Front Page of Clinical Study Protocol of Fruquintinib

CFDA Approval No.: 2013L01502, 2013L01503

Study Protocol

Study Title: Fruquintinib randomised, double-blind, placebo-controlled, multicentre Phase III trial to compare efficacy and safety in combination with BSC vs. BSC in advanced colorectal cancer patients who have progressed after second-line chemotherapy (FRESCO).

Short Title: A Phase III clinical trial of Fruquintinib or placebo in treatment of advanced colorectal cancer patients who have progressed after second-line chemotherapy.

Protocol No.:	2013-013-00CH1
Study Drug:	Fruquintinib (HMPL-013)
Study Objectives:	Efficacy and safety
Sponsor:	Hutchison Medi Pharma Ltd.

Clinical Study Protocol Signature Page_01

Signature of the representative from the Sponsor

Your signature on this page indicates that the final Clinical Study Protocol is accepted.

Name: Ye Hua Title: Head of Clinical Development and Regulatory Affairs

Signature: Date:

Clinical Study Protocol Signature Page_02

Signature of the Principal Investigator

Your signature on this page indicates that the final Clinical Study Protocol is accepted.

Name:

Signature: Date:

(Urgent) Contact Information of the Sponsor

Should any medical emergency occur, please contact the Project Leader of the study team. If the Project Leader is unavailable, please call the Safety Reporting Contact at the corresponding telephone number listed below.

	Name	**Tel**
Project Leader	Songhua FAN	021-20673058 18516082311
Safety Report Contact	Xiaoyun XI	021-20673061 18601688469

Table of Contents

172 # Abbreviations

Terms and abbreviations	Definition
AE	Adverse Event
A/G	Albumin/globulin
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic-pyruvic transaminase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase/glutamic-oxalacetic transaminase
$AUC_{0\text{-}24\ hr}$	Area under the concentration-time curve from 0 to 24 hours after drug administration
BSC	Best supportive care
BUN	Blood urea nitrogen
CEA	Carcino-embryonic antigen
CHOL	Cholesterol
c-MET	Mesenchymal epithelial cells transforming factor
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF/eCRF	Case Report Form/Electronic Case Report Form
CT	Computed tomography
CTC AE	Common Terminology Criteria for Adverse Event
DCR	Disease control rate
DFS	Disease free survival
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EC	Ethics Committee
EOT	End of Treatment
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FIB	Fibrinogen
Glu	Glucose
HFS	Hand-foot syndrome
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International normalized ratio
ITT	Intension to treat
IWRS	Interactive Web Response System
LDH	Lactic dehydrogenase
LOAEL	Lowest Observed Adverse Effect Level
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTC AE	The National Cancer Institute Common Terminology Criteria for Adverse Event
NE	Not evaluable

NOAEL	No observed adverse effect level
NSCLC	Non-small-cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive disease or pharmacodynamics
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free Survival
PK	Pharmacokinetics
p.o.	Per os (oral administration)
PR	Partial response
PS	Performance status
PSA	Prostate specific antigen
PT	Prothrombin time
QD	*quaque die*/once daily
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
TG	Triglyceride
TKi	Tyrosine kinase inhibitor
TP	Total protein
TSH	Thyroid stimulating hormone
TT	Thrombin time
TTP	Time to progression
ULN	Upper Limit of Normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization

173

174 Synopsis

Study Drug Name	Fruquintinib
Protocol No.	2013-013-00CH1
Study Title	Fruquintinib randomised, double-blind, placebo-controlled, multicentre Phase III trial to compare efficacy and safety in combination with BSC vs. BSC in advanced colorectal cancer patients who have progressed after second-line chemotherapy (FRESCO).
Short Title	A Phase III clinical trial of Fruquintinib or placebo in treatment of advanced colorectal cancer patients who have progressed after second-line chemotherapy.
Phase	III
Sponsor	Hutchison Medi Pharma Ltd.
Principal Investigator Co-principal Investigator	Prof. Jin LI Prof. Shukui Qin
Study Sites	Multiple clinical trial sites including Fudan University Cancer Hospital
Planned Number of Subjects	Approximately 400 subjects are planned to be enrolled.
Study Duration	Recruiment period is estimated to be about 15 months. The study duration is estimated to be from Dec 2014 to Sep 2016.
Study Objective	To evaluate the efficacy and safety of Fruquintinib in advanced colorectal cancer patients who have progressed after second-line chemotherapy.
Study Design	This is a randomized, double-blind, placebo-controlled, multicenter Phase III clinical trial to compare the efficacy and safety of Fruquintinib in combination with BSC versus placebo in combination with BSC in patients with advanced colorectal cancer. Approximately 400 subjects will be randomized into either of the following treatment group at the ratio of 2:1 (Fruquintinib vs. placebo): • Fruquintinib 5mg, orally, QD, in combination with BSC. • Placebo in combination with BSC. Rrandomization will be stratified based on the following factors: • Prior use of VEGF inhibitor treatment (Yes vs. No) • K-Ras gene status (wild type vs. mutant type)

	Subjects will receive study treatment with each cycle consisting of 4 weeks (1 cycle includes 3 weeks of continuous medication and 1 week of drug interruption [referred to as "3 wks on/1 wk off" for short]). Tumor evaluation will be performed using imaging method every 8 weeks until progressive disease (PD). Safety parameters include adverse event (AE), laboratory changes, vital signs and ECG changes. The tumor treatment and survival follow up after PD will also be recorded.
Study Drug Active Ingredient/ Dose Mode of Administration Treatment Duration	Fruquintinib Capsule Fruquintinib (HMPL-013) 5mg, QD, 3 wks on and 1 wk off Orally at fasting state Subjects should continue the treatment until the occurrence of the following events or the termination of the trial: • PD confirmed by Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1); • Death; • Unable to return to ≤ NCI CTC AE Grade 1 or the baseline value within 14 days after drug interruption caused by adverse reaction; • Abnormal liver function of NCI CTC AE Grade 4, bleeding of NCI CTC AE Grade 3 and above, artery thrombosis of any grade, or any other fatal adverse reaction of Grade 4; • Subject's withdrawal of consent; • Any subject that should withdraw from the study treatment for his/her best interests according to the investigator; • Pregnancy of subjects during the study; • Subject's poor compliance or unable to follow the Protocol; • Lost of follow up
Control Drug	Matching placebo of Fruquintinib
Indications	Advanced colorectal cancer (CRC)
Evaluation	
－Efficacy	**Primary Efficacy Endpoint:** Overall Survival (OS) **Secondary Efficacy Endpoints:** Progression-free survival (PFS) (According to RECIST Version 1.1)

	Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of response (DOR) and stable disease (SD)
－Safety	Adverse events (AEs) will be judged and graded in accordance with NCI CTC AE Version 4.0 and comprehensive safety and tolerance evaluations will be performed based on the incidence, severity and outcomes of AEs.
Inclusion Criteria	Patients can be enrolled in the study only if they meet all of the following criteria: 1. Fully understand the study and signed the Informed Consent Form (ICF) out of their own will; 2. Histologically and/or cytologically diagnosed with metastatic CRC (Phase IV), any other histological type is excluded 3. Subjects who failed at least second-line standard chemotherapies including Fluorouracil, Oxaliplatin or Irinotecan. Failed chemotherapies are defined as occurrence of PD or intolerable toxicities during the treatment or within 3 months after the last dose. Notes: a) Each line of treatment up to PD includes one or more chemo drugs used for ≥1 cycle; b) Previous adjuvant/neoadjuvant therapy is allowed. If relapse or metastasis occurs during the adjuvant/neoadjuvant treatment period or within 6 months after the completion of the above treatment, then the adjuvant/neoadjuvant therapy is considered as the failure of first-line systemic chemotherapy for PD; c) Previous antitumor treatment regimen including chemotherapy combined with targeting drugs such as EGFR inhibitors (Cetuximab or Panitumumab, etc.) or VEGF inhibitors is allowed. 4. Subjects must not received any systemic anti-tumor therapies such as chemotherapy or radiotherapy, immunotherapy, biological or hormonal therapy in the last 4 weeks, and have not received any VEGFR inhibitor treatment; 5. 18-75 years of age (inclusive); 6. Body weight ≥ 40Kg; 7. ECOG Performance Status (ECOG PS) ≤1(0-1); 8. Heart function test: Left Ventricular Ejection Fraction (LVEF) ≥ 50% (echocardiogram test); 9. Evident measurable lesion (s) that meets the Response Evaluation Criteria in Solid Tumors (RECIST 1.1); 10. Expected survival > 12 weeks.
Exclusion Criteria	Patients shall not be enrolled in this study for any of the following criteria: 1. Absolute neutrophil count (ANC) $<1.5\times10^9$/L, or blood platelet count (PLT) $<100\times10^9$/L, or hemoglobin< 90g/L; blood transfusion within 1 week before enrollment for the purpose of enrollment is not allowed; 2. Serum total bilirubin>1.5×Upper Limit of Normal (ULN); Alanine transaminase (ALT) and/or Aspartate transferase (AST)>2.5×ULN (subject to

	the normal value of each site), or ALT and/or AST > 5×ULN for patients with liver metastases; 3. Creatinine clearance rate < 50mL/min; 4. Uncontrollable hypertension with monotherapy, i.e. systolic blood pressure> 140mmHg or diastolic blood pressure >90mmHg after monotherapy treatment. 5. Clinically significant electrolyte abnormality; 6. Result of urine protein test with 2+ or above, or urinary protein quantity ≥ 1.0g/24 h; 7. Unrecovered from the toxicity of previous anticancer therapy (NCI CTC AE> Grade 1, except for alopecia and neurotoxicity ≤Grade 2 caused by Oxaliplatin), not fully recovered from previous surgeries or the time from the previous anticancer therapy or surgery is less than 4 weeks; 8. Central Nervous System (CNS) metastatic disease or prior cerebral metastasis; 9. Subjects with presence of clinically detectable second primary malignant tumors at the enrollment, or other malignant tumors within the last 5 years (excluding adequately treated skin basal cell carcinoma or carcinoma in situ of cervix). 10. Clinically uncontrolled active infection, such as acute pneumonia, active hepatitis B or hepatitis C, etc. (previous medical history of hepatitis B virus infection regardless of whether controlled by medication, HBV DNA ≧10^4 × copy number or ≧2000IU/mL); 11. Having difficulty in swallowing or known drug malabsorption; 12. Concurrent duodenal ulcer, ulcerative colitis, intestinal obstruction, other gastrointestinal diseases or other conditions that may lead to gastrointestinal bleeding or perforation according to the investigator's judgment; or with a history of intestinal perforation or intestinal fistula, which were not fully recovered after surgery; 13. History of artery thrombosis or deep venous thrombosis within 6 months before enrollment, or having evidence or a history of bleeding tendency within 2 months before enrollment, regardless of severity; 14. Occurrence of stroke or transient ischemic attack within 12 months before enrollment; 15. Activated Partial Thromboplastin Time (APTT) or prothrombin time (PT) > 1.5×ULN (subject to the normal range of each site);

	16. Skin wounds, surgical site, trauma site, severe mucosal ulcers or fracture not completely healed; 17. Acute myocardial infarction, severe/unstable angina or received coronary artery bypass surgery within 6 months prior to enrollment; or patients with cardiac insufficiency of NYHA Grade 2 or above; 18. Pregnant or lactating women, or female subjects of childbearing potentials with positive pregnancy test result before the first dose of the study treatment; 19. Any clinical or laboratory abnormalities or compliance that considered as unfit to participate in this clinical trial according to the investigator; 20. Serious psychological or psychiatric disorders; 21. Participated in any other drug clinical trial during the last 4 weeks.
End of Treatment (EOT)	Subjects are considered to have completed the study treatment should the following conditions occur: 1. PD (Normally, patients should discontinue the investigational products in the event of PD which is confirmed after CT/MRI examination and according to RECIST v1.1. Despite of the occurrence of progressive disease radiographically judged by the treating physician, if the clinical symptoms of the patient are significantly improved or stabilized; or obvious necrosis, liquefaction or degeneration appear in the tumor lesion; the patient can obtain survival benefit from continuation of the investigational products, the patient can continue the study treatment under close observation after obtaining the informed consent of the patient and approval from sponsor and the Leading PI of the leading site. However, the patient will be considered to have developed PD according to RECIST v1.1). 2. Death; 3. End of the entire trial Criteria for Study Treatment Withdrawal 4. Unable to return to ≤NCI CTC AE Grade 1 or baseline value within 14 days after drug interruption caused by adverse reactions; 5. Abnormal liver function of NCI CTC AE Grade 4 and bleeding of NCI CTC AE Grade 3 or above; arterial thrombosis of any severity; any other fatal adverse event of Grade 4. . 6. Pregnancy; 7. In the opinion of the investigator, the subject should withdraw from the study treatment for his/her best interests; 8. Subjects or their legal representatives request to withdraw from the study; 9. Lost to follow up;

	10. Poor compliance, or unable to follow the Protocol.
Drop-out Criteria	All the subjects who have signed the Informed Consent Form, and were confirmed eligible after screening and were randomized into the study have rights to withdraw from the study at any time. 1. Subjects who have only signed the Informed Consent Form and were confirmed eligible after screening but were not randomized into the study will not be considered as drop out; 2. Subjects who have withdrawn from the study for any reason at any time without taking at least one dose of investigational products and were unable to be evaluated for safety, and/or who were inevaluable for efficacy due to the failure to complete one cycle of treatment will be considered as drop-out. For drop-out cases, the reasons for drop out must be recorded in the CRF by the investigator and the related tumor evaluations should be completed as far as possible, and the final visit should be recorded as well. 3. Subjects who have PD after enrolment with clear medical evidence will not be considered as drop out, but radiographical evidence must be provided; subjects who withdraw from the study due to intolerable toxicity will not be considered as drop out either.

Statistical Analysis:

This is a matching placebo-controlled study, in which superiority test will be performed.

Overall survival (OS) is defined as the time interval (days) from randomization to death caused by any reason. For patients without report of death at the time of analysis, the date of last known to survive will be the censoring date. Progression-free survival (PFS) is defined as the time interval (days) from randomization to PD or death. The comparison of OS between the two groups will be done by using the Intention to Treat (ITT) population. The final OS data analysis will be performed when 280 deaths occur in the ITT population.

Stratified log-rank test will be used for the comparison of OS between the Fruquintinib group and the placebo group at a two-sided significance level of 0.05. The same stratification factors used for randomization will be used for statistical analysis: prior use of VEGF inhibitor (yes vs. no), K-Ras gene state (wild type vs. mutant type).

Unstratified log-rank test results will be provided as well. For the median survival time (MST) in each treatment group, Kaplan-Meier estimates will be presented with curves to provide visually intuitive description of the differences between the two treatment groups. The estimation of treatment effects will be presented by the Hazard Ratio (HR) estimated by stratified COX model in a 95% Confidential Interval (CI).

Sample Size Determination

The number of primary endpoint events required for efficacy assessment will be calculated based on the

following assumptions:

- A two-sided significance level of 0.05;
- An 80% test power will be ensured when the true HR of treatment group/control group is 0.7, in other words, the median OS time is extended from 6.3 months to 9 months;
- The enrollment rate is 30 subjects per month, which can be achieved within 3 months after trial initiation;

Under the premise of these assumptions, approximately 400 subjects will be enrolled in nearly 15 months in this study. The final analysis of OS will be performed when about 280 OS (or death) events have been observed in 7 months after the end of enrollment.

