have successfully completed the baseline evaluation and been confirmed as compliant with the inclusion criteria. The randomization system will assign a unique number to each subject and assign the investigational drug to the subject based on this number, and the administration of the investigational drug must be started within 48 h after randomization. Each site must complete the baseline eCRF of all subjects participating in randomization, even if the patients have not been treated by the investigational drug.

Stratification factors for randomization are as follows:

ECOG PS: 0 or 1

Received prior treatment with sorafenib: yes or no

Presence of vascular invasion and/or extrahepatic metastasis: yes or no

4 STUDY DESIGN

4.1 Overall Design

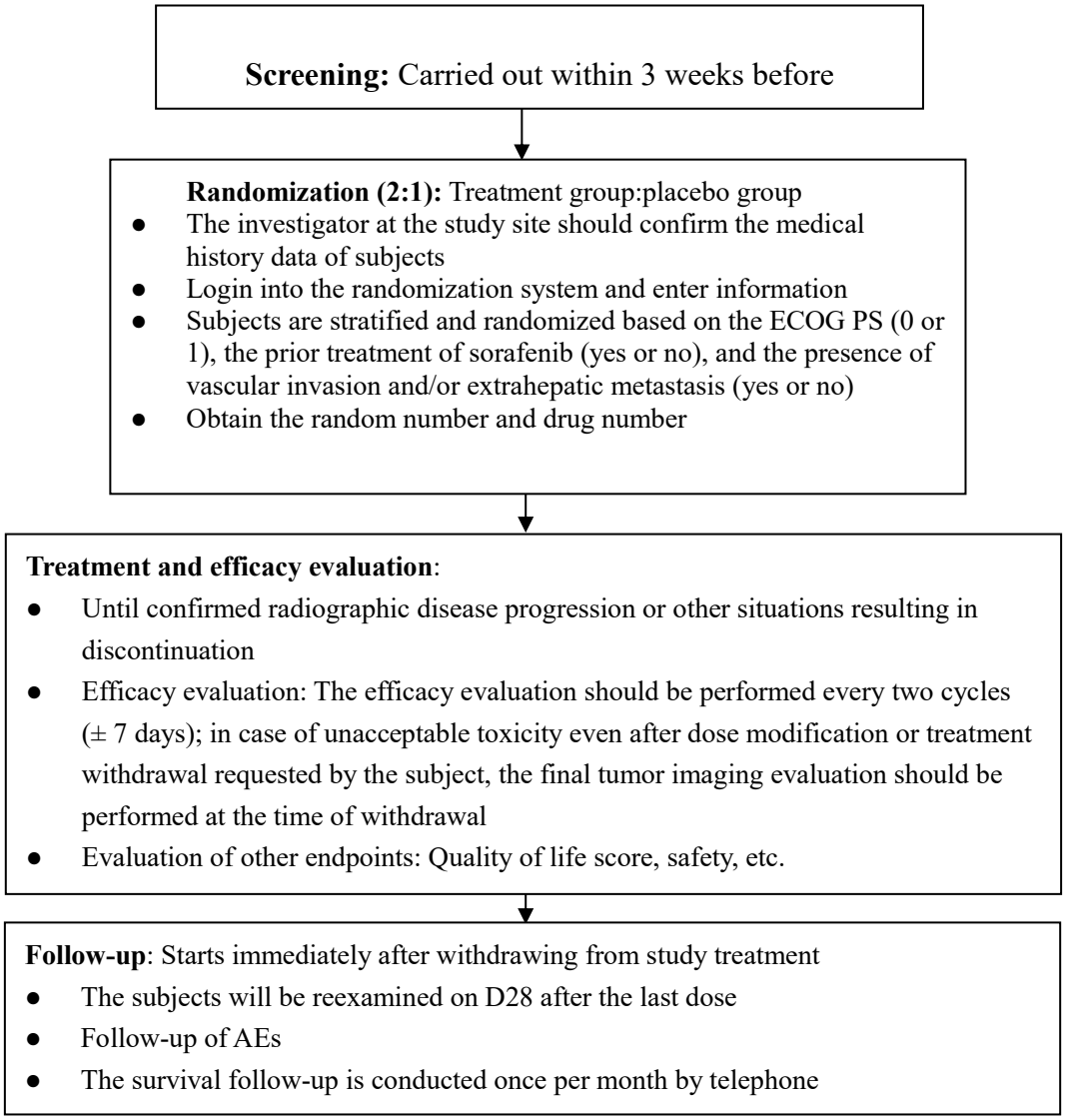
This is a randomized, double-blind, placebo-controlled, nation-wide multi-center phase III clinical trial comparing the efficacy and safety of apatinib and placebo in the treatment of patients with advanced HCC. The overall design is shown in Figure 4.1 below.

This trial plans to be carried out at multiple sites in China. The list of participating study centers is shown in Appendix 6. It is planned to enroll a total of 360 patients with advanced HCC. According to the resolution of scientific committee, additional subjects will be enrolled, i.e., 390 subjects in total, who will be randomly assigned to the treatment group and the placebo group in a 2:1 ratio.

If none of the following conditions occur, such as withdrawal of informed consent from by subject, unacceptable toxicity, or conditions rendering the subject not suitable for further trial participation based on the opinion of the investigator, the study treatment of each subject will be continued until confirmed radiographic progression. The efficacy and safety index should be monitored during the trial.

The 28-day follow-up is necessary after treatment discontinuation, and then the subjects will continue to be followed to gather information on their survival.

Figure 4.1. Overall design



4.2 Type of Comparison

This is a placebo-controlled trial, so a superiority test is used for comparison.

The primary efficacy endpoint of this trial is OS. If the HR is statistically significant and the difference reaches a clinically recognized level (HR ≤ 0.84 in the comparison between the treatment group and the placebo group), the investigational drug is considered to be superior to the placebo.

4.3 Sample Size Estimation

In this trial, placebo is used as a control and a superiority test is performed between the two groups.

For OS, according to the results of the FAS analysis for the phase II clinical trial and relevant literature reports: The median OS in the placebo group is set to 6 months, and the median OS in the apatinib mesylate group is set to 8.5 months. Based on $\alpha_2 = 0.05$, a 80% power of the

test, a 15% lost to follow-up rate in each group, an enrollment period of 12 months, and the duration of the entire study of 36 months, the 2:1 treatment group:placebo group design, and the formula for the sample size of the Log-rank test of OS comparison between two groups (calculated by PASS software), 222 patients are required in the treatment group and 109 patients are required in the placebo group, i.e., a total of 331 patients, as shown in the table below. Considering dropout and other factors, this trial plans to enroll 360 patients, including 240 for the treatment group and 120 for the placebo group. According to the resolution of scientific committee, the enrollment shall be expanded to 390 subjects (see the Resolution of Scientific Committee on 31 Oct., 2016).

Table 7. Results of sample size estimation

Parameter	Type I Error	Median Survival		Sample Size Ratio Treatment: Control	Results		
		Treatment Group	Placebo Group		Treatment Group	Placebo Group	Total Number of Subjects
OS	0.05	8.5	6	2:1	222	109	331

4.4 Randomization and Stratification Factors

The randomization method used in this trial is as follows: Subjects are randomized to two groups in a 2:1 ratio to receive apatinib or placebo treatment.

The subjects are allocated by central randomization and enrolled competitively at all sites. The central randomization system provided by Department of Epidemiology and Health Statistics of Nanjing Medical University will be used for central randomization. After all eligible subjects are screened by study personnel at each study site participating in this trial and confirmed by the investigator of each site, their screening information will be entered into the randomization system to generate the random numbers and drug numbers. Corresponding study drugs will be dispensed based on the drug numbers. Subjects must begin the assigned study treatment within 48 h after randomization.

Stratification factors for randomization include:

ECOG PS: 0 or 1

Received prior treatment with sorafenib: yes or no

Presence of vascular invasion and/or extrahepatic metastasis: yes or no

4.5 Dosing Regimen

4.5.1 Investigational drug

Apatinib mesylate tablets

4.5.2 Dose

Treatment group: Apatinib, 750 mg, q.d.; The dose can be reduced according to toxicity, with the first reduction to 500 mg, q.d., and the second reduction to 250 mg, q.d.; each treatment cycle contains 28 days.

Placebo group: Placebo, q.d. Each treatment cycle contains 28 days.

Considerations for the use of 750 mg in the treatment group:

1. According to the phase I PK data, the C_{max} and AUC of the 850 mg group were both higher than those of the 750 mg group, and it was speculated that the toxicity of the 850 mg group might be higher than that of the 750 mg group;
2. According to the phase II study of apatinib in HCC, the efficacy of the 850 mg group was comparable to that of the 750 mg group (TTP, OS; the DCR in the 850 mg group was slightly higher than that in the 750 mg group); 9 patients in the 850 mg group withdrew from the study due to adverse events with the duration of treatment less than 1 cycle (including 4 cases of gastrointestinal hemorrhage), while 3 patients in the 750 mg group withdrew from the study due to adverse events with the duration of treatment less than 1 cycle (no hemorrhage). Considering that the primary endpoint of phase III trial is OS, the dose of 750 mg, which showed better tolerability in HCC patients, is selected for the study.

4.5.3 Method of administration

Apatinib or placebo is administered orally in a double-blind manner at the dose specified for each group, once a day after meals (the time of administration should be as close as possible on each day).

4.5.4 Treatment cycle

Subjects who achieve complete response (CR), partial response (PR), and stable disease (SD) should continue treatment until PD, unacceptable toxicity, or subjects request to discontinue treatment.

Notes: For subjects with PD, treatment should be discontinued in principle. However, in view of the treatment characteristics of molecular targeted drugs, there are certain defects to adopt the evaluation method of cytotoxic chemotherapy. After receiving molecular targeted therapy, although the tumor of some subjects was enlarged, remarkable necrosis or denaturation was observed inside the tumor, and CT showed that the internal density of the tumor lesion decreased. It is generally considered to be beneficial to subjects under this circumstance. Therefore, it is specified in the study protocol that: if obvious necrosis or denaturation is observed in the tumor tissue, tumor-related symptoms are significantly improved or remained stable, the subject voluntarily continues the treatment, and continuing treatment may achieve

survival benefits as judged by the principal investigator, the subject can continue to receive the treatment until intolerance of toxicity or PD again, with strict observation.

4.6 Efficacy Evaluation and Analysis

Efficacy evaluation should be performed every two cycles (this is based on calendar days and is not affected by treatment interruption), and the evaluation time is ± 7 days at the end of the cycle (except for statutory holidays). CT or MRI examinations are required for evaluation. The radiographic technique should be consistent for all the tests of a subject, and all the images should be retained. If the efficacy reaches CR, PR or SD by imaging, the subject must be reexamined 4 weeks to confirm the evaluation.

In the case of imaging-confirmed PD, the subject should discontinue the treatment and then enter the follow-up period. Other anti-tumor treatments are prohibited before PD.

For subjects who withdraw from the trial due to unacceptable toxicity, the efficacy evaluation by imaging should be conducted upon withdrawal if the efficacy evaluation is not carried out within 4 weeks before withdrawal. Thereafter, the imaging examination is performed with the same frequency, i.e., every 2 cycles until PD or initiating other anti-tumor treatments to get the result of their radiographic PD.

4.7 Follow-up within 28 Days after Treatment Discontinuation

All subjects should continue safety evaluation within 28 days after the last dose. During the follow-up visit on D28 (± 3 days, except for statutory holidays) after the treatment discontinuation, physical examination, ECOG PS, hematology and blood biochemistry tests should be carried out, and adverse events, concomitant medication and the new anti-cancer therapy treatment should be recorded.

4.8 Follow-Up of AEs

Adverse events that have not resolved after discontinuing apatinib treatment should be followed and a final evaluation should be made. The follow-up of adverse events ends on D28 after treatment discontinuation.

4.9 Survival Follow-Up

After the 28-day safety follow-up, the subject, his/her family members, or local physicians should be interviewed by telephone once a month to collect survival (date and cause of death) and post-treatment information (including received treatments) until death, lost to follow-up, or study termination by Hengrui. Each survival follow-up should be documented in the follow-up form in detail.

5 INFORMED CONSENT

The clinical investigator must fully inform the subjects that participation in the clinical trial is voluntary, and subjects have the right to withdraw from the trial at any stage without being discriminated against with their medical treatment and rights unaffected, and they can continue to receive other therapies. All subjects should be informed that the participation of the trial and their personal information will be kept confidential. The subjects should also be informed of the nature, objectives, expected potential benefits, and possible risks and inconvenience of the clinical trial, other alternative treatment options, and rights and obligations of the subjects in accordance with the "Declaration of Helsinki". Subjects are given sufficient time to consider whether to participate in the trial and sign the informed consent form.

6 STUDY DRUGS

6.1 Information

Investigational drug: apatinib mesylate tablets

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: Tablet

Strength: 250 mg/tablet, batch number: ××××, date of manufacture: ××××;

Administration: oral administration after meals (best to take at the same time on each day);

Shelf life: 2 years (tentative);

Storage conditions: kept in a sealed container away from light at room temperature.

Control: Apatinib dummy tablets;

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: tablet;

Strength: 250 mg/dummy tablet, batch number: ××××, date of manufacture: ××××;

Administration: oral administration after meals (best to take at the same time on each day);

Shelf life: 2 years (tentative);

Storage conditions: kept in a sealed container away from light at room temperature.

6.2 Labeling/Packaging

The label is shown in Appendix 7. The drug is packaged in aluminum-plastic blister packs with 10 tablets per pack and 11 packs in each small box, and 6 small boxes in each medium box.

6.3 Drug Dispensation

The stratified randomization method is used in this trial. The randomization table will be generated by the statisticians from Nanjing Medical University using the statistical software SAS. The drug number will be randomly assigned to each site. After eligible patients are enrolled to each site, drug administrators dispense corresponding drugs to each subject according to the order of the enrollment time.

Drug dispensation should be managed strictly. The designated staff in participating study center should keep and fill in the Request and Use Record. Remaining drugs and packages should be timely retrieved during the trial and delivered to the sponsor after the end of trial. In the event of treatment discontinuation, the participating study center should retrieve the remaining drugs at the end of each cycle and dispense study drugs of the next cycle. The monitor should regularly inspect the use and recording of drugs, monitor and handle the retrieval condition at any time.

6.4 Drug Storage and Management

In accordance with GCP, study drugs should be stored, dispensed and retrieved by the participating study center. The study drugs should be kept in a sealed container away from light at room temperature.

Apatinib is not permitted to be used except for this trial.

6.5 Disposal of Remaining Drugs

The investigator should record the date and dose of administration of each subject. The total dose of study drug assigned to each patient is 110% of his/her designed dose. Remaining investigational drugs should be returned to the sponsor after the end of each cycle.

7 CRITERIA FOR DOSE INTERRUPTION AND MODIFICATION

7.1 Dose Level and Use of Drugs

The dose levels in the treatment and placebo groups are: 1) starting dose: 750 mg, q.d.; 2) second dose level: 500 mg, q.d.; 3) third dose level: 250 mg, q.d. The initial dose of each group can be reduced by two levels. After dose reduction, the dose can be resumed to the previous dose level if the toxicity is completely recovered; if the dose is reduced again, no further modification is allowed. The administered doses and dose modification of each group are shown in the table below, and the dose can be modified according to the "Dose Modification" column shown below.

Table 8. Doses and dose level modification of each group

	Treatment Group	Placebo Group
Starting dose	■■■	□□□
First dose reduction	■■	□□
Dose re-modification Toxicity recovery[a]	■■■	□□□
Second dose reduction[b]	■■	□□
Third dose reduction	■	□
Dose re-modification Toxicity recovery[a]	■■	□□
Fourth dose reduction[b]	■	□

Note: ■ = Apatinib mesylate tablets 250 mg/tablet, □ = Apatinib mesylate dummy tablets

a After dose reduction, the dose can be resumed to the previous dose level if the toxicity is completely recovered;

b If the dose is reduced again, it should not be resumed again.

7.2 Dose Modification

According to the results of the phase I clinical trial of apatinib, considering that the exposure levels in men and women are different after apatinib administration, and that the drug shows certain individual differences, the dose of apatinib should be modified appropriately in the trial (assuming continuous administration). The treatment can be interrupted in terms of drug toxicity and be resumed after the toxicity is alleviated; the dose can also be reduced and be resumed to the previous dose level after the toxicity has been completely recovered; if the dose is reduced again due to toxicity, it should not be resumed again. The final study report should include statistics of the dose intensity and time of treatment interruption. Specific rules are as follows:

7.2.1 Criteria for dose interruption or dose reduction

The dose is only allowed to be interrupted and reduced in the case of Grade ≥ III hematological toxicity or Grade ≥ II non-hematological toxicity. Among the events of non-hematological toxicity, controllable nausea and vomiting as well as fever (under 38°C) with a clear cause can be handled with active symptomatic treatments without the need for dose interruption and dose reduction.

7.2.2 Dose interruption

The total duration of drug interruption during each treatment cycle should not be more than 2 weeks, so as to maintain the intensity of the study treatment received by the subjects.

7.2.3 Dose reduction

In each dosing cycle, only one dose reduction is allowed (i.e., the reduction of one dose level); after dose reduction, the dose can be resumed to the previous dose level after the toxicity has completely recovered; however, if the dose is reduced again, it should not be

resumed again. Each subject is only allowed up to two dose reductions, i.e., after the dose is reduced to the third dose level, the dose is not allowed to be resumed, but the dose can be interrupted.

7.2.4 Discontinuation criteria based on LVEF

For asymptomatic subjects, if their LVEF is decreased by ≥ 20% from baseline but not decreased to < 50% of baseline, they can still be treated with apatinib, but their LVEF should be reevaluated after 2 weeks at most. If LVEF is still decreased after reevaluation, apatinib should be interrupted. LVEF is evaluated every 2 weeks thereafter, and the subject can reduce one dose level to restart apatinib treatment after LVEF recovery. For such subjects, LVEF monitoring is still required in Week 2 (± 3 days) and Week 4 (± 3 days) after the administration is restarted, and LVEF monitoring should be performed every 4 weeks (± 3 days) thereafter.

If the LVEF value is below the lower limit of normal specified by the study site or drops to < 50%, the subject should withdraw from the study. The LVEF should be continuously monitored every 4 weeks (± 3 days) thereafter until resolved or after at least 16 weeks of continuous monitoring.

7.2.5 Discontinuation criteria based on prolonged QT interval

1) If the patient's ECG shows QTcF > 480 ms, the use of apatinib should be interrupted, and the following measures should be immediately taken:

(1) Immediately notify the sponsor, safety monitoring committee or scientific committee;

(2) Analyze serum potassium and magnesium, and if it is lower than the lower limit of normal, use supplements to correct serum potassium and magnesium to within the normal range;

(3) The concomitant medication must be reviewed;

(4) The use of apatinib and the compliance with the dose must be verified;

(5) Perform an ECG examination within 1 h after the first episode of QTcF > 480 ms;

(6) If QTcF is still > 480 ms, repeat the ECG examinations at least once a day when clinically needed, until QTcF is < 480 ms;

(7) If QTcF is still > 480 ms in repeated measurements and lasts for more than 2 weeks, apatinib treatment must be discontinued.

2) Guidelines for resuming drug administration:

(1) If the cause of QTcF prolongation (except apatinib) is determined, and if QTcF returns to < 450 ms within 2 weeks after correction and is within 20 ms of the baseline value, apatinib treatment can be resumed at the same dose;

(2) If the cause of QTcF prolongation cannot be determined, and if QTcF returns to < 450 ms within 2 weeks and is within 20 ms of the baseline value, apatinib treatment can be resumed at the same dose;

(3) If QTcF exceeds 480 ms again after the subject is exposed to the investigational drug again, the use of the investigational drug should be discontinued;

(4) After the subject is exposed to the investigational drug again, if QTcF is prolonged by more than 20 ms from baseline or is between 450 and 480 ms and lasts for more than 2 weeks, the dose of the investigational drug should be modified as follows:

- Reduced from apatinib, 750 mg, q.d. to apatinib, 500 mg, q.d.;
- Reduced from apatinib, 500 mg, q.d. to apatinib, 250 mg, q.d.;
- Withdrawal.