Meanwhile the sample size will be adjusted according to the result of Phase II intestinal cancer trial of Fruquintinib (POC) and the overall survival data of the latest third-line and above placebo treatments for advance intestinal cancer at that time.

175
176

1 Background Information

For more details, see Investigator's Brochure in which the comprehensive information on study drug is provided[6].

1.1 Colorectal Cancer

Colorectal Cancer (CRC) is a common malignancy, of which the worldwide incidence ranks the third place in both males and females. Its overall incidence rate in the western countries ranks the second place, and its number of new cases and that of mortality ranks the third place in the US in 2003. According to the International Agency for Research on Cancer (IARC), in Asia, especially economically developed regions, the CRC incidence also increased rapidly, and the number is almost close to that in the western countries. Since 2010, CRC has become the second cancer in morbidity and mortality in China, and its incidence in coastal areas has reached 56/100000, with the morbidity age becoming increasingly younger. In Shanghai, the annual average increase of CRC incidence is 4.2%, ranking the second place in all cancers, accounting for 13.08% of its total population.

The most common therapy for advanced CRC is chemotherapy treatment, and combination regimens of various chemotherapy drugs such as Fluorouracil/Leucovorin (5FU/LV), Capecitabine, Irinotecan, Oxaliplatin and etc. are commonly used. In recent years, monoclonal antibody Bevacizumab against vascular endothelial growth factor (VEGF), and monoclonal antibodies Cetuximab and Panitumumab against the epidermal growth factor receptor (epidermal growth factor receptor, EGFR) are combined with chemotherapy respectively as the first-line treatment of patients with advanced CRC, and patient outcomes have been significantly improved [1-2]. Patients with CRC that are ineffectively treated by first-line therapy are mainly treated with second-line chemotherapy, of which the mechanisms of action of these drugs varies, so the treatment of choice mainly depends on the type of tumor, chemotherapy time, and side effects of the drugs, and the efficacy and safety of some drugs require further evaluation [2-3]. Bayer's multitargeted kinase inhibitor regorafinib, approved by the FDA in 2012, is of strong vascular endothelial growth factor receptor (VEGFR) kinase inhibitor activity and can inhibit angiogenesis well. The CORRECT trial showed that for the treatment of advanced CRC in patients ineffectively treated by second-line chemotherapy, the primary endpoint of median survival of Regorafenib group is 1.4 months longer compared with that of the placebo group (6.4m vs. 5.0m) and the hazard ratio is 0.773, $p = 0.0051$ [4]. In June 2014 at Spanish WCGIC, Bayer published the Phase Ⅲ study (CONCUR trial) results of Regorafinib as third-line or above therapy for the

treatment of colorectal cancer in Asian patients, and the primary endpoint of median survival of Regorafenib is 2.5 months longer than that of the placebo (8.8m vs. 6.3m) and the hazard ratio is 0.55, p = 0.0012.

Angiogenesis is the most critical step in the occurrence and development of malignant tumors. Studies have showed that tumor angiogenesis can provide nutrients and remove the metabolites, and help tumor cells to transfer to the other parts of the body through new blood vessels. Therefore, effective inhibition of angiogenesis in the tumor region can suppress the growth of tumor cells, and reduce the incidence of metastasis. Currently, anti-angiogenesis has become the most promising new strategy for cancer treatment. The development of tumor angiogenesis is associated with a variety of vascular factors, because angiogenesis can be stimulated by a variety of angiogenic growth factors secreted by rapid growing tumor cells in anaerobic condition. One important factor is vascular endothelial cell growth factor (VEGF), which is found to be one of the main inducible factors related to tumor angiogenesis, so the VEGF/VEGFR signaling pathway is considered to be one of the most promising targets in molecular targeted therapies [5].

In recent years, small molecule targeting anticancer drugs have been developed successfully, such as highly selective VEGF monoclonal antibody drug Bevacizumab for the treatment of advanced CRC and breast cancer, and Sunitinib for renal cell carcinoma and Sorafenib for liver cancer and renal cell carcinoma, promoting the transition from conventional treatment to individualized comprehensive ones, and many patients have benefit from controlled tumors and prolonged survival. Among them, Bevacizumab has fully proved the effectiveness of the target VEGF as well as its importance in the research and development of new drugs for its great clinical success. Sunitinib and Sorafenib belong to multiple targets (including VEGFR) small molecule kinase inhibitors, with simultaneous inhibition of tumor angiogenesis and cancer growth signaling kinase. However, great toxic side effects will occur due to excessive kinase inhibitation. Therefore, the development of selective VEGFR II has become a global hotspot.

1.2 Overview of Fruquintinib

Fruquintinib is a small-molecule compound closely related to angiogenesis and targets the VEGF receptor kinase family. It is independently developed by Hutchison Medi Pharma Ltd. (hereinafter referred to as "the Sponsor"), with complete independent interllectual property right. Fruquintinib mainly exerts its function on the VEGFR family transmembrane receptors (VEGFR 1, 2 and 3) in the vascular endothelial cells. According to the tests, half inhibitory concentration (IC50) of Fruquintinib against VEGFR2, VEGFR1 and VEGFR3 are 35nM, 33nM and 0.5nM, respectively, and it has no inhibition (IC50> 3μM) on the activities of a variety of cell proliferation and

cell cycle associated kinases including cyclin-dependent kinases (CDK1, 2, 5), EGFR and mesenchymal-epithelial transition factor (c-Met). Besides, Fruquintinib also has no significant inhibition on the activities of platelet-derived growth factor receptor (PDGFRβ) kinase (IC50>1μM). Therefore, with high kinase selectivity, Fruquintinib has a good selectivity at the molecular level.

The direct killing effect of Fruquintinib is very weak in 13 kinds of cells including primary human umbilical vein endothelial cells (HUVEC) (IC50≥ 30 μM, with IC50 of 18.7μM on primary HUVEC). Compared with the VEGF-dependent proliferation of HUVEC (with IC50 of only 1.7 nM), the difference is of more than 10,000 times. Fruquintinib has high efficiency and low toxicity in the enzymology and cellular levels.

In models of nude mouse subcutaneous transplantation tumor of human colon cancer HT-29, human non-small cell lung cancer NCI-H460 and human renal cancer Caki-1, the doses of Fruquintinib are 0.77, 1.92, 4.8 and 12 mg/kg (2.5 times increment), once daily (QD), oral administration for 3 continuous weeks, Fruquintinib showed a dose-dependent tumor growth inhibition. In refractory tumor models such as malignant melanoma A375, pancreatic BXPC-3, pancreatic Miapaca and hepatoma Bel-7402, the daily doses of 1.5, 5 and 15 mg/kg of Fruquintinib has a significant inhibition of tumor growth. Human gastric carcinoma BGC-823 model is the most sensitive to Fruquintinib, and a daily dose of 2 mg/kg almost completely inhibits its growth.

1.3 Clinical Application Experience for Fruquintinib

1.3.1 Phase I Clinical Study Results of Fruquintinib for the Treatment of Advanced Solid Tumors

This study was conducted in Fudan University Cancer Hospital. A total of 40 subjects with advanced malignant solid tumors were enrolled from Jan 2011 to Oct 2012, among whom 18 were male and 22 were female, and all of them were of Han ethnic group of China.

1. This study confirmed that the maximum tolerated dose (MTD) of Fruquintinib in the treatment of advanced malignant solid tumor patients with the administration mode of “orally, QD, continuous medication” was 4mg; and that for the administration mode of ‘3 wks on/ 1 wk off’ was 6mg.
2. Fruquintinib related adverse events observed in this study were all observed in the clinical studies of similar VEGFR targeted drugs, and no new safety information was obtained. The incidence of adverse events leading to treatment interruption or dose reduction was relatively low since the adverse events were mostly mild to

moderate. The most common adverse events during the study included hand-foot syndrome, hypertension, proteinuria and elevation of thyrotropic hormone, with majority of which were associated with mechanism of action of anti-angiogenesis, and the incidence and severity were similar to those of the same kind of VEGFR targeted drug; the incidence of other nonspecific adverse reactions such as gastrointestinal reaction (nausea, vomiting and loss of appetite, etc.), pain, transaminase increased, serum creatinine increased, and electrolyte abnormality was relatively low.

3. The preliminary efficacy analysis had shown that Fruquintinib had significant effect on subjects with advanced tumors ineffectively treated by multi-line therapies, with significant objective response rate (ORR) and disease control rate (DCR). Among the evaluable subjects, the tumor ORR and DCR for the 4mg dose group were 46.67% and 86.67% respectively; and the ORR and DCR for the 5mg "3 wks on/ 1 wk off" dose group were 57.14% and 85.71% respectively.
4. Fruquintinib deserves further research and development considering its clinical safety, tolerance and preliminary efficacy assessment results. The recommended doses for Phase II clinical study were 4mg, QD, orally, continuous medication, and 5mg, QD, orally, "3 wks on/ 1 wk off".

1.3.2 Phase Ib Study of Fruquintinib as Third-line or above Therapy for Treatment of Advanced Colorectal Cancer

The study "A randomized, open-label, Phase Ib study of Fruquintinib "4mg continuous medication" and "5mg 3 wks on/ 1 wk off" as the third-line or above treatment in patients with advanced colorectal cancer" was started in December 2012 based on the results of Phase I dose escalation study and the proposed recommended dose. The study was conducted in Fudan University Shanghai Cancer Center and Sun Yat-sen University Cancer Center. The objective of this study was to further evaluate the safety, tolerance, PK characteristics and clinical efficacy of the two different modes of administration in treating advanced colorectal cancer, and to recommend better dose and mode of administration for Phase II/III studies.

Conclusion of the Randomized Study (40 Cases)

A total of 40 subjects were enrolled in the 2 sites (24 cases enrolled in site 01, Fudan University Shanghai Cancer Center and 16 cases enrolled in site 02, Sun Yat-sen University Cancer Center) up to 17 Sep 2013. 20 subjects were in the 4mg continuous

medication group (Group A), and the other 20 were in the 5mg, 3 wks on/ 1 wk off group (Group B). All the subjects received at least 2 cycles of Fruquintinib treatment or reached the primary endpoints for interim analysis.

The conclusions of the interim analysis were as follows:

For safety and tolerance: compared with Group A, Group B presented superior safety and tolerance considering the incidence of adverse events of Grade 3 or above and Grade 3 hand-foot syndrome. And the incidence of Grade 3 or above toxicities in Group B was significantly lower than that in the continuous medication group, and the difference was of significance. Also, the incidence of SAEs and AEs leading to permanent drug withdrawal as well as temporarily drug discontinuance/dose reduction was lower in Group B compared to Group A , which however, had no statistical significance.

Group B (5mg, QD, 3 wks on/ 1 wk off) was comparable to Group A (4mg, QD, continuous medication) in efficacy. For Group B, the DCR was 83.3%, and the 16-week PFS rate was 65%, while for Group A, DCR was 76.4%, and the 16-week PFS rate was 35%.

According to the above findings, the mode of administration of Group B (5mg, QD, 3 wks on/ 1 wk off) was chosen for the extension stage of the Phase Ib study, after discussion with investigators. And at the same time, the recommended dose and mode of administration were further defined as “5mg, QD, 3 wks on/ 1 wk off” for Phase III/III study of Fruquintinib.

Conclusion of Extension Trial (5mg 3 wks on /1 wk off, 42 Cases)

A total of 22 subjects were enrolled in extension trial. As of 24 Apr 2014, totally 42 subjects received Fruquintinib 5mg 3/1 treatment throughout the Phase Ib trial, all of which reached the primary endpoint for analysis.

The most common adverse reactions were hand-foot syndrome, proteinuria, hoarseness, elevation of thyrotropic hormone, hypertension, weakness, rash and blood platelet decrease, etc. Toxicities ≥Grade 3 related to study drug was relatively rare, and the only event with incidence＞10% was hypertension (19.4%).

The clinical efficacy observed: 16-PFS%=65%, DCR=83.3%; the median of progression-free survival (PFS) was about 5.3 months. For the 5mg, 3 wks on/ 1 wk off dose group in which 20 cases were randomized, the 6m-OS% was 70%, and 9m-OS% was 50%.

1.4 Recommended Dose for Phase III Clinical Trial

The dose and mode of administration determined for the study are based on the safety and efficacy results of dose tolerance Phase I study (2009-013-00CH1) and Phase Ib study for the treatment of advanced colorectal cancer (2012-013-00CH3). And the recommended dose and mode of administration in Phase III trial are determined as 'Fruquintinib 5mg, QD, 3wks on /1wk off '.

2 Study Objectives

To compare the efficacy and safety of Fruquintinib in combination with best supportive care (BSC) versus placebo in combination with BSC in advanced colorectal cancer patients who have progressed after second-line chemotherapy.

2.1 Primary Efficacy Endpoint

- Overall Survival (OS)

2.2 Secondary Efficacy Endpoints

- Progression-free survival (PFS)
- Objective response rate (ORR= complete response [CR]+partial response [PR])
- Disease control rate (DCR=complete response [CR]+partial response [PR]+stable disease [SD])
- Duration of response (DOR) and stable disease (SD)/treatment duration

3 Study Design

3.1 Overview

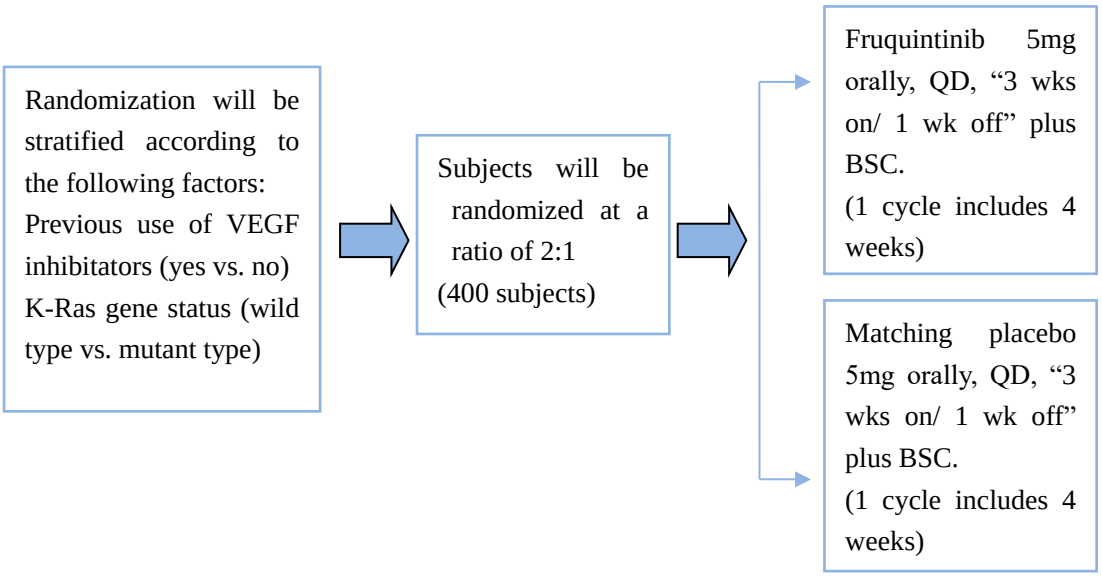
3.1.1 Rationale of Study Design

This is a randomized, double-blind, placebo-controlled, multicenter Phase III clinical trial to compare the efficacy and safety of Fruquintinib in combination with BSC versus matching placebo in combination with BSC in advanced colorectal cancer patients who have progressed after second-line chemotherapy.

After checking the eligibility criteria, subjects will be randomized into either Fruquintinib in combination with BSC group (treatment group) or placebo in combination with BSC group (control group) at a ratio of 2:1. (Figure 1)

- Treatment group: subjects will receive Fruquintinib 5mg orally, QD, in combination with BSC, 3 wks on/ 1 wk off.
- Control group: subjects will receive matching placebo 5mg orally, QD, in combination with BSC, 3 wks on/ 1 wk off.

Figure 1 Overall Study Design



A treatment cycle is 28 days. Subjects' safety assessment and drug accountability will be performed by each treatment cycle. Continuous drug safety monitoring and assessment will be performed through the whole study period (including a 30-day observation period after the end of treatment).

Patients will receive study treatment with each cycle of 4 weeks (1 cycle of study treatment includes 3 weeks of continuous medication treatment and 1 week of drug interruption) or until the occurrence of progressive disease (PD), death, unacceptable toxicity, withdrawal of consent, or other conditions that meet the End of Treatment criteria judged by physician for the best interest of the subjects. The tumor will be evaluated radiographically using CT/MRI imaging method every 8 weeks, until the occurrence of PD. If the subject has premature termination of the treatment for any reason without receving tumor evaluation, a timely imaging examination and tumor evaluation are recommended. Safety parameters include Adverse Event (AE), laboratory parameter changes, vital signs and ECG changes. Besides, the medication and survival follow up after PD will be recorded.

If any subject develops PD, it will be considered as the end of treatment. The subjects who, according to the investigator's discretion, can still benefit from the study treatment after developing PD can continue to take the prior investigational product (Fruquintinib or matching placebo, neither of the investigator, sponsor and the subjects know which investigational product the subject is receiving) after the investigator's consultation with the sponsor. The sponsor then will only provides investigational products and free examination for safety evaluation; and during which data other than SAE, safety data and survival status will not be collected.

This study will be divided into 3 stages, Baseline Period, Treatment Period and Follow-up Period, from the start of treatment to the end of treatment, post-treatment until final death.

Table 1 Time of the 3 Stages of the Study

Screening/Baseline	Treatment	Follow-up
D-21~D1(Before the 1st study drug administration on D1)	D 1 of the 1st cycle until End of Treatment (EOT) (including 1 week of drug interuption)	EOT to End of Study.

The subjects can withdraw from the study in the following 4 conditions:

1. Death
2. Lost to follow-up
3. withdrawal of consent and refuse to provide information afterwards
4. End of Study

3.1.2 Randomization Methods

After screening, subjects who meet the eligibility criteria will be randomized into Fruquintinib in combination with BSC or matching placebo in combination with BSC group at a ratio of 2:1 according to the blinding principles, and stratified randomization will be performed. The stratified factors include prior use of VEGF inhibitors (yes vs. no), K-Ras gene status (wild type vs. mutant type). The Randomized number of each subject will be assigned to the investigator through the interactive web response system (IWRS).

3.1.3 Reasonability of Study Design

Advanced colorectal cancer cannot be cured by surgery. General treatment principles are aiming at controlling disease progression and prolonging survival. Commonly used drugs include Fluorouracil, Oxaliplatin, Irinotecan, Bevacizumab and monotherapy or combination treatment of anti-EGFG antibody that can improve prognosis. However, there are no effective treatment methods for subjects ineffectively treated by the above therapies, so BSC turns out to be the standard treatment. In that case, there are unsatisfying medical needs for subjects who failed to multi-line therapy in prolonged survival (including overall survival and progression-free survival) and the improvement of clinical symptoms. And subjects be enrolled in this study should be the above mentioned patients with advanced colorectal cancer and have received all approved and confirmed regimen and developed PD. As there is no effective standard treatment for the patients with advanced colorectal cancer who failed to second-line therapy, it is reasonable to provide them with BSC and placebo. The dose and mode of administration to be used in this clinical study are on the basis of summary results of dose escalation tolerability Phase I trial for Fruquintinib and the Phase Ib clinical study with third-line or above therapies for the treatment of advanced colorectal cancer.

3.1.4 End of Study

The primary endpoint is Overall Survival (OS), statistical unblinding will be conducted and then PFS will be analyzed and summarized in 1 month after subject enrollment was completed and about 300 PFS events were observed. OS will be analyzed and summarized in 7 months after the enrollment is completed and about 280 OS events are observed (the entire trial is completed).

End of Study requirements: when 280 OS events have been observed. After the End of Study, the sponsor will continue to provide investigational drugs to subjects who do not achieve PFS, but data other than SAE will not be collected.

3.2 Sample Size Determination

The number of primary endpoint events required for efficacy assessment is calculated based on the following assumptions:

- A two-sided significance level of 0.05;
- An 80% test power will be ensured when the true Hazard Ratio (HR) of treatment group/control group is 0.7, in other words, the median OS time is extended from 6.3 months to 9 months;
- The enrollment rate is 30 subjects per month, which can be achieved within 3 months after study initiation;

Under the premise of these assumptions, approximately 400 subjects will be enrolled in this study in nearly 15 months. The PFS will be analyzed and summarized in 1 month after the end of the enrollment and about 300 PFS events are observed. The OS will be analyzed and summarized in 7 months after enrollment is completed and about 280 OS events are observed.

Meanwhile the sample size will be adjusted according to the result of Phase II intestinal cancer clinical trial of Fruquintinib (POC) and the overall survival data of the latest third-line and above placebo treatments for advance intestinal cancer at that time.

4 Study Population

4.1 Inclusion Criteria

Patients can be enrolled in this study only if they meet all of the following criteria:

1. Fully understand the study and signed the Informed Consent Form (ICF) out of their own will;
2. Histologically or cytologically diagnosed with metastasis CRC (Phase IV), any other histological type is excluded;
3. Subjects who failed at least second-line standard chemotherapies including Fluorouracil, Oxaliplatin, Irinotecan. Failed chemotherapies are defined as the occurance of PD or intolerable toxicities during the treatment or within 3 months after the last dose.

Notes: a) Each line of treatments for advanced disease until PD includes one or more chemo drugs used for ≥1 cycle; b) Previous adjuvant/neoadjuvant therapy is allowed. If relapse or metastasis occur during the adjuvant/neoadjuvant treatment period or within 6 months after the completion of the above treatment, that adjuvant/neoadjuvant therapy is considered as the failure of first-line systemic chemotherapy for PD; c) Previous antitumor treatment regimen including chemotherapy combined with targeting drugs such as EGFR inhibitors (Cetuximab or Panitumumab, etc.) or VEGF inhibitors is allowed.

4. Subject must not receive any systematically anti-tumor therapies such as chemotherapy or radiotherapy, immunotherapy, biological or hormonal therapy during the last 4 weeks, and never receive any vascular endothelial growth factor (VEGFR) inhibitor treatment;
5. 18-75 years of age (inclusive);
6. Body weight≥40Kg;
7. ECOG Performance Status (ECOGPS) ≤1 (0-1);
8. Heart function test: Left Ventricular Ejection Fraction (LVEF) ≥50% (echocardiogram test);
9. Evident measurable lesion(s) that meet the Response Evaluation Criteria in Solid Tumors (RECIST 1.1);
10. Expected survival >12 weeks.

4.2 Exclusion Criteria

Patients shall not be enrolled in this study for any of the following criteria:

1. Absolute neutrophil count (ANC) $<1.5\times10^9$/L, or blood platelet count (PLT) $<100\times10^9$/L, or hemoglobin <90g/L; blood transfusion within 1 week before enrollment for the purpose of enrollment is not allowed;
2. Serum total bilirubin>1.5 × Upper Limit of Normal (ULN); Alanine transaminase (ALT) and/or Aspartate transferase (AST)>2.5×ULN (subject to the normal value at each site); or ALT and/or AST > 5×ULN for patients with liver metastases;
3. Creatinine clearance rate < 50mL/min;
4. Uncontrolled hypertension by monotherapy, i.e. systolic blood pressure >140mmHg or diastolic blood pressure >90mmHg after monotherapy treatment.
5. Clinical significant electrolyte abnormality;
6. Results of urine protein detection with 2+ or above, or urinary protein quantity ≥1.0g/24h;

7. Unrecovered toxicity from previous anticancer therapies (NCI CTC AE > Grade 1, except for alopecia and ≤Grade 2 neurotoxicity caused by Oxaliplatin), not fully recovered fromprevious surgeries; or the time from the last anticancer therapy or surgery is less than 4 weeks;
8. Central Nervous System (CNS) metastatic disease or prior cerebral metastasis;
9. Subjects with presence of clinically detectable second primary malignant tumors at enrollment, or other malignant tumors within the last 5 years (excluding adequately treated skin basal cell carcinoma or carcinoma in situ of cervix).
10. Clinically uncontrolled active infection, such as acute pneumonia, active hepatitis B or hepatitis C (previous medical history of hepatitis B virus infection regardless of drug control, HBV DNA ≥10^4 ×copy number or ≥2000IU/mL);
11. Difficulty in swallowing or known drug malabsorption;
12. Duodenal ulcer, ulcerative colitis, intestinal obstruction, other gastrointestinal diseases or other conditions that may lead to gastrointestinal bleeding or perforation according to the investigator's judgment; or with a history of intestinal perforation or intestinal fistula, which were not fully recovered after surgery;
13. History of artery thrombosis or deep venous thrombosis within 6 months before enrollment, or have evidence or a history of bleeding tendency within 2 months before the enrollment, regardless of severity;
14. Occurrence of stroke or transient ischemic attack within 12 months before the enrollment;
15. Activated Partial Thromboplastin Time (APTT) and/or prothrombin time (PT) > 1.5×ULN (subject to the normal range at each site);
16. Skin wounds, surgical site, trauma site, severe mucosal ulcers or fracture not completely healed;
17. Acute myocardial infarction, severe/unstable angina or received coronary artery bypass surgery within 6 months prior to enrollment; or patients with cardiac insufficiency of NYHA Grade 2 or above;
18. Pregnant or lactating women Or female subjects with childbearing potentials with positive pregnancy test result before the first time of study drug treatment;
19. Any clinical or laboratory abnormalities or compliance concerns unfit to participate in this clinical trial according to the investigator's judgment;
20. Serious psychological or psychiatric disorders;
21. Participated in any other drug clinical trial during the last 4 weeks.

4.3 End of Treatment (Withdrawal) Criteria

Subjects are considered End of Treatment should the following conditions occur (Among which, 1-3 is considered as completed the study treatment, while 4-10 is considered as withdrawal from the treatment):

1. PD (Normally, patients should discontinue the investigational products in the event of PD which is confirmed after CT/MRI examination and according to RECIST v1.1. Despite of the occurrence of progressive disease radiographically judged by the treating physician, if the clinical symptoms of the patient are significantly improved or stabilized; or obvious necrosis, liquefaction or degeneration appear in the tumor lesion; the patient can obtian survival benefit from the continuation of the investigational products, the patient can continue the study treatment under close observation after obtaining the informed consent of the patient and approval from sponsor and the Leading PI of the leading site. However, the patient will be considered as the occurrence of PD according to RECIST v1.1);
2. Death;
3. End of the entire trial;
4. Unable to return to ≤NCI CTC AE Grade 1 or baseline value within 14 days after drug interruption;
5. Abnormal liver function of NCI CTC AE Grade 4, bleeding of NCI CTC AE Grade 3 or above, arterial thrombosis of any severity, or any other life-threatening adverse event of Grade 4.
6. Pregnancy of the subjects;
7. In the opinion of the investigator, the subject should withdraw from the study for his/her best interests;
8. Subjects or their legal representatives request to withdraw from the study;
9. Lost to follow up;
10. Poor compliance, or unable to to follow the Protocol.

4.4 Subject Withdrawl During Treatment

In any case, the reasons of subjects' withdrawal must be recorded in Case Report Form (CRF) and subjects' medical records. And all the follow-up results of the subjects who discontinue the treatment must be recorded in CRF, unused investigational products must be counted and returned. In the event that subject's discontinuation of treatment is caused by adverse events or clinical laboratory test

abnormalities, the subject should be continually followed up until he/she recovers from the event, stable disease or the event can be explained by other reasons.

All the subjects who discontinue the treatment (including both Fruquintinib and matching placebo treatment) will enter into the follow-up period. And the subjects discontinue the treatment for any reason will be followed up for survival until recording as death, except for patients' withdrawal consent and clearly expressed to refuse follow-up. The survival state will be evaluated every 2 months after the end of treatment. Subjects will not be followed up at the end of the study. In addition, for subjects who discontinue the treatment and without PD, tumor evaluation will be recorded in the CRF and medical record to the greatest extent until PD.

4.5 Subject Withdrawal During Follow up

Subject must withdraw from the study for the following reasons:

- Lost to follow-up;
- Subjects refuse to continue participating in the study for any reason at any time during the treatment. They will not be adversely affected.
- As per the requirements from the sponsor.

4.6 Subjects Replacement

No replacement will be performed for any subject who withdraws from this study.

4.7 Drop-out Criteria

All the subjects who have signed the Informed Consent Form, and were confirmed eligible after screening and randomized into the study have rights to withdraw from the study at any time.

1. Subjects who have only signed the Informed Consent Form and were confirmed eligible after screening but were not randomized into the study will not be considered as drop out;
2. Subjects who have withdrawn from the study for any reason at any time without taking at least one dose of investigational product and were unable to be evaluated for safety, and/or who were inevaluable for efficacy due to the failure to complete one cycle of treatment will be considered as drop out. For drop-out cases, the reasons for drop out must be recorded in the CRF by the investigator and the related tumor evaluations should be completed as far as possible, and the final visit should be recorded as well.
3. Subjects who have PD after enrolment with clear medical evidence will not be

considered as drop out, but radiographical evidence must be provided; subjects who withdraw from the study due to intolerable toxicity will not be considered as drop out either.

5 Assessment Plan and Procedures

See Table 2 for the schedule of the study (Schedule of Activities).

628 **Table 2 Schedule of Activities**

Protocol activities[22]	**Screening**		**Study Treatment**										**Follow Up Period**	
			Cycle 1				Cycle 2		Cycle 3		Cycle 4	Cycle 5 to EOT	EOT Follow up	Survival Follow Up
	Screening 1 (≦21 days prior to 1st dose)	Screening 2≦7 (days prior to 1st dose)	C1D1 (1st dose）	C1D8 (±2days)	C1D15 (±2days)	C1D22 (±2days)	C2D1 (±3days)	C2D15 (±2days)	C3D1 (±3days)	C3D15 (±2days)	C4D1 (±3days)	C5D1+ (±3days)	Within 30 days after EOT	Every two months after EOT(±7 days)
Informed Consent[1]	X													
Medical History/Oncology History[2]	X													
Surgery[3]	X													
Current Medical History/Baseline Signs and Symptoms		X												
Physical Examination[4]		X		X	X	X	X	X	X	X	X	X	X	
ECOG[5]		X[5]		X	X	X	X	X	X	X	X	X	X	
Demographics	X													

Vital Signs[6]		X		X	X	X	X	X	X	X	X	X	X	
Hematology[7]		X		X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[8]		X		X	X	X	X	X	X	X	X	X	X	
Coagulation[9]		X		X	X	X	X	X	X	X	X	X	X	
Urinalysis[10]		X		X	X	X	X	X	X	X	X	X	X	
Stool Occult Blood Test		X		X	X	X	X	X	X	X	X	X	X	
Pregnancy Test (as appropriate)[11]		X											X	
Carcino-embryonic Antigen	X						X		X		X	X	X	
12-lead ECG[12]	X						X		X		X	X	X	
Thyroid Function[13]	X						X		X		X	X	X	
Echocardiogram[14]	X						X							
Tumor Evaluaiton[15]	X								X			X	X[15]	
Eligibility Assessment		X												
Subject Randomization[16]		X												
Drug Assignment/Dis		X	X				X		X		X	X	X	

pense/Return[17]														
Study Treatment[18]			X	X	X	X	X	X	X	X	X	X		
Concomitant medication/ Concomitant Procedure[19]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-Tumor Therapy													X	X
Survival Follow Up[21]														X
Collection of Biomarker Samples[23]	X													

Notes:

1. ICF must be obtained prior to any study-specific procedure, and signature before 21 days prior to 1st dose is acceptable.
2. Medical History/Oncology History: Oncology History includes the date of primary diagnosis of CRC and its type; date of first metastasis; type of previous treatment, start/end date, best overall response, date of PD; adverse reaction with severity above 3 grades. Prior use of anti-VEGF (yes vs. no) and previous K-ras gene status (If K-ras gene detection was not performed previously, it should to be done during Screening). Radiation Therapy includes start/end dates and site of radiation.
3. Surgery: operations (non-invasive diagnostic or therapeutic procedures, such as digestive endoscope, and biopsy, etc.) including start/end date, name of procedure and operation site must be recorded in CRF.
4. Physical examination includes Height (baseline only), weight, head, eyes, ears, nose, throat, neck, heart, chest (including the lung), abdomen, limbs, skin, lymph nodes, nervous system, and general condition.
5. ECOG: ECOG is to be performed during Screening 2.