7.2.6 Discontinuation criteria based on liver function

1) If the subject has ALT > 5 × ULN and total bilirubin > 2 × ULN, the following measures must be taken:

(1) Immediately discontinue the use of the investigational drug and give active symptomatic treatments;

(2) Complete the SAE form and handle it in accordance with the requirements for SAE in Section 11 of this protocol;

(3) Follow-up the event according to the requirements for "Follow-up of Adverse Events" in Section 4 of this protocol, and check liver function every week until it returns to the baseline level;

7.3 If the subject experiences any of the following conditions:

ALT > 8 × ULN or ALT > 5 × ULN for more than 2 weeks: The patient must be reexamined within 3 days after the first occurrence of the event, and then reexamined weekly to monitor whether the ALT value continues to increase. If the ALT value continues to increase, the use of the apatinib should be interrupted. The liver function should be reexamined within 2 weeks. If the treatment is effective and the subject is willing to continue to receive the apatinib treatment after obtaining the results of the liver function test, the subject can resume the apatinib treatment at the next lower dose level after obtaining the permission of the investigator and the medical director of the sponsor, and the liver function of the patient should be monitored every 2 weeks until it returns to the baseline level.

Other rules

To ensure the consistency of dose modifications throughout the study, treatment should be first discontinued before undergoing a dose modification for each dose cycle. The dose can only be reduced if the subject still cannot tolerate the dose after dose interruption.

8 CONCOMITANT MEDICATION

8.1 Medications Prohibited or Used with Caution during the Study

8.1.1 Drugs that interfere with liver P450 enzymes

Apatinib has a strong inhibitory effect on CYP3A4, YP2C9 and CYP2C19 (IC_{50} < 0.5 μM). Omeprazole should be used with caution during the treatment. CYP3A4 inducers (carbamazepine, rifampicin and phenobarbital) and inhibitors (ketoconazole, itraconazole, erythromycin and clarithromycin), CYP3A4 substrates (simvastatin, cyclosporine and pimozide), and other drugs metabolized via CYP3A4 (such as benzodiazepines, dihydropyridine, calcium ion antagonist and HMG-COA reductase inhibitors) should be used with caution. CYP2C9 substrates (diclofenac, phenytoin, piroxicam, S-warfarin, and tolbutamide) and CYP2C19 substrates (diazepam, imipramine, lansoprazole, and S-mephenytoin) should be used with caution.

8.1.2 Drugs that prolong the QT interval of the heart

As tinib drugs may cause toxicities of prolonged QT interval in clinical applications, drugs that may prolong the QT interval should be used with caution during the trial, including antibiotics, antiarrhythmics, antipsychotics, antifungal drugs, antimalarial drugs, and antidepressants (such as clarithromycin, quinidine, risperidone, fluconazole, mefloquine, amitriptyline, azithromycin, sotalol, fluphenazine, ketoconazole, chloroquine, imipramine, erythromycin, amiodarone, droperidol, clomipramine, roxithromycin, disopyramide, haloperidol, dosulepin, metronidazole, procainamide, thioridazine, doxepin, moxifloxacin, pimozide, olanzapine, and clozapine).

8.1.3 Traditional Chinese medicine and immunological agents with anticancer effects

NMPA-approved Chinese medicine preparations for liver cancer (including Delisheng injection, Kanglaite injection, Aidi injection, Huaier granule, GFL tablets) and immunomodulators (interferon and interleukin-2) are prohibited during the trial.

8.2 Medications and Treatments that May be Used Concomitantly during the Trial

The patient could receive the best supportive care. Bisphosphonates for bone metastasis is permitted while the subject is receiving study medication. If systemic or local analgesia is not effective in controlling painful lesions of bone metastases, a small area of palliative radiotherapy (the area of the radiotherapy must be <5% of the bone marrow region, and the percent bone marrow in human skeleton is shown in the figure of Appendix 8) is allowed. Comorbidities and various AEs should be actively treated. All concomitant medications should be documented in the eCRF in strict accordance with the GCP regulations.

8.3 Recommended Symptomatic Treatment for Common Adverse Drug Reactions

8.3.1 Hand-foot-skin reaction

Hand-foot-skin reaction (HFSR) is s skin toxicity with palmar-plantar dysesthesia or acral erythema and manifests especially in areas under pressure or force. It may occur in patients with tumor during chemotherapy or molecular targeted therapy. HFSR is characterized by numbness, dysesthesia, paraesthesia, tingling, no pain or pain, skin swelling, or erythema, desquamation, chapping, scleroma-like blisters, and severe pain.

Grading of HFSR:

Grade 1: numbness/dysesthesia/paraesthesia, painless swelling or erythema of the hands and/or feet and/or discomforts that does not affect normal activities.

Grade 2: painful erythema and swelling of the hands and/or feet and/or discomforts affecting patients' activities of daily living.

Grade 3: wet desquamation, ulcers, blisters or severe pain of hands and/or feet and/or severe discomfort that causes the patients to be unable to work or perform activities of daily living. Intense pain and loss of skin function, relatively rare.

Symptomatic treatment and management of HFSR:

Some necessary symptomatic and supportive treatments must be taken, including: strengthen skin care, keep skin clean, and avoid secondary infections; avoid pressure or friction; use moisturizers or lubricants, topically use lotions or lubricants containing urea and corticosteroids; topically use antifungal or antibiotic treatment if necessary.

8.3.2 Hypertension

Management of treatment-related hypertension

- Monitoring and handling of hypertension: Blood pressure should be monitored once a week during the first 6 cycles of the targeted pharmacological treatment. Once hypertension occurs, the following standard treatments can be given: Angiotensin II receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACEI), beta blocker, diuretics, etc., or the combined application of above drugs.
- Preferably selected medications (drugs not metabolized through the liver):
    1) Valsartan (Diovan), 80–320 mg q.d.;
    2) Atenolol (Tenormin), 50–100 mg q.d.;
    3) HCTZ (Hyzaar), 12.5–100 mg q.d.;
    4) Telmisartan (Micardis), 20–80 mg q.d.;
    5) For those with difficulty controlling blood pressure: Amlodipine (Norvasc), 2.5–10 mg q.d.

Clinical staging of hypertension and routine treatment at each stage

- Pre-hypertension: (120–139/80–89 mmHg, or a systolic blood pressure of 120–139 mmHg)

  There is no indication for the use of antihypertensive drugs, and only blood pressure monitoring is needed;

- Grade 1 hypertension: (140–159/90–99 mmHg, or a systolic blood pressure of 140–159 mmHg)

  Use of antihypertensive drugs and monitoring of blood pressure; most patients use thiazide-type diuretics, while ARB, ACEI, β blockers and calcium channel blockers can also be considered;

  The administration of apatinib can be continued, and a combination of two antihypertensive drugs can be considered if the antihypertensive effect is not ideal.

- Grade 2 hypertension: (160–179/100–109 mmHg, or a systolic blood pressure of 160–179 mmHg)

  Combination use of two drugs (usually a combination of thiazide-type diuretics with ARB, ACEI, β blockers, or calcium channel blockers); monitoring of blood pressure;

- Grade 3 hypertension: (≥ 180/110 mmHg, or a systolic blood pressure of ≥ 180 mmHg)

  Combination use of two drugs (usually a combination of thiazide-type diuretics with ARB, ACEI, β blockers, or calcium channel blockers); the blood pressure is closely monitored; other risk factors (such as target organ damage, diabetes and other accompanying clinical symptoms) are evaluated, and appropriate measures are taken;

- Hypertensive crisis: Refers to a serious clinical condition featured by an excessively elevated blood pressure and a diastolic blood pressure exceeding 16.0–17.3 kPa (120–130 mmHg). At present, there is no unified classification of hypertensive crisis in China and abroad. Recently, hypertensive crisis is usually divided into two types from the perspective of clinical treatment: (1) Hypertension emergencies: A diastolic blood pressure of > 16.0 kPa (120 mmHg), accompanied with acute or progressive target organ damage, such as cerebral infarction, intracranial or subarachnoid hemorrhage, and hypertensive encephalopathy, etc. Among them, progressive or acute hypertension based on chronic essential hypertension is the most common (about 40%–50% of all cases). (2) Hypertension urgencies: A diastolic blood pressure of > 16.0 kPa (120 mmHg) without or with only slight organ damage; in such patients, sodium nitroprusside or nifedipine is used to rapidly reduce the blood pressure, diazepam and phenobarbital are used to prevent seizures, and furosemide and mannitol are used to induce dehydration and reduce intracranial pressure, etc.;

Note: For those with hypertensive crisis, the application of apatinib should be discontinued immediately and the subjects should withdraw from this clinical trial.

8.3.3 Management of gastrointestinal hemorrhage

Gastrointestinal hemorrhage, including fecal occult blood (++) and above, hematemesis or bloody stool, should be given active symptomatic treatment. Patients with upper gastrointestinal hemorrhage should be fasted and given acid suppression, gastric mucosal protection, hemostasis (transamin, reptilase, etc.), as well as octreotide if necessary; patients with lower gastrointestinal hemorrhage should be given hemostasis, blood transfusion and supportive care, etc.; for those whose bleeding cannot be controlled, assistance from the surgery department should be requested.

8.3.4 Suggestions for the treatment of proteinuria

For those with two consecutive episodes of urine protein (++), a 24 h urine protein test is required.

Table 11. Suggested treatments for proteinuria

UPC < 3 g	Treatment is continued at the same dose level and the patient is monitored as clinically indicated
UPC ≥ 3 g	Step 1: Obtain 24-h urine protein Step 2: If the 24-h urine protein is < 3 g, the subject can continue the treatment at the same dose level; If the 24-h urine protein is ≥ 3 g, interrupt the treatment until UPC returns to < 3 g, and then resume the treatment at a lower dose, and monitor the UPC throughout the entire subsequent treatment. If UPC is ≥ 3 g, obtain 24-h urine protein. Step 3: If the 24-h urine protein is still ≥ 3 g after repeated dose reductions, discontinue the trial and follow up the subject according to the protocol.

Note: In case of nephrotic syndrome, the treatment with the investigational drug should be discontinued and the subject should withdraw from the clinical trial.

8.3.5 Interstitial pulmonary fibrosis

The clinical physicians should fully understand the conditions of subjects and be familiar with the drugs that may lead to pulmonary toxicity. The clinical symptoms of the patients and their changes in chest X-ray or CT should be monitored closely. Once a patient shows acute lung symptoms of cough, chest tightness, labored breathing, dyspnea, and hemoptysis of unknown causes, the investigational drug should be interrupted immediately to promptly identify the cause of the symptoms and exclude other causes (such as infection and heart failure). It is recommended to add a chest CT imaging examination, etc. Alveolar lavage fluid analysis and surgical lung biopsy are important means to diagnose interstitial lung disease. Currently, no therapy yields a satisfactory result against pulmonary fibrosis, and correction of hypoxemia and timely administration of corticosteroids are recommended following "Guidelines for Diagnosis and Treatment of Idiopathic Pulmonary (Interstitial) Fibrosis (draft)" issued by the Chinese Medical Association Respiratory Diseases Branch.