6. Vital Signs include blood pressure, heart rate, respiration rate and temperature. For subject with a baseline history of antihypertensive medications, blood pressure should be monitored at 3 hours (±2 hours) after the daily doses of anti-hypertensive medication
7. Hematology includes red blood cells, hemoglobin, platelet count, neutrophils and white blood cell differential absolutes. If neutrophils $\leq 1 \times 10^9$/L or platelets$\leqslant 25 \times 10^9$/L, the test frequency should be increased to once every 2 or 3 days. For subjects whose dose is interrupted or adjusted due to blood toxicity, hematology test should be performed every week.
8. Blood chemistry parameters include total protein (TP), albumin (ALB), globulin (G), A/G, blood glucose, urea nitrogen, creatinine, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, AST, ALT, calcium, phosphorus, magnesium, potassium, sodium, chloride, pancreatic amylase and uric acid. The frequency of blood chemistry test for subject with ALT or AST increase by over 3 times compared to baseline, or ALT or AST increase by over 2 times of baseline value should be increased (1-2 times/week). Creatinine clearance rate should be calculated by using the baseline creatinine values according to the formulas: for males: Ccr = (140 - age) × weight (kg) / [72 × Scr (mg/dl)] or Ccr = [(140 - age) × weight (kg)] / [0.818 × Scr (umol/L)], and the unit of the creatinine clearance should be taken into consideration during the calculation, and that for females should be the calculated value according to the above fomulas × 0.85).
9. Coagulation includes prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB) and international normalized ratio (INR).
10. Urinalysis parameters include pH, specific gravity, protein, urinary casts, white blood cell, red blood cell, urine glucose and urine ketone. If urinary protein is in the level of + + or above during the medication period, 24-hour urinary protein quantity should be tested within 1 week.
11. Pregnancy: All female patients of childbearing potential must complete blood pregnancy test at screening and within 30 days after EOT. Pregnancy test should be repeated for subjects with suspected pregnancy. This is not applicable for postmenopausal female subjects, but the date of menopause should be recorded instead.
12. 12 lead ECG parameters include PR interval, QRS time, QT interval, QTc, and diagnostics.
13. Thyroid function includes serum free triiodothyronine (fT3), serum free thyroxine (fT4) and thyroid stimulating hormone (TSH).
14. Echocardiography includes left ventricular ejection function and assessment.
15. Baseline tumor evaluation should be completed within 3 weeks before the first dose. CT/MRI Scans of check, abdomen and pelvis are required. Tumor evaluation shall be performed per RECIST 1.1. Baseline and follow up assessment should be performed by the same investigator using the same imaging method. Tumor evaluations shall be performed on C3D1, C5D1, and every D1 of every another cycle afterwards until PD. Tumor evaluation schedule and time window are calculated from C1D1, and it won't be affected by dose interruption. If tumor evaluation is not performed within 28 days of the last

dose, it should be completed at EOT/study withdrawal. Bone scan shall be performed at baseline for subjects with bone metastasis, and for subject with bone lesion at baseline, the local bone lesions should be followed up. For cases with suspected PD before the start of the next assessment, an additional tumor evaluation should be performed. For all the subjects with tumor response and withdraw from the study for reasons other than PD during the treatment, it is recommended to collect the verification information of tumor response by using the same methods as those at baseline and during the study. The efficacy data after the discontinuation of treatment including subsequent anti-cancer therapies, date of PD and death shall be recorded in the eCRF.

16. Subject randomization: after verifying subject's eligibility, site will log into the IWRS and randomize the subjects to treatment arm on Day-1. Subject randomization number will be obtained. At the same time, drug assignment is performed in IWRS. Each subject will be provided with a serial number and then receive a drug bottle with the same serial number. Site will take investigational product of the serial number from inventory and dispense them to the subjects in 2 days (on C1D1). Subjects should take 1st dose on C1D1.
17. Drug Assignment/Dispense/Return: subject should take care of all untaken drugs and drug containers and then return them to site during study visits. On Day-2 to Day -1, only subject randomization and drug assignment will be performed. Subject should start the 1st dose on C1D1. Subject should return the untaken drugs and containers of the previous cycle on D1 (date of visits) of each following cycle, and new drugs will be dispensed on the same day. If tumor evaluation shows PD for previous cycle and new drugs have been dispensed, subject needs to return all untaken drugs at the observation follow up after EOT. If lab results and previous AEs indicate that dose adjusting standard is met, (for dose adjustment from 5mg to 4mg), the subject needs to return to the investigational site and return all untaken drug. Site needs to log into the IWRS, adjust the dose and reassign drug serial number and dispense new drugs for the subject. If dose is adjusted from 4mg to 3mg, the site should log into the IWRS and record the dose adjustment. It's not necessary to reassign new drug serial number to the subject.
18. For administration method, see Protocol Section 6.2.
19. Concomitant Medications/Treatments: All Concomitant Medications within 21 days before randomization must be recorded in the case report forms (CRF), including: generic name of the drug and daily dose; reasons for using this medication; start and stop date of medication.
20. Adverse event (AE) should be collected from the time of the first dose to 30 days after EOT. AEs and laboratory abnormalities that recovered or unexplained need to be collected till their recovery or until they can be otherwise explained. SAE shall be collected from the signing of ICF to 30 days after the last dose. Only SAEs related to the study drugs should be collected on 30 days after the last dose.
21. Survival follow-up (telephone follow-up) should be performed every 2 months after EOT. All subsequent anti-tumor therapy and study-related SAEs shall be collected. For the subjects without PD, if the tumor evaluation results are available, the results during follow up shall be recorded in the CRF

until confirmation of PD. Record the date and cause of death (if applicable). Subjects who withdraw consent shall also enter into follow-up period. If the subjects clearly expressed his/her refusal to follow-up after the withdrawal of consent, he/she will terminate the study and no followed up for survival will be performed.

22. All follow up and data collection will be continued until the end of study.
23. Collection of biomarker samples: biomarker samples collection from the subjects are required at screening, but only samples of the randomized patients will be sent to the sponsor.

5.1 Screening Examination and Qualification Form

Signed ICF must be obtained before any study-specific assessment and procedure.

Complete Medical History Should be Recorded During Screening:

- Demographics:
  Date of birth, gender, ethnic group/race, body weight and height;
- Previous medical history (previous medical history that meet the following standards should be collected):
  Excluding the indications of the study drug; Conditions existing before signing the ICF; Medical conditions that are considered to be related with the study;
- Other baseline characteristics:
  Baseline medical history related to disease factors of the patient including:
  Diagnostic date, type and stage of CRC; K-Ras gene status (if unknown, it needs to be tested at screening); Time of the first diagnosis of metastatic disease;
  Previous anti-cancer therapies: The start time and duration of previous medication of the first-line chemotherapy/second-line chemotherapy and follow-up treatment regimens (including the best effect of each line therapy, date of failure or PD of each line therapy, toxicities of Grade 3 or above);
  Prior use of VEGF inhibitors or EGFR inhibitors (yes vs. no); ECOG Performance Status (the evaluation standard is specified in Appendix 1);
  All the drug treatment and significant non-drug treatment used within 21 days before enrollment must be recorded in the case report forms (CRF), including: generic name of the drug and daily dose; reasons for using this medication; starting and stopping date of medication or whether the drug will be continued during the study.

5.2 Subjects Enrollment Procedures

All the subjects will be assessed by the screening criteria. And the investigator should complete the IWRS worksheet to record the screening by login the IWRS through the internet.

The judgment for previous history of chemotherapy and inclusion criteria 3 during screening should be medically verified and confirmed by the sponsor before

randomization. Subjects meeting all the eligibility criteria will be randomized. The subject will get a randomized number, and participate in the study.

Subjects withdraw from the study after signing the ICF and before the randomization will be considered as 'screening failure'. Subjects who failed to the prior screening can be screened again, and then receive a new subject number re-assigned by IWRS. In this case, the sponsor is required to review their medical histories one by one. A subject can only be re-screened once.

5.3 Clinical Assessment

5.3.1 Efficacy

5.3.1.1 Efficacy Endpoints

Primary Efficacy Endpoint:

- OS

Secondary Efficacy Endpoints:

- PFS (as per RECIST v1.1)
- ORR (According to RECIST Version 1.1)
- DCR, of which SD ≥8weeks (±3 days)
- Duration of response and SD

5.3.1.2 Efficacy Assessment

Tumors should be evaluated according to the standard of RECIST Version 1.1, and the evaluation criteria are specified in Appendix 2. Either CT or MRI Tumor imaging evaluation method can be used at the discretion of the investigator, but PET scan as imaging evaluation method is unacceptable. The evaluation methods, machines used and technical parameters (include thickness of scan plies) should be consistent in the entire study period; if no contraindications are implicated, contrast agents should be used; the evaluation should be performed by the same investigator/imaging experts. The result of tumor evaluation performed within 21 days prior to the first dose in the same hospital using the same method can be used as baseline tumor evaluation result. Baseline tumor evaluation should include the chest, abdomen, pelvis, and any other site with suspected tumor lesions. For patients with bone metastases, bone scan should be used for the follow up of the lesion, and the scan plies is 5mm.

Record of target lesions: number of lesions, site, description, maximum diameter of each lesion (except lymph nodes) and lymph nodes minimum diameter, including the total length of all target lesions.

Tumors will be evaluated using imaging method every 8 weeks after receiving treatment, until the occurrence of PD. Should the subject interrupt the medication due to AEs or other reasons, tumor evaluation should be conducted as scheduled. If the subject has premature termination of the treatment for any reason without receving tumor evaluation, a timely imaging examination and tumor evaluation are recommended. For suspected cases of PD before the start of the next evaluation, additional tumor evaluation should be performed.

To achieve more accurate tumor evaluation results, all the subjects' CT or MRI will be delivered to a third party for independent evaluation in addition to the evaluation of the investigator, but the other evaluation will not affect the investigator's judgment.

5.3.2 Performance Status

ECOG PS score: ECOG PS score throughout the entire study period is recommended to be conducted by the same investigator at baseline and at each visit. Details are specified in Appendix 1.

5.3.3 Clinical Safety Assessment

5.3.3.1 Safety Endpoints

Safety endpoints include adverse events, laboratory results (hematology, clinical chemistry, clinical urinalysis and stool for occult blood), vital signs (blood pressure, heart rate, respiratory rate, and temperature), weight, electrocardiogram (ECG) and echocardiography (UCG).

Comprehensive safety of the two groups will be assessed by severity and incidence of AEs, and classified in accordance with the NCI CTC AE Version 4.0. Safety endpoints include:

- The overall incidence of Treatment Emergent Adverse Events (TEAEs);
- The incidence of AEs of Grade 3 and above;
- The incidence of SAEs;
- The incidence of AEs leading to permanent drug discontinuation; and
- The incidence of AEs resulting in drug interruption or dose adjustment.

5.3.3.2 Assessment of AEs, Safety Laboratory Parameters and Other Test Results

The clinical safety of the study treatment should be evaluated according to NCI CTC AE Version 4.0 throughout the study period. The occurrence of adverse events of the subjects should be assessed at each clinical visit. The start time of AE, the highest degree of NCI CTC AE, end time, and its causality to the investigational products, impact to the study, whether additional treatment is given, and recovery should be recorded in the electronic case report form (eCRF).

Physical examination should be performed at baseline and at each visit, or its frequency should be increased according to clinical indications. Physical examination parameters should include vital signs (heart rate, blood pressure, body temperature and respiration), body weight and other related organ systems.

12-lead ECG examination should be performed at baseline, on Day 1 of each treatment cycle (except for Cycle 1) and 30 days after EOT. Echocardiography examination should be performed at baseline and on Day 1 of the second treatment cycle. Carcino-embryonic antigen (CEA) examination should be performed at baseline, on Day 1 of each treatment cycle (except for Cycle 1) and 30 days after EOT.

Hematology tests and urinalysis should be performed at baseline, treatment period and the observation period after EOT according to the study schedule.

Test parameters should include:

- Hematology: red blood cells, hemoglobin, neutrophils, platelet count and WBC classification; thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB) and international normalized ratio (INR);
- Urinalysis: pH, specific gravity, protein, urinary casts, white blood cell (quantified), red blood cell (quantified), urine glucose and urine ketone;
- Stool for occult blood test;
- Blood clinical biochemistry: total protein (TP), albumin (ALB), globulin (G), A/G, blood glucose, urea nitrogen, creatinine, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, AST, ALT, calcium, phosphorus, magnesium, potassium, sodium, chloride, amylase and uric acid;
- Routine thyroid function test: should at least include serum free triiodothyronine (fT3), serum free thyroxine (fT4) and thyroid stimulating hormone (TSH);

- 12-lead ECG: including PR interval, QRS time, QT interval, QTc, and diagnosis;
- Particular attention should be paid to left ventricular ejection function evaluation in the echocardiography examination.

5.4 Biomarker Exploratory Study

5.4.1 Biomarker Observation Endpoints

Fruquintinib is a tyrosine kinase inhibitor that blocks the tumor growth by inhibiting tumor angiogenesis. The biomarker study will be conducted to investigate whether there is any biomarker that can predict the efficacy of Fruquintinib in combination with BSC for the treatment of patients with advanced colorectal cancer through retrospective analysis. The biomarker study will be planned to use only tumor biopsy specimens.

Biomarker analysis can be classified as 'nongenetic' (such as related protein) or 'genetic association' (such as related RNA or DNA). In the current study, it is planned to perform the analysis with nongenetic and genetic association. The subjects will be required to sign a separate ICF so that their specimens can be used for gene analysis. During the biomarker analysis, the subject's personal information should be protected to the full extent. For the collection, disposition and transportation of the biomarkers, see the Laboratory Guidance (provided separately).

All the subjects are required to provide previously archived diagnostic biopsy specimens for biomarker analysis, but a specific biopsy is not necessary. Subjects can still enter into the study even though they refuse to provide biomarker specimens or their analysis specimens are unavailable.

5.4.2 Specimen for Biomarker Analysis and Time of Collection

The specimens for biomarker analysis are biopsy specimens:

- Biopsy specimens obtained from previously preserved ones for diagnostic purpose or by other means should be provided by the subjects during screening. The genetic and nongenetic detections can be completed by using the biopsy specimens obtained during screening. Therefore, to complete those two detections, there is no need to collect biopsy specimen repeatedly. Gene detection will be conducted only by using the biopsy specimens from subjects who have signed the separate ICF.

  Acceptable biomarkers include:

  Tumor biopsy specimens can be used to determinate the expression and

mutation (e.g. K-ras mutation, vascular endothelial growth factor and vascular endothelial growth factor receptor, etc.) as DAN origin. Biopsy specimen can also be used for quantitative determination of the expression of protein (e.g. VEGF, HIF-1, etc.) of special interest, so as to investigate the features of the protein related to drug efficacy.

In addition to the above protein and gene listed, other biomarkers possibly related to this study can also be detected. However, the sponsor reserves the right of not perform all or partial of analysis of the above gene biomarkers. The results obtained from the analysis can be associated to those obtained from this study (e.g. clinical efficacy, toxic reactions, etc.).

Subjects can still be enrolled in the study if he/she refuses to provide biomarker specimens or have no biomarker specimens suitable for biomarker detection and analysis.

6 Investigational Products and Administration

6.1 Investigational Products

6.1.1. Drugs Provider

The study drug Fruquintinib capsule and the matching placebo used in this study will be provided by the sponsor.

6.1.2. Specifications and Storage Life of the Investigational Products

Fruquintinib and matching placebo will be manufactured and packaged by the GMP-certified company authorized by the sponsor. The sponsor should be responsible for the technical guidance and quality control.

Table 3 Information of the Investigational Products

Name	Dosage Form	Specification	Administration Method	Storage Life
Fruquintinib	Capsule	5mg	Oral	2 years
Fruquintinib	Capsule	1mg	Oral	2 years
Matching placebo*	Capsule	5mg	Oral	2 years
Matching placebo *	Capsule	1mg	Oral	2 years

**: The appearance of the matching placebo is identical to that of the study drug.*

6.1.3. Labeling of the Investigational Products

For details of sample packaging and labeling, see the Investigator Site File. The drug number on the packaging of the investigational products should be unique.
Re-supply of investigational products during the study will be managed by the IWRS system, and details are specified in the IWRS manual.

6.1.4. Storage of the Investigational Products

All the investigational products shall be stored in a closed, safe and cool place according to the requirements. The storage temperature shall be between 10℃-30℃, and the actual temperature should be documented and kept in the corresponding file.
All the investigational products provided are for research use only in this study.

6.1.5. Randomization of the Investigational Products

Subjects who meet all the inclusion and exclusion criteria confirmed by the investigator will enter the Interactive Web Response System (IWRS). The eligible subjects will be randomized according to the blinding principles at a ratio of 2:1 to receive either Fruquintinib in combination with BSC or matching placebo in combination with BSC. Randomization will be stratified according to the stratified factors: include previous use of VEGF inhibitor (yes vs. no), K-Ras gene status (wild type vs. mutant type). The randomized number of each subject will be provided to the investigator by IWRS.
And the subject shall start the treatment within 2 days after randomization.

6.1.6. Investigational Products Accountability

The investigator/pharmacist/staff responsible for the investigational products accountability must keep record of the drugs sent to the site, inventory quantity in the central inventory, drug quantity consumed by each subject, and return all of the remaining drugs to the sponsor or destroy the drugs according to the requirements.
Records described above will include the date, quantity, serial number (drug number), expiration date (used before XXXX) and the investigational products and the patient's unique study number. In addition, while returning the remaining drugs to the sponsor, the investigator/pharmacist/staff responsible for investigational products accountability should make sure that the subjects have returned all the unused drugs (well packaged) or remaining drugs (with packages already opened) , and that there is no remaining investigational products s at the site.
Drugs used by each subject will be calculated according to the formula: drugs used = drug dispensed - drugs returned - drugs lost.

6.1.7. Investigational Products Disposition

All remaining investigational products and the unused drugs collected from the subjects after the end of study should be returned to the sponsor for destruction; if destruction is performed by the site, the following written documents should be provided:

- Disposing of drug identification (drug number or subject treatment assignment).
- Number of disposing
- Method of disposing
- Signature and date of the person (or institution) responsible for drug disposing.

6.2 Administration Method

6.2.1 Dosage and Cycle

Treatment group: The subjects will receive oral Fruquintinib 5mg, QD for 3 consecutive weeks and then the medication will be interrupted for 1 week. One treatment cycle is 28 days.

Control group: The subjects will receive oral matching placebo 5mg, QD for 3 consecutive weeks and then the medication will be interrupted for 1 week. One treatment cycle is 28 days.

Subjects will receive double blinded study treatment orally according to their dose regimens until the occurrence of PD, death, intolerable toxicity, or withdrawal of informed consent, and conditions that requires for treatment termination such as subject should discontinue the treatment judged by the investigator for the subject's best interests.

6.2.2 Mode of Administration

The drugs should be taken at fasting state with 100-200 mL of tepid water. Each subject should record in the patient diary the date of drug administration and amount of drugs taken. And it is recommended to take the drugs 1 hour before or 2 hours after breakfast.

During the study, every effort should be made to ensure that the subject take the drugs according to the protocol. Should the subject miss the dose in the morning, the missed dose can be taken on the same day at any time before 18:00. However, if the subject misses one dose, and failed to take it in the same day, he/she must take the next prescribed dose on time, and the missed dose will no longer be taken. Missing dose must be recorded in the administration diary, and on the CRF/eCRF.

Smoking, alcohol and caffeinated beverages should be prohibited during the study. Grapefruit, pomelo or drinks containing the above fruits should be avoided during the

study (see Appendix 3).

6.3 Dose Adjustment During the Study

6.3.1 Treatment Principles for Toxicities During the Study

If subjects experience any toxicity during the study, the treatment of toxicity, drug interruption and dose reduction must comply with the following principles. Treatment of toxicity possibly related with Fruquintinib is specified in Section 6.3.2. And dose adjustment due to Fruquintinib related toxicities is specified in Section 6.3.3.

- Should intolerable toxicity occur during the study treatment period, drug interruption should be considered firstly; if the toxicity returns to baseline within 14 days, the dose can be continued or reduced to the last previous dose (for detailed dose adjustment information, see Table 4, Table 4-1 through Table 4-6 in Section 6.6.3); if the toxicity cannot be recovered to baseline within 14 days, it should be considered as the end of the treatment period, and the subject should enter follow-up period;
- Should several AEs occur at the same time, the dose should be adjusted based on the most serious one;
- The time of drug interruption should not be too long, in principle, medication can be continued when the toxicity returned to Grade 1 or baseline level;
- In each dosing cycle, the dose can be adjusted at any time according to the intolerable toxicity. The dose reduced cannot be adjusted again to the previous level; A maximum of two dose adjustments is allowed for each subject (dose can be reduced to 4 mg QD “3 wks on/ 1 wk off” at the first time, and 3mg QD “3 wks on/ 1 wk off” at the second time); if the dose is adjusted to 3mg QD “3 wks on/ 1 wk off”, other dose adjustment is not allowed, but dose interruption is allowed.
- Should dose interruption or dose reduction occur, the treatment cycle will not be adjusted in principle. Total drug administration should not exceed 21 days while continuous drug interruption should not exceed 14 days. Should drug interruption is between 7-14 days during the study treatment period in 1 cycle, a complementary drug administration of no more than 5-day doses can be considered in the first 5 days of drug interruption period (in the last 7 days), but

drug administration is not allowed in the last 2 days of the drug interruption period.

6.3.2 Treatment of Toxic and Side Effects Possibly Related to Fruquintinib

The toxic and side effects possibly related to Fruquintinib according to the investigator shall be treated with corresponding intervention measures by following the treatment principles in Section 6.3.1. The results of Phase I study (2009-013-00CH1) and Phase Ib study (2012-013-00CH3) have indicated that Fruquintinib-related adverse reactions mainly include Hand Foot Syndrome (HFS), hypertension, proteinuria, diarrhea, stomatitis, thrombocytopenia, elevated TSH, fatigue, hoarseness and rash, etc.

Treatment of Hypertension

- ✓ For the treatment principle of anti-hypertensive drugs for mild and moderate hypertension, see the Hypertension Treatment Guidelines (Appendix 6);
- ✓ For the treatment of severe hypertension, please refer to the following procedures: When diastolic BP increases to ≥110mmHg or systolic BP increases to ≥180mmHg, the following procedures should be followed:
  1. Interrupt the investigational product;
  2. Use positive anti-hypertensive therapy;
  3. If damage in target organ occurs, venous anti-hypertensive treatment shall be provided in addition to oral treatment.
  4. If hypertensive crisis occurs, invite relevant experts and personnel to perform BP stabilization and even rescue treatment for the subject;
  5. Consider re-administration of the investigational product when subject BP is reduced to <140/90mmHg.

The investigator should follow the dose adjustment schedule (see Table 4-3) for hypertension occurred during the Fruquintinib treatment. Also, the investigator should monitor hypertension and strongly recommend appropriate measures to effectively control the occurrence of hypertension during the treatment. The selection of antihypertensive drugs should be performed according to investigator's judgment by referring to the hypertensive treatment guideline and combining with the opinions from the cardiologists.

Treatment of Proteinuria

If the subject urine protein was detected with 2+ in urinalysis test during the treatment, please collect 24-hour urine for urine protein quantitation. If urinalysis or 24-hour urine protein quantitation is assessed as NCI CTC AE Grade 1, close monitoring should be performed; if Grade 2 proteinuria presented with 24-hour urine protein quantitation <2g, close monitoring and active treatment should be provided; if 24-hour urine protein quantitation ≥2g, interrupt the investigational product and then continue treatment with reducing dose if toxicity recovers to lower than Grade 1 within 14 days; if toxicity does not recover to Grade 1 after 14 days of drug interruption, the investigational product shall be terminated.

Treatment of Hand-foot Syndrome (HFS)

If the subject presents HFS ≤Grade 2, symptom treatment can be provided. Hands and feet shall avoid friction, pressure and contact with high temperature objects. Keeping the skin of hands and feet moist and using appropriate uremic frost or cream containing lanolin oil is beneficial for symptom alleviation and focus recovery. Subjects with severe symptoms (especially with pain) can apply Shaoshang Zhitong Ruangao (produced by Wuhan Jianmin Pharmaceutical Groups Corp. LTD and provided by the sponsor) or take oral Diclofenac Sodium Enteric-coated Tablets (Voltaren), etc. for symptom alleviation.

If any subject presents HFS of Grade 3 or above (severe skin reaction including exfoliation, blister, edema with pain, which affect daily activities), the drug should be interrupted in accordance with the treatment principle in Section 6.3.1. Drug of previous or reduced dose can be continued if toxicity recovers to lower than Grade 1 within 14 days.

Treatment of Diarrhea

If any subject presents diarrhea of Grade 1-2, either close monitoring or drug therapies for intestinal functions improvement is acceptable; if diarrhea of Grade 3 occurs, Loperamide Hydrochlo-ride Capsules (Imodium) and/or other drugs for improvement of intestinal functions can be used. The event generally will recover in 3 days, and if so, the drug can be continued; for subject fails to recover within 3 days, the drug shall be interrupted.

Treatment of Mucositis

If any subject presents stomatitis of Grade 1-2 (including oral ulcers, mucositis, gingivitis, throat discomfort and angular cheilitis, etc.), local application of antibiotics

(including anaerobic bacteria resistant antibiotics), antifungal agents, mucosal protective agents, local anesthetics, oral antacids as well as Xiguashuang Spray and Yinhuang Jiedu Pian for oral treatment is acceptable, and the investigational product can be continued. Drugs containing iodine and long-term use of hydrogen peroxide should be avoided; soft and nonirritating diet is recommended while spicy, acid and irritating food should be avoided. If the subject cannot swallow food or take liquid diet, parenteral liquid or nutrition support may be needed.

If stomatitis does not recover after treatment and food intake and body weight are affected, the investigational product should be discontinued; continuous drug of previous or reduced dose shall be considered if toxicity recovers to Grade 1 within 14 days.

Treatment of Hypothyroidism and TSH Elevation

If any subject presents hypothyroidism (with or without clinical symptoms) with clinical diagnostic significance, or continuous TSH elevation with clinical symptoms (with or without decrease of T4), hormone replacement therapy (HRT) is recommended.

Treatment of Decreased Platelet Count

If any subject presents decreased platelet count ($<70\times10^9$/L), drug interruption and dynamic observation are recommended; if there is bleeding tendency or the platelet count level fails to recover to Grade 1 or baseline level after 3 days of drug interruption, active treatments for platelet elevation are recommended; infusion of platelet suspension is also suggested for subjects with decreased platelet count of Grade 4.

Treatment of other toxic and side reactions shall be performed in accordance with the above-mentioned principles for toxicities. Appropriate process and treatment should be provided for the subjects' best interests.

6.3.3 Standard for Dose Adjustment Induced by Investigational Products Related Toxicities

Should drug-related toxicities occur, the toxicity shall be classified according to NCI CTC AE Version 4.0. And dose of the Investigational Products should be adjusted according to the following preset doses:

Dose Level 0	5mg	Fruquintinib of 5mg, 1 capsule, or

(Original dose)	once daily	1 capsule of the matching placebo
Dose Level -1 (the 1st dose reduction)	4mg once daily	Fruquintinib of 1mg, 4 capsules, or 4 capsules of the matching placebo
Dose Level -2 (the 2nd dose reduction)	3mg once daily	Fruquintinib of 1mg, 3capsules, or 3 capsules of the matching placebo

The investigational products related toxicities and corresponding dose adjustment regimens are specified in Table 8, among which, toxicities of HFS, proteinuria, hypertension, decreased platelet count, bleeding, and abnormal liver function are excluded from that in Table 4 but listed respectively in Table 4-1 to Table 4-6 specially.

Table 4 Dose Adjustment Induced by Investigational Products Related Toxicities (excluding HFS, proteinuria, hypertension, decreased platelet count, bleeding, and abnormal liver function)[a]

Grade of AE (NCI CTCAE Version 4.0)	Drug Interruption	Dose Adjustment
Grade 1	drug administration as scheduled	No adjustment
Grade 2	drug administration as scheduled	No adjustment
Grade 3[b]	Interrupt the dose until the toxicity returns to ≤Grade 1 or baseline level	Reduce the dose to the last level
Grade 4	Treatment termination	Treatment termination

a: Should any artery thrombosis occur, the treatment should be terminated.

b: including Grade 3 diarrhea and stomatitis, etc. that ineffectively treated by drug therapies, but excluding Grade 3 menstrual cycle extension.

Table 4-1 Dose Adjustment for HFS

AE Grading Standard	Dose Adjustment	Treatment Opinions
Grade 1: numb, paresthesia, dysesthesia, erythema, painless edema, desquamation, thicken skin and hand and foot discomfort which does not affect the normal activities; without any pains	Continue drug treatment with the same dose	Active supportive treatment can be adopted to relieve the symptoms; for example, urea cream can be used.
Grade 2: erythema with pains accompanied by hand and foot	The drug can be interrupted; and the drug can be reduced to	Shaoshang Zhitong Ruangao manufactured by Wuhan

swelling and /or discomfort, which affects normal activities	the last dose level should the AE recovers to Grade 1 within 14 days	Jianmin Pharmaceutical Group Co, Ltd. is recommended.
Grade 3: wet desquamation, ulcer, blister or severe hand and foot pain or severe discomfort which affects work or normal activities.	The drug can be interrupted and then resumed or reduced should AE recover within 7 days; the drug should be reduced to the last dose level if the AE recovers to Grade 1 within 14 days	Should the same AE occur for 3 times or still occurs after 2 times of dose adjustment, the drug should be terminated.