Note: The suggestions for the symptomatic treatments of above adverse events are for reference only. For specific countermeasures, please consult a specialist.

9 STUDY PROCEDURES

9.1 Screening Period (from signing informed consent form to obtaining random numbers)

Subjects must sign the informed consent form before undergoing any screening procedures.

Unless otherwise stated, the following screening procedures should be completed within 21 days prior to randomization.

- Patients sign the informed consent form.
- Collection of medical history, including past treatment history, current medical history, drug allergies, and concurrent diseases.
- Physical examination, height, weight, and vital signs (body temperature, blood pressure, heart rate, and respiratory rate).
- Chest x-ray, not required if the subject have undergone chest CT.
- CT or MRI of the chest, abdomen, pelvis and other relevant lesions.
- Brain CT/MRI, required for clinically suspected metastases to the central nervous system only.
- Bone scan, required for clinically suspected bone metastasis only.
- Test of hepatitis B and hepatitis C markers, and HBV DNA.
- Test of serum AFP.

The following information should be collected within 7 days before randomization:

- ECOG PS.
- Hematology, urinalysis, and routine stool test.
- Hepatic and renal function (total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, AKP, r-GT, LDH, total protein, albumin, blood urea nitrogen, creatinine, uric acid).
- Electrolytes (potassium, sodium, chlorine, calcium, phosphorus).
- Coagulation function (PT or INR).
- Pregnancy test (serum or urine, only for women of childbearing potential).
- Echocardiography (mainly to observe LVEF).
- 12-Lead ECG (the QTc interval must be indicated), for 3 times with about 5 minutes apart.
- Quality of life score (EORTC QLQ-C30 and HCC18).
- Randomization should be carried out after all screening evaluations are completed.

9.2 Treatment Period

- Check the blood pressure once a week post-administration. If the blood pressure is abnormal, follow up with the blood pressure every day, and check the blood pressure three times a week for two cycles after the blood pressure returns to normal, and once a week thereafter.
- Within the first two cycles of administration, carry out the following examinations every two weeks (± 3 days, except for statutory holidays): hematology, urinalysis (not required for female subjects during their menstrual period), hepatic and renal function, and electrolytes. From Cycle 3, the examination is carried out once only at the end of each cycle (± 3 days, except for statutory holidays).
- Within the first three cycles of administration, a 12-Lead ECG is carried out at the end of each cycle (± 3 days, except for statutory holidays), and then carried out at the end of every two cycles (± 7 days, except for statutory holidays). Each examination is carried out after administration for 3 times with about 5 min apart and QTc interval indicated. If there are symptoms such as precordial pain and palpitations, the myocardial zymogram (creatine kinase, lactate dehydrogenase) should be tested immediately, and ECG should be performed at any time. For clinically significant ECG abnormalities, echocardiography (LVEF) should be performed.
- Physical examination, vital signs, PS score, and coagulation function tests are performed every cycle (± 3 days, except for statutory holidays).
- CT or MRI examination and objective efficacy evaluation of tumor are performed once at the end of every two cycles (± 7 days, except for statutory holidays). If the efficacy reaches CR, PR or SD, the subject must be reexamined 4 weeks after the first evaluation.

Note: For subjects who withdraw from the trial due to unacceptable toxicity, the efficacy evaluation should be conducted upon withdrawal if the efficacy evaluation is not carried out within 4 weeks before withdrawal. Thereafter, the imaging examination is performed at the same frequency, i.e., every 2 cycles until PD or use of other anti-tumor treatments. The radiographic evidence of PD of these subjects must be obtained.

- The quality of life score must be evaluated before each objective efficacy evaluation of tumor.
- Serum AFP is tested once at the end of Cycle 2 (± 7 days, except for statutory holidays) and at the end of Cycle 5 (± 7 days, except for statutory holidays). There is no strict requirement after Cycle 5.
- If patients have abnormal stools such as hematochezia or melena, the fecal occult blood examination should be performed.
- AEs should be observed and recorded frequently.

9.3 Follow-Ups

9.3.1 28-day follow-up after the end of treatment

All subjects should continue safety evaluation within 28 days after the last dose. During the follow-up visit on D28 (± 3 days, except for statutory holidays) after the end of treatment, physical examination, vital signs, ECOG PS, hematology, and hepatic and renal function tests should be carried out, and adverse events, concomitant medication and concomitant treatment should be evaluated.

9.3.2 Follow-up of AEs

Adverse events that have not resolved after discontinuing apatinib treatment should be followed and a final evaluation should be made. The follow-up of adverse events ends on D28 after treatment discontinuation.

9.3.3 Survival follow-up

After the 28-day safety follow-up, the subject, his/her family members or local physicians should be interviewed by telephone once a month to collect survival (date and cause of death) and post-treatment information (including received treatments) until the death endpoint, lost to follow-up, or study termination by Hengrui. Each survival follow-up should be documented in the follow-up form in detail.

10 EFFICACY EVALUATION

10.1 Primary Endpoint and Observation Method

Overall survival (OS):

Defined as the time from the date of randomization to death from any cause.

10.2 Secondary Endpoints and Observation Methods

- PFS

  PFS is defined as the time from randomization until the date of documented progression or death from any cause, whichever occurs first.

  The PFS is assessed as per RECIST 1.1. The analysis of this endpoint includes all tumor assessments during the treatment period and the follow-up period. If the patient has several endpoints that can all be evaluated as PD, then use the first documented PD when analyzing PFS. The study endpoint also includes relapse, the occurrence of new lesions, and death. The initiation of other systemic or targeted anti-tumor treatment is also considered disease progression.

- 3-, 6-, and 12-month PFS rates

  Refer to the proportions of evaluable patients without disease progression from the start of the trial to 3, 6, and 12 months.

- Time to progression (TTP)

  Refers to the time from randomization to any documentation of radiologic progression.

  The PFS is assessed as per RECIST 1.1. The analysis of this endpoint includes all tumor assessments during the treatment period and the follow-up period.

- Objective response rate (ORR)

  Refers to the proportion of patients who achieve tumor shrinkage to a certain volume and maintain for a certain period of time, including CR and PR. Objective response is evaluated based on RECIST 1.1. Subjects must have measurable lesions at baseline. The tumor can be accessed as complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD) according to RECIST 1.1 criteria.

- Disease control rate (DCR);

  Refers to the proportion of evaluable patients with confirmed CR, PR, or SD (≥ 4 weeks).

- The percentage of evaluable patients with stable disease (SD) of ≥ 4 weeks (confirmed SD in particular)

- 6- and 12-month mortalities

- Quality of life score (QoL);

In reference with EORTC QLQ-C30 (version 3, Chinese version) and HCC-18. See Appendix 9 for details.

Evaluation method: Observe and score the changes in the clinical symptoms and objective test results of tumor patients before and after treatment. Timing of evaluation: Pre-treatment and at the end of Cycles 2 and 3 of treatment. At the end of every two cycles, the quality of life scale should be recorded and evaluated, and the scores of the various areas of the scale should be recorded in the eCRF according to the requirements in the Appendix.

11 SAFETY EVALUATION

11.1 Definitions

11.1.1 Adverse event (AE)

An adverse event (AE) refers to any untoward medical occurrence in a clinical investigation subject and which does not necessarily have a causal relationship with the treatment. AEs include but are not limited to: Abnormal laboratory findings; clinically significant symptoms and signs; allergies;

According to the needs of management, safety monitoring (reporting of AEs or SAEs) should be performed from the signing of the informed consent form by the subject to 28 days after the last dose.

11.1.2 Adverse drug reaction (ADR)

All toxicities and unintentional reactions to a drug associated with any dose should be considered as adverse drug reactions (ADRs). A drug reaction means that a potential causal relationship between the drug and AE is at least reasonable, which means that the relationship cannot be excluded.

11.1.3 Serious adverse event (SAE)

An SAE refers to a medical occurrence during the clinical trial that results in hospitalization, prolonged hospitalization, disability, incapacity, life threatening events or death, or congenital malformation. The following unexpected medical events are included:

- Events resulting in death;
- Life-threatening events (defined as events where the subject is at immediate risk of death at the time of the onset);
- Events resulting in hospitalization or prolonged hospitalization;
- Events resulting in permanent or serious disability/incapacity;
- Congenital anomalies or birth defects.
- Overdose.
- Pregnancy during the clinical trial.

Criteria for other SAEs specified in the protocol:

- Cardiac insufficiency - defined as any symptom or sign of reduced LVEF (NCI CTCAE Grade 3), or LVEF reduced by ≥ 20% from baseline and below the lower limit of normal (or reduced to < 50%).

- ALT > 5 × ULN and total bilirubin > 2 × ULN (such as direct bilirubin > 35%; the bilirubin ratio should be measured).

Note: If possible, the bilirubin ratio assay should be completed. If the test cannot be performed due to limited capacity and the subject has reached the criteria of total bilirubin of > 2 × ULN, the event should be reported as an SAE.

Progressive disease

Progressive disease (including progressive signs and symptoms) should not be reported as an SAE. However, death due to progressive disease during the trial or safety reporting period should be reported as an SAE. Hospitalizations due to signs and symptoms of progressive disease should not be reported as an SAE. During the trial or safety reporting period, if the final outcome of the cancer is death, then the event leading to death should be reported as an SAE.

Other anti-tumor treatments

If a subject is to start another anti-tumor treatment, AEs except death will be reported until the start of the new anti-tumor treatment. Death that occurs within the SAE reporting period after study treatment is completed should be reported regardless of whether the patient received other treatment.

Hospitalization

During the trial, AEs resulting in hospitalization or prolonged hospitalization should be considered serious AEs. Any initial hospital admission by a medical facility meets this criterion (even if less than 24 hours).

Hospitalization does not include the following:

- Hospitalization at a rehabilitation institution
- Hospitalization at a sanatorium
- General emergency admission
- Day surgery (e.g., outpatient/same-day/ambulatory surgery)

Hospitalization or prolonged hospitalization not related to the worsening of adverse events is not considered an SAE. For example:

- Hospitalization due to pre-existing disease without occurrence of new AEs or worsening of the pre-existing disease (e.g., for testing persistent laboratory abnormalities that started before the study);
- Hospitalization for management reasons (e.g., annual routine physical examination);

- Hospitalization during the study as specified in the study protocol (e.g., as required by the protocol);
- Elective hospitalization unrelated to the deterioration of an AE (e.g., elective cosmetic surgery);
- Scheduled treatment or surgery that should be documented in the entire study protocol and/or in subject's individual baseline information;
- Hospitalization merely for use of blood products.