Table 4-2 Dose Adjustment for Proteinuria

AE Grading Standard	Dose Adjustment	Treatment Opinions
Grade 1: Proteinuria + by the urinalysis; 24-hour urine protein quantitation < 1.0g	Continue drug treatment with the same dose	Active treatment can be adopted to relieve the symptoms; for example, urea cream can be used.
Grade 2: Proteinuria ++ by the urinalysis; 24-hour urine protein quantitation is between 1.0-2.0g (excluding 2.0g)	Continue drug treatment with the same dose	Active treatment and urinalysis should be performed (every 1 week), accompanied by nephrology consultation if necessary.
Grade 2: Proteinuria ++ or above by urinalysis; 24-hour urine protein quantitation is between 2.0-3.5g (excluding 3. 5g)	The drug can be interrupted and then reduced to the last dose level should the AE recovers to Grade 1 within 14 days	Active treatment should be performed, accompanied by nephrology consultation if necessary;
Grade 3: 24-hour urine protein quantitation ≥3.5g	The drug can be interrupted and then reduced to the last dose should the AE recovers to Grade 1 within 14 days	Active treatment should be performed, accompanied by nephrology consultation if necessary; and the drug should be terminated should the AE occur for the 3rd time.

Table 4-3 Dose Adjustment for Hypertension (patients that receiving anti-pressure treatment at baseline should monitor blood pressure after antihypertensive drug administration once daily)

AE Grading and Definitions	antihypertensive therapy	Dose of Fruquintinib
Grade 1: prehypertension: (systolic pressure of 120-139mmHg or	None	Continue drug treatment of with the same dose.

diastolic pressure of 80-89mmHg)		
Grade 2: SBP of 140-159mmHg or DBP of 90-89mmHg; or DBP symptomatic increase >20mmHg	Treatment objective: keep the BP at the level of lower than 140/90mmHg. If the patient has received the antihypertensive treatment, the dose of the antihypertensive drug should be increased or adopt other antihypertensive therapies; If the patient does not receive any antihypertensive treatment, a single antihypertensive therapy should be used.	Continue drug treatment with the same dose. For the use and dose adjustment of antihypertensive drugs, please refer to the antihypertensive drug treatment guideline and invite the nephrology for consultation if necessary.
Grade 3: SBP of 140-159mmHg or DBP of 90-89mmHg; or DBP symptomatic increase by >20mmHg	Treatment objective: keep the blood pressure at the level of lower than 140/90mmHg. Start to use antihypertensive drug or increase the dose of the antihypertensive drug in use or adopt other antihypertensive therapies additionally; For the use and dose adjustment of antihypertensive drugs, please refer to the antihypertensive drug treatment guideline and ask the nephrologist for help if necessary.	For patient with BP exceeding 160/100mm Hg for more than 7 days after using antihypertensive drug or adjusting the dose of the drug in use, Fruquintinib should be interrupted; Should the BP of the patient recover to Grade 1 or the baseline level, one time of dose reduction shall be made.
Grade 4: Life threatening (such as malignant hypertension, temporary or permanent neurological deficits and hypertensive crisis)	Emergent medical treatment	The drug should be terminated.

1097

1098 **Table 4-4 Dose Adjustment for Decreased Platelet Count**

AE Grading	Dose Adjustment	Treatment Opinions
Grade 1: Platelet Count of 100~75×10^9/L	Continue drug treatment with the same dose	Perform follow up visit as scheduled.
Grade 2: Platelet Count of 75~50×10^9/L	The drug can be interrupted and continue the drug treatment with the same dose should the AE recovers to Grade 1 or baseline level within 7 days	Hematology examination should be performed every 2-3 days; active treatment for platelet elevation is recommended. Hematology examination should be performed once every week in the follow up visit.

	The drug can be interrupted and then reduced to the last dose level should the AE recovers to Grade 1 or baseline level within 7-14 days	Hematology examination should be performed every 2-3 days; active treatment for platelet elevation is recommended. Hematology examination should be performed once every week in the follow up visit.
Grade 3: Platelet Count of 50~25×10^9/L	The drug can be interrupted and reduced to the last dose level should the AE recovers to Grade 1 or baseline level within 14 days.	Hematology examination should be performed every 2-3 days; active treatment of platelet elevation or infusion of platelets suspension is recommended. Hematology examination should be performed once every week in the follow up visit.
Grade 4: Platelet Count <25×10^9/L	The study treatment should be terminated	Hematology examination should be performed once daily until the AE recovers to Grade 2 or a lower grade; infusion of platelets suspension or other active treatment should be provided

Table 4-5 Dose Adjustment for Bleeding in Any Site

AE Grading	Dose Adjustment	Treatment Opinions
Grade 1	Continue drug treatment with the same dose	Perform follow up visit as scheduled.
Grade 2	The drug can be interrupted and then reduced to the last dose level should the AE recover to Grade 1 or lower level within 14 days.	Active treatment
Grade 3 or above	The study treatment should be terminated.	Emergent medical intervention.

Table 4-6 Dose Adjustment for Abnormal Liver Function (including clinically significant abnormalities such as increasing of ALT, AST or total bilirubin)[a]

AE Grading	Dose Adjustment	Treatment Opinions
Grade 1	Continue drug treatment with the same dose.	Perform follow up visit as scheduled.
Grade 2 (with normal baseline value)	Drug interruption can be considered, and the dose should be reduced to the last dose level if the AE recovers to Grade 1 or baseline within 14 days.	Active liver protection treatment should be provided, and the liver function should be monitored closely once every week.
Grade 2 (with abnormal	Continue drug treatment with the same dose.	Active liver protection treatment should be provided, and the liver function should be

baseline value)		monitored closely once every week.
Grade 3	The drug can be interrupted and then reduced to the last dose level should the AE recovers to Grade 1 or baseline within 14 days.	Active liver protection treatment should be provided, and the liver function should be monitored closely (twice every week until the toxicity recovers to Grade 1, baseline level or can be reasonably explained).
Grade 4	The study treatment should be terminated.	Active liver protection treatment should be provided, and the liver function should be monitored closely (twice every week until the toxicity recovers to Grade 1, baseline level or can be reasonably explained).

a: Should total bilirubin >2×ULN and/or aminopherase >3×ULN occur in patients with normal baseline values, or total bilirubin > 2×baseline value and/or aminopherase >3× baseline value occurs in patients with abnormal baseline values, please report it as special event and provide treatment to the patient according to the Protocol.

6.3.4 Treatment of Drug Overdose

If overdose (defined as administration of more than one dose within 24 hours, i.e. from 8 am to 8 am of the next day) occurs, symptomatic and supportive treatment should be provided.

If the dose of the investigational product exceeds the dose specified in the study protocol, but with no corresponding symptoms or signs presents, it is required to report as protocol violation. If overdose accompanied by AE occurs, the AE shall be recorded in “AE Form”.

6.4 Blinding

The subjects will be randomized to either Fruquintinib treatment group or the corresponding placebo treatment group using double-blind method. The drug administered for treatment remains unknown for investigator, the sponsor and the subjects. The allocated randomized numbers are based upon the information provided by IWRS.

Fruquintinib and its matching placebo present identical appearance to ensure the implementation of blinding and the subject shall take 1 capsule of 5mg, PO, QD. For the purpose of blinding, the investigational product (Fruquintinib or corresponding placebo) shall be marked by unique drug numbers which are pre-printed on each package bottle, and be distributed to each subject through the IWRS.

Emergency unblinding: unblinding shall be performed only under emergency circumstances. On condition that unblinding is required for treating SAE of a certain subject, project leader from the sponsor must be contacted by PI in advance before unblinding. Unblinding of the subjects shall be performed by PI through IWRS

system.

6.5 Concomitant Treatment

Subjects are not allowed to receive other antineoplastic treatment, including cytotoxic drugs (except for non-antineoplastic chemotherapy), radiotherapy (except for palliative radiotherapy for symptom control), biotherapy, endocrine therapy or any other study treatment during the enrollment and the whole process of this study. Traditional Chinese Medicine with antineoplastic indications is prohibited during this study (see Appendix 3). Systemic antineoplastic treatment and treatment with other investigational products must be terminated at least 4 weeks before the subject's enrollment of this study.

6.6 Other Concomitant Treatments

The investigator should comply with the following guiding principles, cautiously select concomitant medication during the study and make every effort to protect the safety of the subjects.

- According to the investigator's judgment, for the sake of subject's health, all drugs with the expectation of not interfering with the study assessment can be used. All the concomitant treatments (include start/end date, route and indications) must be recorded in subject's original medical record and CRF.
- Fruquintinib has been proved to be metabolized through hepatic cytochrome P450 3A4 according to pre-clinical study. Strong inducers of enzyme CYP3A4 such as Phenytoin, Phenobarbital, Rifampin and other drugs (not limited to the above-mentioned drugs) as well as strong inhibitors of enzyme CYP3A4 such as Ketoconazole, Itraconazole, Fluconazole, Indinavir, Erythromycin, etc. (not limited to the above-mentioned drugs) may significantly influence the in vivo metabolism of Fruquintinib. Investigators should be cautious for enrollment of the subjects received confirmed combination with inducers and inhibitors of enzyme CYP3A4. If concomitant medication of the above type is applied during the study, cautions are required as well as close monitoring of drug exposure and adverse reactions. See Appendix 3 for detailed information.
- Subjects are allowed to take anticoagulants (e.g. Warfarin) during the treatment period while monitoring of relevant coagulation indicators such as INR is required; LMWH Sodium is acceptable when required by the treatment;

All drugs used including the study drug during the process of treatment should be recorded in the CRF/eCRF.

6.7 Treatment Compliance

The investigators should record the amount and date of investigational products dispensing and collection, as well as actual dose of administration of each subject timely and accurately. The actual dose of administration should be consistent with the dose required in the Protocol. Drug treatment compliance shall be determined according to the amount of drug dispensed and collected from each subjects and the amount of drug lost by the subject at the end of each treatment cycle and at the time of study withdrawal. And self-reported dose missing/overdose/drug losing etc. from the subjects shall also be determined comprehensively.
The patients are required to return all bottles of used and unused investigational products to the site at the end of treatment for compliance assessment. All remaining materials and drugs must be returned to the sponsor at the end of study.

7 Safety

7.1 Safety Parameters and Definitions

7.1.1 Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence occurring after the patient has received the medication, regardless of whether or not considered related to the investigational products. Therefore, an AE can be any adverse or untoward sign (including laboratory abnormalities), symptom or disease which has a temporal relationship with the medication but is not necessarily related to the drug.
In addition, AEs also include complications induced by medical intervention regulated in the Protocol. For instance, complications induced by biopsy and other invasive operations, and worsening of the disease that considered by the investigator as pre-existed during AE reporting (except for tumor progression) are also considered as AE.

7.1.2 Serious Adverse Events (SAEs)

Serious adverse event (SAE) refers to any AE that meets at least one of the following criteria:
- **Results in death:** AE resulting in death of the subject, excluding death resulted from PD, unless it was considered to be related to the use of test drug or administration system according to the investigator;
- **Is life-threatening:** this refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it became more severe.

- **Requires hospitalization or prolongation of an existing hospitalization:** AE results in hospitalization treatment (not including emergency or outpatient treatment), or that occurs during hospitalization of the subject and prolongs the existing hospitalization;
- **Results in persistent or significant disability or incapacity:** AE results in substantial harm to the subject's capacity of conducting daily activities (incapacity does not include events with secondary clinical significance, such as headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g. ankle strain, etc.);
- **Is a congenital abnormality or birth defect:** A congenital abnormality or birth defect exists in the newborn (fetus) or born (aborted) by a female subject with drug exposure or the female companion of a male subject with drug exposure;
- **Other important medical events:** An important medical event may not result in immediate risk to life, death or hospitalization. However, it may jeopardize the subjects or require immediate medical interventions such as drug or surgical treatments to prevent the occurrence of the above-mentioned outcomes (death of subjects, life-threatening, result in hospitalization, prolonged hospitalization, and result in persistent or significant disability or incapacity and congenital abnormality).

7.1.3 Special Events Stipulated in the Protocol

The sponsor shall provide continuous close monitoring on potential drug-induced liver damage even though it is rare.

Close monitoring of blood biochemistry should be performed if the subject presents the following condition:

The subject presents elevation of ALT or AST over 3 times of the normal value with normal transaminase at baseline, or elevation of ALT or AST over twice of baseline value with increased transaminase at baseline, close monitoring of blood biochemistry parameters (ALT, AST, ALP and TBiL) should be performed and the frequency of monitoring should be increased (1-2 times/week);

For subject presenting early symptoms of liver damage (such as anorexia, nausea, vomiting, discomfort in upper right stomach, and fatigue, etc.) before detection of abnormal blood biochemistry, immediate blood biochemistry test should be performed and the frequency of monitoring should be increased if above-mentioned abnormalities occur.

Special events regulated by the Protocol are as follows:

- Subjects presenting normal hepatic function (ALT, AST and bilirubin are all within their normal ranges) at baseline is tested with AST and/or ALT elevation >3×ULN combined with TBiL elevation >2×ULN by using the same blood sample collected.
- Subjects presenting increased transaminase at baseline is detected with AST

and/or ALT elevation >twice of baseline value combined with TBiL elevation >2×ULN by using the same blood sample collected.

When subject presents the above-mentioned special events, close monitoring of blood biochemistry parameters (ALT, AST, ALP and TBiL) should be performed and the frequency of monitoring should be increased (1-2 times/week).

In addition, for subject presenting early symptoms of liver damage (such as anorexia, nausea, vomiting, discomfort in upper right stomach, and weakness, etc.) before detection of abnormal blood biochemistry, immediate blood biochemistry test should be performed. And frequency of monitoring should be increased if the requirements of special events specified in the Protocol are met.

7.2 Safety Parameters Collection and Assessment

7.2.1 Definition of AE Reporting Time

Table 5 Definition of AE Reporting Time

Time Period	Reporting Requirements
Since signing the ICF to the time before first administration of the investigational product	Report all SAEs
Since administration of the first dose till 30days after the final dose of the investigational products	Record all AEs and SAE (including special events regulated by protocol).
Post-treatment period (since 30 day after the final dose till the end of the study)	Report only SAE considered to be related to the investigational products.

7.2.2 AE Severity Assessment

The severity of all AEs shall be graded into 5 grades (Grade 1 to Grade 5) in accordance with NCI CTC AE V4.0. AEs not listed in NCI CTC AE shall be determined according to the following table (Table 6).

Table 6 Determination of AE Severity

CTC Grading	Equivalent to	Definition
1	Mild	Discomforts are observed while regular daily activities not affected.
2	Moderate	Discomforts are sufficient to reduce or affect daily activities: treatment or medical intervention is not adopted, even though they are capable of improving life quality of the patient or relieving symptoms

CTC Grading	Equivalent to	Definition
3	Severe	Incapable of working or fulfilling daily activity, treatment or medical intervention has been adopted to improve life quality of the subject or relieve symptoms, treatment delay will not place the patient in immediate risk of death
4	Life-threatening or incapacitating	With immediate risk of death or permanent mental or physical damage, incapable of working or fulfilling daily activities, treatment or medical intervention is required to sustain life
5	Fatal	AEs resulting in death

The seriousness and severity of AEs should be differentiated. Severity refers to the intense extent of AEs (e.g. mild, moderate or severe headache) while the event itself presents comparatively slight clinical significance (e.g. severe headache) and cannot be determined as SAE unless it conforms to the criteria of SAE. Therefore, seriousness and severity should be evaluated independently during AE/SAE recording.