Diagnostic or therapeutic invasive (e.g., surgery) or non-invasive procedures should not be reported as adverse events. However, the disease condition leading to such procedures should be reported if it meets the definition of an adverse event. For example, acute appendicitis during the adverse event reporting period should be reported as an adverse event and the appendectomy should be documented as the treatment method for the event.

11.2 Recording and Evaluation of Adverse Events

All AEs should be described by terms in NCI-CTCAE 4.0 and recorded in eCRF accordingly. In addition, SAE Report Form (including initial or follow-up reports) should be completed. All subjects participating in the trial must be summarized. Reasons for withdrawal or rejection should be explained. A detailed individual report should be prepared if there is any death or serious toxic reaction in the trial. The cause of death, especially the relationship with the investigational drug, should be investigated. All AEs in the follow-up should be closely monitored until such events are properly resolved or the subject's condition is stable.

The following aspects of each AE should be recorded in the eCRF:

(1) Onset time (start time) and recovery time (end time)

(2) Assessment and classification of AE by investigator in accordance with NCI-CTCAE version 4.0. If the severity of several AEs is not classified in NCI-CTCAE, the investigator can evaluate the grade in accordance with NCI-CTCAE.

(3) The potential relationship between the AE and the investigational drug can be assessed with 5 grades of causality: Definitely related, probably related, possibly related, unlikely related, and not related. Events that are assessed to be "definitely related", "probably related", and "possibly related" are considered related to the investigational drug. When calculating the incidence of adverse drug reactions, the total number of these three categories is used as the numerator and the total number of subjects in safety set is used as the denominator.

Table 12. Criteria for the causality between AEs and investigational drug

Criteria	Definitely Related	Probably Related	Possibly Related	Unlikely Related	Not Related
Reasonable temporal relationship	Yes	Yes	Yes	Yes	No
Is the adverse reactions for this drug known?	Yes	Yes	Yes	No	No
Can the reasons for removal be improved?	Yes	Yes	Yes or No	Yes or No	No
Does the same event recur after re-challenging?	Yes	No	No	No	No
Can the event be explained by other reasons?	No	No	No	No	No

(4) Measures taken for the investigational drug (such as continued medication, dose reduction, continued medication after interruption, discontinuation, and other conditions, please explain in details).

(5) Outcome defined as follows: resolved, improved, not improved, and aggravated.

Note: If a patient experiences the same AE several times, it must be recorded and re-evaluated each time.

11.3 SAE Reporting Procedures

Serious adverse events that occur starting from the signing of the informed consent form until 28 days (inclusive) after the last dose should be reported. Any SAE occurring during the trial must be immediately reported to the clinical research associate (CRA), the principal investigator, the PLA Tumor Center of the 81st Hospital of the Chinese People's Liberation Army and the Medical Director of Jiangsu Hengrui Pharmaceuticals Co., Ltd. via fax or phone. Meanwhile, the "New Drug Clinical Trial Serious Adverse Event (SAE) Report Form" should be completed, signed, dated, and submitted to NMPA within 24 hours.

During the continued treatment period, SAE should be reported to the sponsor within 24 hours. All information regarding the SAE should be documented in the SAE form. SAEs that occur during the continued treatment period until 28 days after the last dose should also be reported. SAEs that occur 28 days after the last dose are generally not reported unless suspected to be related to the investigational drug.

SAEs should be documented in detail, including symptoms, severity, date of onset, time of treatment, measures taken, time and method of follow-up, as well as outcome. If the investigator believes that an SAE is unrelated to the investigational drug but potentially related to study conditions (e.g., termination of the original treatment, or complications during the trial), then this relationship should be detailed in the SAE page of the case report form. If the severity of an ongoing SAE or its relationship to the investigational drug changes, a follow-up report of the SAE should be submitted to Jiangsu Hengrui Pharmaceuticals Co., Ltd. immediately. All SAEs should be followed until resolved or stabilized.

Table 13. Contact information of each institution

Institution	Contact	Telephone	Fax
National Medical Products Administration	Safety Supervision Department	010-68313344-1003	010-88363228
PLA Tumor Center of the 81st Hospital of the Chinese People's Liberation Army	Shukui Qin Xiufeng Liu	025-84453667	025-84453906
Jiangsu Hengrui Pharmaceuticals Co., Ltd.	Shunjiang Yu	021-68868768	021-50819731

11.4 Emergency Unblinding

The emergency unblinding table is a sealed document provided by the sponsor that contains the treatment allocation for each subject. Unless there is a mandatory medical reason, the investigator should not unblind the subjects at will. Only when a subject experiences an emergency situation such as an SAE, the responsible investigator at the study site and the principal investigator can jointly decide whether to unblind. The blind code should be kept by dedicated technicians from the Department of Epidemiology and Health Statistics of Nanjing Medical University. If unblinding is necessary, the medical director of the sponsor should be notified and the dedicated technicians should be contacted to obtain the blind code within 24 h. Once unblinded, the subject should immediately withdraw from the trial.

11.5 Safety Monitoring Committee

During the trial, a drug safety monitoring committee composed of the principal investigator, the medical director of Hengrui and the person in charge of drug safety will be established to review the safety data generated during the trial. If a significant safety signal is found, such as the occurrence of an SAE or the need to interrupt the treatment, the drug safety monitoring committee can also host meetings to review and discuss the corresponding relationship between the safety data and the drug along with major changes to the protocol.

12 DATA MANAGEMENT AND STATISTICAL ANALYSIS

12.1 Data Collection and Management

Data will be collected and managed using the electronic case report form (eCRF).

12.1.1 Data collection

Data will be collected using the eCRF. Jiangsu Hengrui Pharmaceuticals Co., Ltd. will provide an electronic data capture (EDC) system. Company staff will deliver EDC system training to the designated staff of study site. Access to EDC system will only be granted to the study site staff who have completed the training. The PI or dedicated data entry person (CRC) should input data into the EDC system in accordance with the requirements of the visit procedures and the eCRF completion guide. The logic verification program in the system will verify the integrity and logic of the clinical trial data entered into the EDC system

and generate an error message prompt for questionable data. The PI or CRC is permitted to modify or explain the problematic data. After the database is locked, the investigator will receive a CD-ROM or copy of subject data to archive at the study site.

12.1.2 Data management and quality control

To ensure authenticity and reliability and improve the quality of the clinical data, the CRA will monitor the integrity, consistency, and accuracy of the trial data in the database, and guide the study site staff to add or correct the data whenever necessary. The CRA or data manager will send electronic query form to the PI or CRC for problematic data. The PI or CRC must respond and provide correction or explanation of the problematic data. Multiple queries may be raised when necessary until the problem is solved. The medical director and data manager should perform consistency comparison of SAEs periodically.

At the end of the study, the data manager and medical personnel will conduct a final quality control on all data in the database, summarize all protocol deviations and violations during the trial, and hold a data verification meeting. Database locking and unblinding will be carried out after the quality requirements have been met. The data manager will export the data to the statistics department for data analysis.

12.1.3 Data review and study site monitoring

Before the initiation of the study, a representative from Jiangsu Hengrui Pharmaceuticals Co., Ltd. will introduce study protocol and eCRF (Part 2) to the investigator and staff at the initial visit to the study site. During the study, the CRA will visit the study site regularly to monitor the completeness of the subject's records and the accuracy of the eCRF, compliance with the study protocol and GCP, and enrollment progress, and to ensure that the investigational drugs are stored, dispensed, and counted as required. During these visits, the major research personnel are required to assist the work of CRA.

The investigator must keep the source documents of each subject, including all medical records and visit records (outpatient or inpatient record), such as demographic indicators, medical information, lab results, ECGs, and result of other examinations and evaluations. All information on the eCRF must come from the source documents of the subject. The investigator must also keep the informed consent forms signed by the subjects.

The investigator must ensure all source documents are available for monitoring to verify the consistency with the eCRF. Jiangsu Hengrui Pharmaceuticals Co., Ltd. requires to completely monitor the signed informed consent forms, compliance with inclusion/exclusion criteria, SAEs records, and all data required for evaluation of primary endpoints and safety endpoints. Additional monitoring will be performed on consistency of source data and eCRF according to monitoring plan specified by the trial. No information related to subjects' identity in the source document will be disclosed.

12.2 Statistical Analysis of Trial Data

- Full analysis set (FAS): According to the intention-to-treat (ITT) principle, all randomized subjects who have received 1 dose of study medication are included for efficacy analysis. For subjects whose entire course of treatment cannot be observed, the last observation data can be transferred to the final study results (LOCF).
- Per-protocol set (PPS): All subjects who are in compliance with the protocol, have good compliance, have received at least 1 cycle of treatment (except for those with clear medical evidence of PD), and have completed the eCRF according to protocol requirements, and have not taken any prohibited medications during the trial. No imputation is made for missing data. The statistical analysis will be performed for the drug efficacy based on the FAS and PPS. Before database locking, the principal investigator, statistician, and sponsor should determine the final PPS during the data review meeting.
- Safety analysis set (SAS): All enrolled subjects who have received at least one dose of the investigational drug and have safety data after the dose are included in the safety set. This dataset is used for safety analysis.

12.3 Statistical Analysis Plan

Time for efficacy analysis and safety assessment: Based on the full analysis set, when 312 deaths (≥ 80% of patients died) occur, a final verification of the data in eCRF shall be performed. After the data integrity is verified and all quality assurance (QA) and quality control (QC) procedures on the data management are performed, the randomization protocol must be disclosed, and the data from the clinical database will be retrieved to record and statistically analyze the efficacy and safety data. In the efficacy analysis, the data cutoff date is the date when the 312th death occurs. In the analysis of overall survival (OS), if the subject does not die at or before the cutoff date, and if there are data (study visits, survival follow-ups, etc.) confirming that the subject has died or is still alive after the cutoff date, the subject data will be reviewed on the cutoff date. If the last date of known survival of a subject is before or at the cutoff date, the data of the subject will be reviewed on the day of last known survival. In the analyses of progression-free survival (PFS) and time to disease progression (TTP), if the subject has neither disease progression events (for TTP and PFS) nor death (for PFS only) at or before the cutoff date, then the data of the subject will be reviewed on the subject's last day of radiographic tumor assessment on or before the cutoff date, except for the following case: For any radiographic tumor assessment as per the RECIST v1.1 criteria that indicates no evidence of progression, the review date will be set as the cutoff date.