7.2.3 Drug-event Relationship

The relationship of the investigational product with AE and the role of the investigational products in AE can be classified as 4 categories of definitely unrelated, unlikely related, possibly related and definitely related. The following classification and criteria can be referred to for determination:

1. Definitely unrelated: Other factors (other diseases, tumor progression, environment, or other drugs, etc.) are determined as the cause after medical judgment.
2. Unlikely related: The investigational product is considered unlikely related to AE after medical judgment:
   a) No temporal relationship exists between the drug application and occurrence of AE.
   b) AE may be caused by other factors such as change of disease course, environment or use of other drugs for treatment.
   c) Occurrence of AE is unrelated to the known characteristics of the drug.
   d) AE does not recur or aggravate after investigational product re-administration.
3. Possibly related: (the previous two items are a necessary condition) if the following conditions are met after medical judgment, AE is considered to be

possibly related to the investigational product.

a) Temporal relationship exists between the drug application and AE occurrence.

b) The causality between AE and change of course of disease, environment or application of other drugs for treatment cannot be excluded.

c) Occurrence of AE is consistent to the known characteristics of the drug.

4. Definitely related: (the first 3 items are indispensible) if the following conditions are met after medical judgment, AE is considered to be related to the investigational product:

a) Obvious temporal relationship exists between drug application and AE occurrence.

b) AE cannot be interpreted by factors like change of disease course, environment or application of other drugs for treatment.

c) AE disappears or relieves after dose reducing or drug interruption, and recurs after drug re-administration.

d) Occurrence of AE is consistent to the known characteristics of the drug.

During SAE report, if the SAE is judged as unlikely related or definitely unrelated, the investigator is required to provide other potential causes leading to the SAE. If the Investigator's judgment is possibly related or definitely related, reasonable possibility must be provided to explain that the SAE is caused by the investigational product.

7.3 Recording and Reporting of Safety Parameters**AE Recording**

During the AE reporting period stipulated in the Protocol, the investigator is responsible for collecting all AEs and recording them in the CRF/eCRF. In terms of AE recording, the investigators should use correct and normative medical terminology and avoid spoken language and abbreviations. The content of record should include the start time of AE, the highest degree of NCI CTC AE grading, end time, causality with the study drug, influence to the study, whether concomitant therapy exist and recovering conditions.

Diagnosis vs. Symptoms and Signs

If diagnosis exists, the result should be recorded rather than single symptom and sign (e.g. record of hepatic dysfunction, rather than separate record of elevation of transaminase and asterixis; record of acute pancreatitis rather than separate record of the abdominal pain, abdominal distension, vomiting and elevation of amylase). However, if the symptoms and signs cannot be categorized as a single diagnosis during reporting period, each single event should be recorded as an AE. On condition that the diagnosis is confirmed afterwards, CRF/eCRF should be updated for

diagnosis recording.

AEs Secondary to Other Events

Generally, the primary events should be recorded for AEs secondary to other events (e.g. induced by other events or clinical sequelae), unless the secondary events present more severe in severity or become SAEs.

However, the secondary events with obvious clinical significance should be recorded as independent AEs if they have different time of occurrence with the primary events. If the causality between the secondary events and primary events remains unclear they should be recorded respectively.

Continuous, Intermittent or Single AE (Frequency of AE)

Continuous AE refers to an AE exists continuously through the whole process without remission, for example, a continuous upper respiratory infection which lasts for 5 days. This type of AE should be recorded in the CRF/eCRF once only. The highest grade of severity throughout the event should be recorded during severity assessment.

Intermittent AE refers to an AE without outcome with obvious clinical significance but presents occasional variation or remission in terms of symptoms, signs or laboratory tests through the whole process, for example, nausea and vomiting continuing for days and alleviates comparatively during the process; subjects with hypertension presents comparatively continuous course of disease during multiple BP tests despite of intermittent remission. This type of AE should be recorded in CRF/eCRF for only one time. The highest grade of severity throughout the event should be recorded during severity assessment.

Single AE refers to an AE that can logically only occurs individually, or occurs only once independently during the study, such as an accident of falling down that the subject experiences during the period of drug administration or one occasional vomiting that the subject experiences during the trial. This type of AE should be recorded in the CRF/eCRF only once.

It's important to note that if the above-mentioned AEs have presented recovery with obvious clinical significance, and the subsequent identical AE is considered to have no consistency in terms of disease course with the previous case, the two events should be recorded respectively in the CRF/eCRF.

Laboratory Results and Vital Signs Abnormalities

All the results of laboratory tests can be recorded on the page for laboratory results in the CRF. Not all the laboratory tests/vital signs abnormalities are required for AE

recording. The Investigator is responsible for reviewing all the laboratory results and vital signs abnormalities, and determining whether to record them as AE after medical judgment. If any of the above-mentioned abnormalities present obvious clinical significance, or at least one of the following conditions occur, AEs should be recored:

- Accompanied by clinical symptoms
- Leading to change of study drug application (e.g. dose adjustment, interruption or termination)
- Require medical intervention or concomitant treatment alteration (e.g.: increase, interruption, discontinuation or other change of concomitant medication, treatment or process).
- Having obvious clinical significance according to the investigator.

If the laboratory results or vital signs abnormalities with clinical significance are the representations (such as elevation of ALT/AST and hemobilirubin resulted from damage of hepatic function) of a certain disease or syndrome, only the diagnosis (damage of hepatic function) should be recorded in the AE Record of the CRF/eCRF. Otherwise, the laboratory results or vital signs abnormalities should be recorded in the AE Record of the CRF/eCRF and specify whether the tested value is higher or lower than the normal range requires specification (e.g.: record as “serum potassium elevation” rather than “serum potassium abnormality”). If standard clinical terminology corresponding to the laboratory tests or vital signs abnormalities exists, the terminology (e.g. serum potassium elevation up to 7.0 mmol/L should be recorded as “hyperkalemia”) should be recorded in CRF/eCRF.

Progressive Disease

Event definitely consistent with the anticipated progression pattern of primary tumor should not be considered as AE. Hospitalization induced by simply PD is not considered as an SAE. If symptoms cannot be confirmed to be completely induced by PD or does not consist with the anticipated progression pattern of tumor, the relevant clinical symptoms can be recorded as AE.

Death

As for the recording of death event, if AEs leading to death exist, they should be recorded in the CRF/eCRF and the event should be considered as SAE for expedited reporting. If the cause of death remains unknown, “cause of death unknown” should be recorded in firstly CRF/eCRF and considered as SAE for expedited reporting and then the exact cause of death should be investigated further. The record/report should

be updated when the cause of death is confirmed.

Pre-existing Medical Conditions

The pre-existing condition of subject during the study screening shall be recorded as AE only if the degree of severity, frequency and nature has worsened (except for deterioration of the disease under study) after enrollment. Change from the previous condition should be documented in the record, such as "increased frequency of headache", 'hypertension exacerbation', etc.

Hospitalization or Prolonged Hospitalization

Any AE leading to hospitalization or prolonged hospitalization should be recorded and reported as SAE, except for the following conditions:

- Scheduled hospitalization or prolonged hospitalization as required by the Protocol (e.g. for drug administration and efficacy assessment, etc.)
- Hospitalization due to pre-existing and unchanged medical condition before participation in the study, such as scheduled selective surgery or treatment before enrollment of the study; subject hospitalization as scheduled to receive surgery or other treatments during the study shall not be considered as AE.

Surgery

If the surgery-treated disease is cleared out, this disease should be recorded as AE, but not surgery itself (e.g. subject experiences the inguinal hernia repair, AE should be recorded as 'inguinal hernia', but not 'inguinal hernia repair'); if the cause of surgery is unknown, the surgery can be recorded as AE (e.g. for subject experiences abbreviated laparotomy, abbreviated laparotomy can be recorded as AE).

Pregnancy

If female subject becomes pregnant during the study, the IP should be terminated immediately and the investigator should be informed. The Investigator should report it to the Sponsor within 24 hours, and discuss the risk of pregnancy continuation and potential impact on the fetus with the subject. Monitoring of the subject should be continued to the end of pregnancy. All pregnancies within 30 days after the last dose of the IP should be reported to the Investigator.

Abortion should be recorded and reported as SAE whether it is artificial or spontaneous. Any congenital abnormality/birth defect of the infant born by female subject or female partners of male subjects that have used the IP should be recorded and reported as SAE.

7.3.2. Expedited Reporting of SAEs

If any SAE is discovered by the investigator during the course of study, regardless of whether it is related to the investigational product, a finished SAE Report should be submitted to drug administration of relevant province, autonomous region and municipality as well as China Food and Drug Administration (CFDA), informed of the sponsor and reported immediately to Ethics Committee within 24 hours after awareness of the SAE. The Investigator should finish and submit the follow-up report within the same time limit after obtaining the follow-up information. When a non-serious adverse event progresses into an SAE, the SAE and relevant follow-up report should also be reported within 24 hours. Proper treatment is required for all SAEs, regardless of whether related to the IPs, until the subject has recovered from the event or the event has become less urgent or the condition has become stable according to the investigator.

To ensure the sponsor's timely and full access to the safety data, the Investigator should fill out the *Clinical Trial SAE Report* provided by the sponsor in addition to the *SAE Report* provided by CFDA for all SAEs and submit them to the sponsor designated CRO company by the by fax or email within 24 hours. Investigator should actively cooperate with the sponsor to conduct the SAE survey and provide relevant information and medical recordings.

7.3.3. Reporting of Special Events Stipulated by the Protocol

All the special events stipulated by protocol should be reported to the Sponsor regardless of whether they are SAEs or related to the investigational product.

- Events conforming to the requirements of SAE should be reported according to the SAE expedited reporting procedures (see Section 7.3.2);
- For events not conforming to the requirements of SAE, please complete the required SAE report and submit it by fax or email to the CRO company designated by sponsor within 24 hours.

7.4 Subjects Follow-up

7.4.1 Follow up of AEs

The Investigator should follow-up all AEs until occurrence of any of the following conditions:

- AE is relieved or improved to baseline level.
- No further anticipated improvement will present according to the investigator.
- Death of the subject.

- Lost contact with the subject.
- The AE is unrelated to study treatment according to the investigator.
- Subject initiates new anticancer treatment
- No clinical or safety data will be collected any more, or database are finally closed.

The final outcome (including AE remission or date of death) of each AE is required to be recorded in the CRF/eCRF.

7.4.2 Follow up of SAEs

The tracking and follow-up of subjects with SAEs by the investigator will not only help to protect subjects' safety (active treatment, tracking the disease condition), but also help to collect information on SAE as much as possible. The investigator should keep positive close aware of the disease initiatively, provide necessary treatments, and collect complete case information and follow up and report the information timely.

When the causality that SAE is related to investigational product is completely excluded, the investigator may no longer collect information on that SAE; when the causality cannot be excluded, the investigator should continue tracking and following up until the death of the subject, SAE recovery or lost of follow up, and the information required in SAE reporting should be completed at the same time.

7.4.3 Follow-up of Special Events Regulated by the Protocol

For all special events regulated by protocol, follow-ups should be performed with reference to the *Clinical Evaluation of Liver Damage* provided in Appendix 5 in addition to regular SAE follow-ups, so as to obtain more effective information for the evaluation of this type of events.

7.5 Emergency Unblinding

The principal investigator of the site should determine whether to perform emergency unblinding by combining the actual emergency condition and need of rescue once major safety event occur. Unblinding should be performed with IWRS after informing of the clinical head from the project leader of the sponsor when necessary. Once unblinding is performed, treatment for that subject shall be terminated.

8 Statistical Analysis Plan

8.1 Primary and Secondary Endpoints

8.1.1 Efficacy Endpoint

Primary Endpoint:

Survival: defined as time from date (days) of randomization to death caused by any reason. For any subjects without report of death at the time of analysis, his/her last follow up date of known survival will be considered as censored date.

Secondary Endpoints:

Secondary efficacy endpoints include PFS, tumor ORR, DCR, DOR and duration of SD.

Progression-free Survival: refers to the time interval between the randomized date and the initial record of PD or date of death whichever comes first. The presence of PD shall be determined in accordance with the result of evaluation performed by the investigator with RECIST v1.1. For patients who do not present PD or death, the censored date will be the date of final tumor evaluation. For patients who did not perform tumor evaluation at post-baseline stage, the censored date will be the next day after the randomization date (randomization date+1 day). The imaging results demonstrating PD should be obtained as far as possible.

Tumor ORR: defined as the occurrence rate of confirmed Complete Response (CR) or Partial Response (PR). The target lesions and non-target lesions are evaluated with confirmed radiological method and determined by RECIST v1.1. Subjects who have not performed tumor evaluation at post-baseline stage shall be regarded as patients without response. Subjects who are qualified for evaluation of CR or PR should have at least one available lesion for measurement with RECIST v1.1.

DCR: defined as the occurrence rate of confirmed CR, PR and SD. The target lesions and non-target lesions are evaluated with confirmed radiological method and determined by RECIST v1.1.

Duration of PR: defined as the time (days) from the first time that the objective response reaches PR or CR, whichever comes first, until the occurrence of PD or death (if the death of the subject occurs before recording the PD). The duration of response is just applied to effective patient who presents CR or PR. The calculation is performed based on the actual completion date of tumor scan. The date of last tumor

evaluation will be considered as truncation for patients without PD or death at the time of analysis.

Duration of stable disease: (only for evaluation of subjects whose BRS have not reached CR or PR): defined as time (days) from date of randomization to the time of first record of PD or death (if death of the subject occurs before recording of PD). The calculation is performed based on the actual completion date of the tumor scan. The date of last tumor evaluation will be considered as truncation for patients without PD or death at the time of analysis.

8.1.2 Safety Endpoints:

Safety endpoints shall include AE, laboratory tests, vital signs and weight, ECG, UCG (especially left ventricular ejection fraction [LVEF]) and ECOG PS. All the subjects who have received treatment for at least once shall be included in the safety assessment.

All the adverse events, whether related to the drug or not, will be recorded in the CRF including the start/end date, measures taken, treatment effected (yes vs. no) and the outcome. For all the events, the causality with the treatment and the severity will be determined by the investigator.

8.2 Statistics and Analysis Method

8.2.1. Statistical Model

Primary efficacy endpoint: OS

Stratified log-rank test will be used for the comparison of OS of the Fruquintinib with placebo group at a two-sided significance level of 0.05. The same factors used for randomization will be used for stratification: prior use of VEGF inhibitor (yes vs. no), K-Ras gene state (wild type vs. mutant type).

Unstratified log-rank test result will be provided as well. For the median survival time (MST) in each treatment group, Kaplan-Meier estimates will be presented with curves to provide visually intuitive description of the difference between treatment groups. The estimation of treatment effects will be presented by the Hazard Ratio (HR) estimated by stratified COX model in a 95% Confidential Interval (CI). OS analysis will be performed for the ITT population.

Secondary endpoints: PFS, ORR, DCR, duration of response or stable disease (DOR)

For the median PFS in each treatment group, Kaplan-Meier estimation will be

presented with curves to provide visually intuitive description of the difference between the 2 treatment groups. The estimation of treatment effects will be presented by Hazard Ratio (HR) estimated by stratified COX model in a 95% Confidential Interval (CI). The analysis of PFS will be based on ITT set.