Pre-set subgroup analysis: Subgroups will be pre-defined based on the following factors for a confirmatory subgroup analysis in this study: age ≤ 65 years or > 65 years; ECOG score 0 or 1; with or without vascular invasion; with or without extrahepatic metastases; with or without vascular invasion and extrahepatic metastases; positive or negative HBV; and with or without past history of sorafenib treatment.

All statistical analyses will be performed using SAS. All statistical analyses are performed using two-tailed tests. $P \leq 0.05$ is considered statistically significant, and 95% confidence is used for confidence intervals.

Analyses were performed as per groups based on the initial dose and the dose at the end of treatment, respectively.

The baseline data is analyzed based on the full analysis set (FAS). All efficacy endpoints are analyzed based on the FAS and the per protocol set (PPS). The analysis of primary efficacy endpoint OS is carried out mainly in the ITT, but the PPS is additionally used for verification in the final analysis. The safety analysis is carried out based on the safety analysis set (SS).

The measurement data obtained from various treatment groups during various visits will be statistically described by mean ± standard deviation or median (minimum, maximum). For comparison with baseline values of the screening period, paired t-tests are used to compare pre and post intra-group differences. Changes occurring in each group before and after treatment should be compared by the analysis of variance (ANOVA) or rank sum test. The frequency data obtained from various treatment groups during various visits will be statistically described by frequency (proportions). Changes occurring in each group before and after treatment should be compared by $\chi 2$ test (exact test) or nonparametric test.

- Dropout analysis: Descriptive analysis is mainly used. If necessary, the total dropout rate of each group and the comparison of dropout due to AEs will be tested by χ^2 test or Fisher's exact test.
- Balance analysis of baseline values: ANOVA or χ^2 test is used to compare demographic data and other baseline values to evaluate the balance of various groups.

The demographics include: age, gender, course of disease, ECOG PS, pathological grade, clinical stage, vascular invasion and/or extrahepatic metastasis (such as portal vein invasion, N1 (regional lymph node metastasis) or M1 (distant metastasis), yes or not), past treatment (surgical history of primary lesions, history of interventional procedures, history of radiotherapy, history of neoadjuvant chemotherapy), etiology of liver cancer (HBV infection, HCV infection, alcoholic cirrhosis or other), and α-fetoprotein (AFP) (low, normal, or high).

All statistical parameters and analyses at baseline are determined based on characteristics obtained before first study medication (before randomization for subjects who have not received treatment). Unless otherwise stated, the baseline value of a specific variable is defined as the last value of the parameter obtained before the first study medication.

- Efficacy analysis:

For the comparison of 3-, 6-, and 12-month PFS rates, objective response rate (ORR), disease control rate (DCR), the percentage of patients with stable disease (SD) of ≥ 4 weeks (confirmed SD in particular), and 6- and 12-month mortalities, CMH-χ^2 tests with and without central stratification are used to compare the efficacy between the two groups. In addition, the 95% confidence interval of the difference between the two groups is also calculated. Based on the product limit method and the actual condition of the data, 25%, 50% (median) and 75% of PFS and TTP, as well as PFS and OS at different time points after the start of treatment, are calculated and the endpoints are compared between the two groups using the Log-Rank test.

- Safety analysis: Descriptive statistical analysis will be mainly used. The AEs and SAEs, treatment-related AEs and SAEs, and AEs and SAEs of special interest (e.g., hypertension, proteinuria, and hand-and-foot syndrome) are listed and summarized. If necessary, the incidence and severity of AEs and SAEs between different groups are compared using Fisher's exact test. For laboratory results, the cases in which the pre-treatment values are normal but the post-treatment values are abnormal will be described, and the relationship between the abnormal changes and the investigational drug will be evaluated.

13 DROPOUTS

All eligible subjects who have signed the informed consent form have the right to withdraw from the clinical trial at any time. Subjects who have not received 1 cycle of treatment and undergone safety and efficacy assessments are considered drop-outs, regardless of the time and reason for withdrawal (withdrawals due to clear medical evidence of progression are not drop-outs). After a subject drops out, the investigator must document the reason for the drop-out in the eCRF, complete all the assessments possible, and document the last visit in the eCRF. Any drop-outs due to adverse drug reactions, which are determined to be related to the investigational drug during follow-up, must be documented in the eCRF and the investigator must be notified. Subjects who have undergone screening but withdrawn without obtaining a medication number are not considered dropouts. When conducting the safety assessment, a statistical analysis should also be performed for subjects who complete an entire treatment cycle and have detailed documents available.

Subjects who withdraw are not permitted to be enrolled again, and the subjects' number may not be reused.

14 QUALITY CONTROL AND ASSURANCE

- The clinical study sites must be NMPA-approved drug research sites with clinical research qualifications;
- Study staff must be physicians trained for clinical trials, and must work under the supervision of senior professionals;
- Before the trial is started, the clinical wards must be inspected to ensure that standard requirements are met and first-aid equipment are available;
- Professional nursing staff are responsible for administering the drugs and they must be fully aware of the administration process to ensure subject compliance;
- Study sites must carry out the study in strict accordance with the protocol, and the eCRF must be completed truthfully;
- The scientific committee must be established. The scientific committee is chaired by Professor Jianming Xu, and is composed of Professor Shukui Qin, Professor Ying Cheng, Professor Jun Liang, Professor Xuenong Ouyang, Professor Hao Yu (statistician), and sponsor's representative. The scientific committee is responsible for providing general guidance on execution and implementation of the trial, including (but not limited to) safety and enrollment rate, as well as providing guidance on published data from perspective of science.
- The CRA should follow the standard operating procedure and monitor the clinical trial to ensure that all data are documented and reported accurately and completely, all eCRFs are entered correctly and consistent with source data, and the trial is implemented as per protocol;
- In the event of SAEs, the CRA must inform all study sites immediately and temporarily suspend the trial whenever necessary;
- Participating sites must allow audits by the sponsor and regulatory authorities. It is especially important for the investigator and study staff to provide time and convenience for monitoring and auditing.

15 DISCUSSION, APPROVAL, AND AMENDMENT OF TRIAL PROTOCOL

The above "Clinical Study Protocol" and "Clinical Study Case Report Form" shall be formulated after discussion by the principal investigators of participating centers, approved by Jiangsu Hengrui Pharmaceuticals Co., Ltd., and implemented upon approval by the ethics committees of participating centers. During the clinical trial, any revisions to the protocol should be reported to the Ethics Committee for approval or filing.

16 LAWS, REGULATIONS AND ETHICS

Laws and Regulations

According to the requirements of relevant regulations in China, an application should be submitted to the NMPA to obtain a clinical trial approval number before starting a clinical trial of a new drug. The clinical trial approval number of this investigational drug, apatinib, is 2014L00877. Before the start of this trial, it should be approved or archived by relevant regulatory authorities. The clinical trial should also be implemented in compliance with all applicable regulatory requirements.

Ethical Standards

This clinical trial must comply with the "Declaration of Helsinki" (1996), NMPA's "Good Clinical Practice" (GCP)[15], and related regulations.

Ethics Committee

This trial protocol must be reviewed and approved by the ethics committee of each site prior to implementation. During the review by the ethics committee, the sponsor and the investigator should provide the ethics committee with relevant clinical trial documents, including but not limited to: "Ethical Review Application", "Clinical Study Approval" from NMPA, "Clinical Study Letter of Authorization", "List of Clinical Trial Staff", "Certificate of Analysis of the Investigational Drug", "Sample Informed Consent Form", "Clinical Trial Protocol", "Case Report Form (CRF)", and "Investigator's Brochure" for clinicians. During the trial, revisions to this protocol must be reported to the ethics committee and put on record.

Confidentiality of Subject Information

In the course of this trial, a great effort will be made to protect the personal privacy of all subjects. The sponsor's forms, study reports, publications, and any other published materials must not include the name of subjects unless required by law. This trial will use highly confidential methods to transmit data in order to prevent the leakage of the personal data of the subjects.

17 TRIAL PROGRESS

The trial is expected to be carried out from November 2013 to March 2018.

18 TRIAL PROTOCOL COMPLIANCE

The investigator shall try his/her best to avoid protocol violations. At any time, the investigator should not contact Jiangsu Hengrui Pharmaceuticals Co., Ltd. and ask for approval of protocol violations, because any authorized protocol violation should never be allowed. If the investigator believed that a certain protocol deviation could improve the implementation of the trial, the investigator must consider protocol revisions. However, the revised protocol can only be implemented after it is approved by Jiangsu Hengrui Pharmaceuticals Co., Ltd. and the medical ethics committee. All major protocol violations should be recorded and reported on the clinical trial report.

Appendix 1. Response Evaluation Criteria in Solid Tumors RECIST Version 1.1.

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable lesions

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable);
- 20 mm by chest X-ray
- Malignant lymph nodule: pathologically enlarged and measurable, single lymph nodule must be ≥ 15 mm in short axis by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and during follow-up, only the short axis will be measured and followed.

Non-measurable lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodule with ≥ 10 mm to < 15 mm short axis) as well as truly non-measurable lesions. Non-measurable lesions include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangitis carcinomatosa of the skin or lung, abdominal masses unable to be diagnosed or followed by imaging techniques, and cystic lesions.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions;
- Lytic lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by tomography techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above;

- Blastic lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment;

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually considered non-measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by Methods of Measurements

Measurements of lesions

All measurements should be recorded in metric notation if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days (4 weeks) before the beginning of the treatment.

Method of evaluation

The same method and technique should be used to assess lesions at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of cutaneous lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both imaging and clinical examination, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, especially when tumor progression is an important clinical endpoint, since CT is more sensitive, particularly in identifying new lesions. Chest X-ray is only applicable when the measured lesion boundary is clear and the lungs are well ventilated.

CT, MRI: CT is currently the best available and reproducible method for efficacy evaluation. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness greater than 5mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for whole body scans).

Ultrasound: Ultrasound should not be used as a method to measure lesion size. Ultrasound examinations are operation-dependent, and cannot be reproduced at a later date. It cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead.

Endoscopy and laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm CR when biopsies are obtained, or to determine relapse in trials where recurrence following CR or surgical excision is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. However, if the marker levels exceed the upper normal limit at baseline, they must return to the normal levels for evaluation of complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line treatment in ovarian cancer.

Cytology/histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual benign tumor tissue is commonly observed in lesions of germ cell neoplasm). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met the criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. TUMOR RESPONSE EVALUATION

2.1 Evaluation of Target Lesion

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, compared to baseline.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase of at least 5mm (the appearance of one or more new lesions is also considered disease progression).

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.2 Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. eCRFs or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become too small to measure: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm could be assigned. (Note: It is less likely that this rule will be used for lymph nodules since they usually have a definable size when normal and are frequently surrounded by adipose tissues as in the retroperitoneum; however, if a lymph nodule is believed to be present and is faintly seen but too small to measure, a default value of 5 mm could be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false evaluation based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.

Lesions that split or coalesce: When non-nodal lesions fragmented, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced

such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

2.3 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodules must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease (PD): Unequivocal progression of existing non-target lesions. Note: the appearance of one or more new lesions is also considered disease progression.

2.4 Special Notes on the Assessment of Progression of Non-Target Lesions

The concept of progression of non-target disease requires additional explanation as follows: When the patient also has measurable disease, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that the overall tumor load has increased sufficiently to the point where treatment must be discontinued. A modest increase in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study inclusion to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease load based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. For example, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in treatment". Examples include an increase in a pleural effusion from trace to large, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as

"sufficient to require a change in therapy". If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of radiographically detected lesions; however, the finding of a new lesion should be unequivocal. For example, it should not be attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some new bone lesions that may be simply healing, or re-occurrence of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, which it is not.

A lesion identified on a follow-up study that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued treatment and follow-up evaluation are required to clarify if it represents a truly new disease. If repeated scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial identification.

While FDG-PET response assessments generally need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible new disease). New lesions on the basis of FDG-PET imaging can be identified according to the following process:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, PD is confirmed.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the imaging examination, this is not PD.

2.6 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements is made at an evaluation, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) has/have no effect on the assigned time point response.

2.7 Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodules decrease to a normal size of < 10 mm, they may still have a measurement reported on scans. This measurement should be recorded even though the nodules are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of zero on the eCRF.

In trials where confirmation of response is required, repeated "NE" time point evaluations may complicate best response determination. The analysis plan for the trial must address how missing data/evaluations will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with an overall deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as symptomatic deterioration. Efforts should be made to evaluate objective progression even after discontinuation of treatment. Symptomatic deterioration is not a description of an objective response: it is a reason for discontinuation of treatment. The objective response status of such subject is to be determined by evaluation of target and non-target lesions as shown in Attached Tables 1-3.

Conditions that are defined as early progression, early death and not evaluable are study specific and should be clearly described in each protocol (depending on treatment duration and treatment cycle).

In some circumstances it may be difficult to distinguish residual lesions from normal tissues. When the evaluation of complete response depends upon this definition, it is recommended that the local lesion be investigated via biopsy before assigning a status of complete response. FDG-PET may be used to confirm a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Attached Table 1. Time point response-patients with target (+/– non-target) lesions

Target Lesion	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluable	No	PR
PR	Non-PD or not all evaluable	No	PR
SD	Non-PD or not all evaluable	No	SD
Not all evaluable	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = non evaluable.

Attached Table 2. Time point response-patients with non-target lesions only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluable	No	Not evaluable
Equivocal PD	Yes or No	PD
Any	Yes	PD

Note: For non-target lesions, "Non-CR/non-PD" is preferred over SD. Since SD is increasingly used as an endpoint for efficacy evaluation, non-CR/non-PD response is developed to address the absence of lesion measurability.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled evaluation. If at the next scheduled evaluation, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Attached Table 3. Best overall response when confirmation of CR and PR required

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD (provided minimum criteria for SD duration met, otherwise, PD)
CR	PD	SD (provided minimum criteria for SD duration met, otherwise, PD)
CR	NE	SD (provided minimum criteria for SD duration met, otherwise, NE)
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD (provided minimum criteria for SD duration met, otherwise, PD)
PR	NE	SD (provided minimum criteria for SD duration met, otherwise, NE)
NE	NE	NE

Note: CR is complete response, PR is partial response, SD is stable disease, PD is progressive disease, and NE is non-evaluable. a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even the disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD is met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.8 Confirmatory Measurement/Duration of Response

Efficacy confirmation

In non-randomized trials where tumor response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. However, in studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time criteria are first met for CR until the first date that recurrent or progressive disease is truly documented.

Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum in trial (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of SD.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment cycle and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

2.9 PFS/TTP

Many trials of advanced tumors use PFS or TTP as the primary endpoint. If the protocol requires the presence of measurable lesions in all patients, the evaluation of progress will be relatively simple. An increasing number of trials allow the participation of patients with and without measurable lesions. In this case, the clinical findings of progressive disease in patients without measurable lesions must be described in detail. Because there is often a deviation in the determination of the date of progress, the observation time points for different treatment groups should be the same.

Appendix 2 Child-Pugh Score

Parameter	Score		
	1	2	3
Hepatic encephalopathy	No	Grade 1–2	Grade 3-4
Ascites	No	Mild	Moderate and above
Prothrombin time prolonged or INR	1–3 s < 1.7	4-6 s 1.7-2.3	> 6 s > 2.3
Bilirubin total (μmol/L)	< 34	34-51	> 51
Serum albumin (g/L)	> 35	28-35	< 28

Note: Class A is 5 to 6 points; Class B is 7 to 9 points; Class C is 10 to 15 points;

Subjects with Class A or good Class B (i.e., a score of 7) can be enrolled.

Appendix 3 BCLC Staging (Barcelona Clinic Liver Cancer Staging System, 2010)

Stage	PS Score	Tumor Status		Hepatic Function Status
		Number of Tumors	Tumor Size	
Stage 0: very early stage	0	Single	< 2 cm	Portal hypertension absent
Stage A: early stage	0	Single Within 3	Any < 3 cm	Child-Pugh A-B
Stage B: intermediate stage	0	Multiple nodular tumors	Any	Child-Pugh A-B
Stage C: advanced stage	0	Multiple nodular tumors	Any	Child-Pugh A-B
Stage D: terminal stage	0	Any	Any	Child-Pugh C

Note: PS score: ECOG Performance Status Score.

Appendix 4 ECOG Performance Status Scoring Criteria

0 Fully active, able to carry on all pre-disease performance without restriction;

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work;

2 Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours;

3 Capable of only limited selfcare, confined to bed or chair 50% or more of waking hours;

4 Completely disabled; cannot carry on any selfcare, totally confined to bed or chair;

5 Death

Appendix 5 New York Heart Association (NYHA) Functional Classification

Heart Function Classification	Manifestation	Grade of Heart Failure
Class I	No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea. i.e., cardiac functional compensatory period	
Class II	Slight limitation of physical activity. Comfortable at rest, ordinary physical activity results in fatigue, palpitations, dyspnea, or angina. Also known as Grade I or mild heart failure.	I
Class III	Marked limitation of physical activity, comfortable at rest, less than ordinary activity causes the above symptoms. Also known as Grade II or moderate heart failure.	II
Class IV	Unable to carry on any physical activity. Symptoms of congestive heart failure or angina at rest; if any physical activity is undertaken, discomfort increases. Also known as Grade III or severe heart failure.	III

Appendix 6 List of Participating Study Centers

No.	Name of Participating Study Center
1	The 81st Hospital of the Chinese People's Liberation Army
2	The First People's Hospital of Changzhou
3	Nantong Tumor Hospital
4	The First Affiliated Hospital of Bengbu Medical College
5	Sir Run Run Shaw Hospital, Zhejiang University School of Medicine
6	Zhongshan Hospital, Fudan University
7	Affiliated Hospital, Academy of Military Medical Sciences
8	302 Hospital of the Chinese People's Liberation Army
9	The Affiliated Hospital of Qingdao University
10	Cancer Hospital, Chinese Academy of Medical Sciences
11	Fuzhou General Hospital of Nanjing Military Region
12	Cancer Hospital of Shantou University Medical College
13	The First Affiliated Hospital of Guangzhou Medical University
14	Sun Yat-sen University Cancer Center
15	Guangdong Provincial People's Hospital
16	Zhongshan Hospital, Xiamen University
17	The First Affiliated Hospital of Guangzhou University of Chinese Medicine
18	Harbin Medical University Cancer Hospital
19	Jilin Cancer Hospital
20	The Sixth People's Hospital of Shenyang
22	The Second Hospital of Dalian Medical University
23	The First Hospital of China Medical University
24	The Third Affiliated Hospital of Army Medical University
25	West China Hospital of Sichuan University
26	Jiangxi Cancer Hospital
27	The Fourth Hospital of Hebei Medical University
28	Fujian Cancer Hospital
29	Beijing Cancer Hospital
30	The First Affiliated Hospital, College of Medicine, Zhejiang University
31	Chinese PLA General Hospital
32	Beijing Friendship Hospital, Capital Medical University
33	Hunan Cancer Hospital

Appendix 7 Labels of Apatinib Mesylate Tablets as a Second-Line Treatment for Advanced HCC

Treatment group: 750 mg q.d. Label:

Initiation of administration: Administration at the initial dose in Cycles 1–6

Pack label

Apatinib Mesylate Tablets for a Phase III Clinical Trial on HCC
Strength: 250 mg/tablet
Indication: For the treatment of advanced hepatocellular carcinoma
Method of administration: 3 tablets daily (please follow the prescription when the dose is reduced or resumed to the previous dose)
Once a day after meals (the dosing time on each day should remain the same whenever possible)
Batch No.: ××××××
Shelf life: Tentatively 2 years, till XX Day XX Month 20XX

Small box label

Apatinib Mesylate Tablets for a Phase III Clinical Trial on HCC
For clinical use only
Clinical approval No.: 2014L00877
Drug No.:
Medication for Cycle X
Quantity: 10 tablets per pack, 11 packs per box
Strength: 250 mg/tablet
Indication: For the treatment of advanced hepatocellular carcinoma
Method of administration: 3 tablets daily (please follow the prescription when the dose is reduced or resumed to the previous dose)
Once a day after meals (the dosing time on each day should remain the same whenever possible)
Storage: Store in a sealed container away from light at room temperature.
Batch No.: ××××
Shelf life: Tentatively 2 years, till XX Day XX Month 20XX
Study Site: Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Note: Please return the remaining products to the pharmacist

Medium box label

Apatinib Mesylate Tablets for a Phase III Clinical Trial on HCC

For clinical use only

Clinical approval No.: 2014L00877

Drug No.:

Quantity: 6 small boxes per medium box

Strength: 250 mg/tablet

Indication: For the treatment of advanced hepatocellular carcinoma

Method of administration: 3 tablets daily (please follow the prescription when the dose is reduced or resumed to the previous dose)

Once a day after meals (the dosing time on each day should remain the same whenever possible)

Storage: Store in a sealed container away from light at room temperature

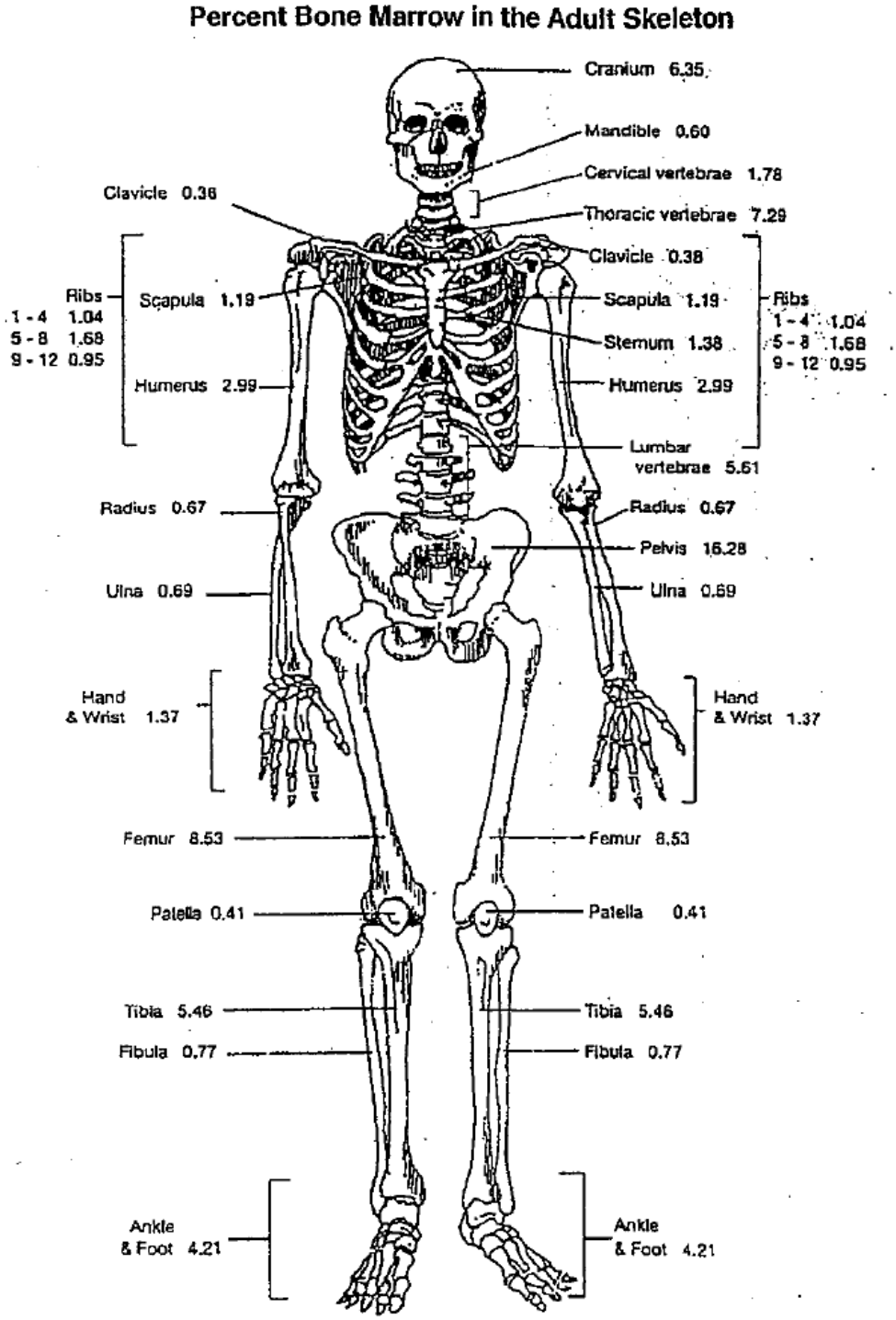
Batch No.: ××××

Shelf life: Tentatively 2 years, till XX Day XX Month 20XX

Study Site: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining products to the pharmacist

Appendix 8 Percent Bone Marrow Content in Human Skeleton



Woodward Holoday E. A summary of the data of Mechanik on the distribution of human bone marrow. Phys Med Biol. 1960;5:57-59

Appendix 9 Quality of Life Score (EORTC QLQ-C30 V3.0 and HCC-18)

We would like to know about you and your health status. Please answer all the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information you provide will be kept strictly confidential.

Please fill in your code (No.): _____

Date of Birth (DD/MM/YYYY): _____

Today's Date (DD/MM/YYYY): _____

	Not at all	**A little**	**Quite a bit**	**Very much**
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, bathing or using the toilet?	1	2	3	4
During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions, please circle the number from 1 to 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

During the past week:	Not at all	A little	Quite a bit	Very much
31. Did you feel thirsty?	1	2	3	4
32. Was there any problem with your taste?	1	2	3	4
33. Was your arm or leg muscle reduced?	1	2	3	4
34. Did you have bloating?	1	2	3	4
35. Were you troubled by the appearance of your belly?	1	2	3	4
36. Were you troubled by the yellowing of your skin or eyes (jaundice)?	1	2	3	4
37. Did you feel itchiness?	1	2	3	4
38. Did you have shoulder pain?	1	2	3	4
39. Did you have abdominal pain?	1	2	3	4
40. Did you have fever?	1	2	3	4
41. Were you afraid of cold (rigors)?	1	2	3	4
42. Were you worried that you would not get enough nutrition?	1	2	3	4
43. Did you feel full soon after you started eating?	1	2	3	4
44. Were you worried that you are underweight?	1	2	3	4
45. Did you feel less energetic than expected?	1	2	3	4
46. Did you find it difficult to get things done?	1	2	3	4
47. Did you need to sleep during the day?	1	2	3	4

In the past four weeks:

48. Did the disease or treatment affect your sexual life?

Note:

1. Quality of life assessment instructions:

EORTC's QLQ-C30 (V3.0) is the core questionnaire for all cancer patients, with a total of 30 items. Items 29 and 30 have a 7-point scale, scoring 1-7 points depending on the answer. Other items have a 4-point scale: Not at all, A little, Quite a bit, and Very much, scoring 1-4 points.

2. Calculation of EORTC QLQ-C30 scale (dimension) score (coarse score)

For the convenience of statistical analysis and application, the scale is often divided into scales. A scale is an aspect of a quality of life component, also known as a dimension, which is analyzed as an independent variable. The EORTC QLQ-C30 (V3.0) comprises 30 items divided into 15 scales, including 5 functioning scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain and nausea/vomiting), 1 global health status/quality of life scale, and 6 single-item scales (each one is a scale). Refer to the following for breakdown of these scales.

To get the score of each scale, add up the scores of the items in each scale and divide by the number of items in each scale (Raw Score RS), that is, RS = (Q1+Q2+...+Qn)/n.

Classification of various scales in EORTC QLQ-C30

	Items	Item Number
Physical Functioning	5	1-5
Role Functioning	2	6-7
Emotional Functioning	4	21-24
Cognitive Functioning	2	20-25
Social Functioning	2	26-27
Global Health Status	2	29-30
Weariness	3	10, 12, and 18
Nausea and Vomiting	2	14-15
Pain	2	9, 19
Dyspnoea	1	8
Insomnia	1	11
Appetite Loss	1	13
Constipation	1	16
Diarrhea	1	17
Financial Difficulties	1	28

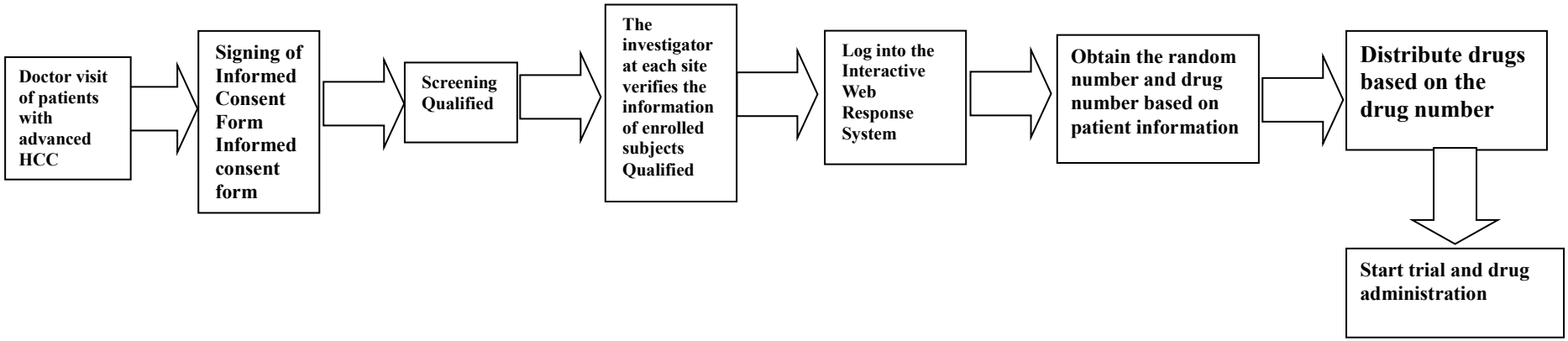
3. Calculation of EORTC QLQ-C30 Standard Score

To compare the scores between each scale, a linear transformation is further carried out to standardize the RS so that the standard score (SS) ranges from 0-100. In addition, another purpose of the transformation is to reverse the direction of the score. Except for items 29 and 30 which are reversed items (the larger the score, the worse the quality of life), the scoring rules for QLQ-C30 clearly state that the higher the score for functional scale and global health status, the higher level of functioning and QoL, but a high score for symptom scale represents a high level of symptoms/problems (worse QoL). Therefore, the score of functional scale needs to be reversed when being standardized. Specifically, the following formula is used (where R is the full score range for each domain or item).

Functional scale: $SS = [1 - (RS - 1)/R] \times 100$

Symptom scale and global health status: $SS = [(RS - 1)/R] \times 100$

Appendix 10 Flow Chart of Randomization and Enrollment for the Clinical Trial of Apatinib Mesylate Tablets as a Second-Line Treatment for Advanced Hepatic Carcinoma



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