DCR and ORR analysis will be performed based on the subjects of ITT population with measurable lesions of baseline disease. The estimated value of DCR and ORR in each treatment group and their 95% CI are calculated separately. Comparison of CR between treatment groups is performed using stratified Mantel-Haensze test. The CI of CR difference between treatment groups shall be calculated using the approximate normal distribution method of binomial distribution.

Duration of response (DOR) only applies for patients who have responded to the treatment. Statistical test will not be conducted as patients with response are not randomized. Descriptive analysis will be adopted for DOR. For each treatment group, results will be presented by Kaplan-Meier estimates and distribution curve. Similar analysis method will also be used for duration of SD.

8.2.2. Types of Analysis

8.2.1.1 Efficacy Analysis

Intention to Treat (ITT) Set: The ITT population, including all randomized patients, will be analyzed by randomized treatment group according to the principle of intention-to-treat.

Safety Analysis Set (SAS): All randomized patients that received at least one time of IP treatment should be included in the SAS.

8.2.1.2 Safety Data Analysis

Safety population includes patients who have received at least one time of study treatment after signing the ICF. All safety parameters shall be summarized and listed by using the safety population.

Frequency table (overall and intensity classification) shall be listed in accordance with classification of human body systems for treatment emergent adverse events (TEAE) data. In the list of overall TEAE occurrence rate, subjects presented the same TEAE for more than once shall be calculated once only in the frequency table.

Laboratory data shall summarized by using statement changes and frequency table at the same time by each sampling time point. All TEAEs and abnormal laboratory variables shall be evaluated by the NCI CTC AE Version 4.0 Classification System.

ECOG PS will be summarized by using Descriptive statistics. Vital signs, ECG and UCG shall be listed.

8.3 Statistical Analysis Plan

See Statistical Analysis Plan (SAP) for details.

OS analysis: OS will be analyzed and then the study will be finally summarized after 280 OS events are observed after 7 months of follow-up after the enrollment of the last patient.

8.4 Sample Size

The number of primary endpoint (events) required for efficacy assessment is calculated based on the following assumptions:

- A two-sided significance level of 0.05;
- An 80% test power will be ensured when the true HR of treatment group/control group is 0.7, in other words, the median OS time is extended from 6.3 months to 9 months;
- An enrollment rate of 30 subjects per month, which should be achieved within 3 months after trial initiation;

Under the premise of these assumptions, approximately 400 subjects will be enrolled in nearly 15 months in this study. OS will be analyzed and then the study will be finally summarized when 280 OS events are observed in 7 months after the end of enrollment.

Meanwhile the sample size will be adjusted according to the result of Phase II intestinal cancer clinical trial of Fruquintinib (POC) and the overall survival data of the latest third-line and above placebo treatments for advance intestinal cancer at that time.

9 Data Quality Assurance

Electronic data management system will be used in this study.

Access permission: Data administrators shall create account respectively for different identities including the investigator, sponsor, monitor and auditor, etc. and grant different access permission, e.g. the investigator of each site can access only the content of their own site and is granted with the right of data modification. The sponsor is limited to browse the data of all cases only; and monitors and auditors can review the case conditions of all sites with permission of inserting comments and raising queries but has no right of data modification.

Data entry: The clinical investigator or data entry personnel (clinical coordinator) designated by the investigator shall input the data in study medical record to eCRF timely and accurately. eCRF shall not be used as original record and the content is originally from “study medical record”.

Data queries and answers: the monitor can propose queries online when problems are found during the monitoring. And investigators shall answer the queries online and correct data errors. The monitors are allowed to propose repetitive queries under necessary conditions.

Data locking and output: The data administrator shall perform data locking after accuracy confirmation of monitors when each subject has completed the study, until the completion of data locking for the last subject. When all data is locked, it shall be imported to designated database by data administrator and submitted to statistical staff for statistical analysis.

When the study is completed, eCRF and all queries shall be archived in burned discs as necessary. The data management center shall reserve the electronic data till 5 years after the marketing of the drug and during which, the data management center can unlock the system at any time after appointment of CFDA for inspection.

10 Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) shall be established in this study. The subjects’ safety will be determined by the evaluation of risk/benefit at regular data review meeting. At the same time, DMC will formally recommend whether to continue or terminate the study.

The committee will consist of at least 3 independent oncologists and 1 independent statistician. The data review meetings will be regularly held as specified in the DMC

agreement. The study enrollment will continue during the DMC meetings.

Upon completion of data review, DMC shall provide suggestions on whether to continue the study or not, whether modification of the protocol or study termination is required. The final decision shall be made by Hutchison Medi Pharma Ltd.

11 Ethics

11.1 Local Regulations/Declaration of Helsinki

The investigator shall guarantee that the study will be conducted in full compliance with "Declaration of Helsinki" as well as the local laws and regulations, and make every effort to protect the subjects. The study must keep full compliance with the principle of "Good Clinical Practice" (since Jan. 1997) in ICH three-way guideline or local laws and provide subjects protection to a larger extent.

11.2 Informed Consent

The responsibility of investigators or the personnel designated by investigators (if permitted by local law) is to obtain the written ICF from the subjects participating in the study after adequate explanation of study objectives, methods, expected benefits and potential risks. For patients that unqualified or unable to provide legal consent, written ICF must be obtained from his/her legal guardian. If the patient and his/her legal guardian cannot read, a notary public must be on the spot during the whole process of informed consent. With verbal consent of study participation from the patient and his/her legal guardian, the notary public shall sign the ICF to demonstrate the accurate explanation and full understanding of the information in it. Investigators and other designated personnel are also required to make the subjects understand that they can refuse participating in or withdraw from the study for whatever reason at any time. The CRF of this study contains a certain part for recording the patients' informed consent and it should be completed appropriately. If new safety information induces significant change of risk/benefit evaluation, the ICF shall be updated when necessary. All patients (including patients receiving treatment) should be informed with the new information and provided with a modified ICF. Their consent of continuous participation in the study should be obtained.

11.3 Independent Ethics Committee (IEC)/Institution Review Board

(IRB)

The study protocol, other related materials (such as Address to the Patients or study description), advertisements and compensations provided to the patients shall be submitted to the Ethics Committee by the investigator. EC approval must be obtained before starting the study and recorded in the form of letters to the investigators, including dates of EC meeting and approval.

Any modification to the study protocol after receiving the EC approval letter shall be submitted to the Ethics Committee by the investigator according to the applicable procedures as well as laws and regulations.

12 Protocol Modification

The study protocol and procedure shall not be changed without consent from both the investigator and the sponsor.

If the study protocol requires modification, the modified content or updated version (modified version) of the protocol shall be submitted to the Ethics Committee for written approval before implementation. Besides, the modified protocol shall be submitted to the local drug administration or obtain its approval when required and requirements of local departments must be complied.

If modification of site ICF is required due to protocol modification, the sponsor and the site Ethics Committee must be informed. The modified ICF must be approved by the Ethics Committee in written form before application.

The sponsor shall distribute the protocol amendment and the modified protocol to every principal investigator and the principal investigators shall be responsible for distributing the documents to the corresponding Ethics Committee and other study personnel.

13 Conditions of Study Termination

Both the sponsor and the investigator can stop the study at any time. If study termination is a must, it shall be stopped after review and negotiation of both parties. When stopping the study, the sponsor and investigators shall spare no effort in protecting the interests of the subjects.

14 Study Documents, CRFs and Records Retention

14.1 Investigators Files/Records Retention

The investigator should preserve all the study materials for at least 5 years, including the materials of confirmation to all the subjects (for effective verification of different recording materials, such as CRF/eCRF and original hospital records), original ICF of all subjects, CRF/eCRF and detailed drug distribution records, etc. After the expiration for study documents retaining at the institution, please contact the sponsor for the subsequent retention matters.

All the materials of this clinical study are the property of the sponsor, and any provision to any third party in any form or publication of the study data is prohibited without prior authorization of the sponsor.

14.2 Original Documents and Background Materials

The original documents shall be archived at the site since they can demonstrate the existence of the patients and verify the completeness of collected data.

The data transferred to the CRF/eCRF from the original documents must be consistent with the original documents and explanation is required for any discrepancy. In accordance with condition of the study, investigators may require the previous medical records, hospital transfer records or the current medical records. All data in CRF/eCRF must be obtained from the original documents.

14.3 Direct Access to the Original Data and Documents

The investigators/sites shall accept study-related monitoring, audits, IRB/IEC review and inspections by the regulatory authorization, and allow direct access to all related original data/documents. CRF/eCRF and all the original documents including disease condition record and copies of laboratory tests and medical tests results shall be provided for examinations by the clinical research associates (CRA) and auditors of the sponsor as well as the health administrative departments at any time.

15 Study Monitoring

Before the enrollment of the first subject, CRA designated by the sponsor are required to be on the site and:

- Ensure the completeness of the facilities and equipment;
- Discuss the responsibilities of study team members and CRAs during the study with the investigator (or other members) and sign the related agreements;
- Pay regular visits to the site and keep close connection with the investigator during the study
- Provide adequate information and support to the investigator
- Ensure that the study facilities and equipment are still complete
- Ensure that the study team keeps full compliance with the Protocol and records data to CRF/eCRF and drug accountability sheet with accuracy;
- Ensure the completeness of original data review (check the consistency of CRF/eCRF data and hospital medical record with other study-related records). The access to the original record of each subject is necessary.

16 Confidentiality of the Study Documents and Patients' Records

The investigator is required to ensure anonymity for patients and prevent patient identity disclosure to unauthorized parties. On the CRF/eCRF or other documents submitted to the sponsor, the patients shall be identified only by codes instead of names.

The investigator should keep a record of patients' enrollment registration with revealed patient code, name and address. Investigators should keep some certain documents including patient ICF under restrict preservation and submission of these documents to Hutchison Medi Pharma Ltd. is prohibited.

17 Data Publication and Business Confidentiality Protection

The study result may be published or released on scientific meetings. Investigators shall agree to submit all manuscripts or abstracts to Hutchison Medi Pharma Ltd. in advance before scheduled submission, if applicable. Thus the patent information of the sponsor can be protected and due to the possibility that the investigator may not know other study information, the sponsor can also propose suggestions.

In accordance with the standard of publication and ethical specifications, Hutchison

Medi Pharma Ltd. supports generally the publication of data from multi centers but not that from a single center. Under such circumstances, a coordinating investigator shall be designated after agreement of both parties.

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Appendix 1 ECOG Performance Status

Eastern Cooperative Oncology Group Performance Status Assessments

ECOG PERFORMANCE STATUS*

Grade	ECOG
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 self-care but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completed disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 2 Response Evaluation Criteria in Solid Tumors RECIST Version 1.1

(Response Evaluation Criteria in Solid Tumors RECIST Version 1.1)

Since no formal Chinese version of RICIST can be found at present, the in-house translated version is adopted. For more detailed information, please see the English Version (European Journal of Cancer 45 (2009) 228-247).

ABSTRACT

Background

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarized in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

Highlights of revised RECIST 1.1:

Major changes include:

Number of lesions to be assessed: based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumor burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum).

Assessment of pathological lymph nodes is now incorporated: nodes with a short axis of ⩾15mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumor response. Nodes that shrink to <10 mm short axis are considered normal.

Confirmation of response is required for trials with response primary endpoint but is no longer required in randomized studies since the control arm serves as appropriate means of interpretation of data. Disease progression is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very small. Furthermore, there is guidance offered on what

constitutes ‘unequivocal progression’ of non-measurable/non-target disease, a source of confusion in the original RECIST guideline. Finally, a section on detection of new lesions, including the interpretation of FDG-PET scan assessment is included. Imaging guidance: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions.

Future work:

A key question considered by the RECIST Working Group in developing RECIST 1.1 was whether it was appropriate to move from anatomic unidimensional assessment of tumor burden to either volumetric anatomical assessment or to functional assessment with PET or MRI. It was concluded that, at present, there is not sufficient standardization or evidence to abandon anatomical assessment of tumor burden. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression. As is detailed in the final paper in this special issue, the use of these promising newer approaches requires appropriate clinical validation studies.

Keywords: Response criteria, Solid tumors, Guidelines

1. Background

1.1. History of RECIST Criteria

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics. Both tumor shrinkage (objective response) and time to the development of disease progression are important endpoints in cancer clinical trials. The use of tumor regression as the endpoint for phase II trials screening new agents for evidence of anti-tumor effect is supported by years of evidence suggesting that, for many solid tumors, agents which produce tumor shrinkage in a proportion of patients have a reasonable (albeit imperfect) chance of subsequently demonstrating an improvement in overall survival or other time to event measures in randomized phase III studies. At the current time objective response carries with it a body of evidence greater than for any other biomarker supporting its utility as a measure of promising treatment effect in phase II screening trials. Furthermore, at both the phase II and phase III stage of drug development, clinical trials in advanced disease settings are increasingly utilizing time to progression (or progression-free survival) as an endpoint upon which efficacy conclusions are drawn, which is also based on anatomical measurement of tumor size.

However, both of these tumor endpoints, objective response and time to disease progression, are useful only if based on widely accepted and readily applied standard

criteria based on anatomical tumor burden. In 1981 the World Health Organization (WHO) first published tumor response criteria, mainly for use in trials where tumor response was the primary endpoint. The WHO criteria introduced the concept of an overall assessment of tumor burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment. However, in the decades that followed their publication, cooperative groups and pharmaceutical companies that used the WHO criteria often 'modified' them to accommodate new technologies or to address areas that were unclear in the original document. This led to confusion in interpretation of trial results and in fact, the application of varying response criteria was shown to lead to very different conclusions about the efficacy of the same regimen. In response to these problems, an International Working Party was formed in the mid 1990s to standardize and simplify response criteria.

New criteria, known as RECIST (Response Evaluation Criteria in Solid Tumors), were published in 2000. Key features of the original RECIST include definitions of minimum size of measurable lesions, instructions on how many lesions to follow (up to 10; a maximum five per organ site), and the use of unidimensional, rather than bidimensional, measures for overall evaluation of tumor burden. These criteria have subsequently been widely adopted by academic institutions, cooperative groups, and industry for trials where the primary endpoints are objective response or progression. In addition, regulatory authorities accept RECIST as an appropriate guideline for these assessments.

2. Purpose of this Guideline

This guideline describes a standard approach to solid tumor measurement and definitions for objective assessment of change in tumor size for use in adult and paediatric cancer clinical trials. It is expected these criteria will be useful in all trials where objective response is the primary study endpoint, as well as in trials where assessment of stable disease, tumor progression or time to progression analyses are undertaken, since all of these outcome measures are based on an assessment of anatomical tumor burden and its change on study. There are no assumptions in this paper about the proportion of patients meeting the criteria for any of these endpoints which will signal that an agent or treatment regimen is active: those definitions are dependent on type of cancer in which a trial is being undertaken and the specific agent(s) under study. Protocols must include appropriate statistical sections which define the efficacy parameters upon which the trial sample size and decision criteria

are based. In addition to providing definitions and criteria for assessment of tumor response, this guideline also makes recommendations regarding standard reporting of the results of trials that utilize tumor response as an endpoint.

While these guidelines may be applied in malignant brain tumor studies, there are also separate criteria published for response assessment in that setting. This guideline is not intended for use for studies of malignant lymphoma since international guidelines for response assessment in lymphoma are published separately.

Finally, many oncologists in their daily clinical practice follow their patients' malignant disease by means of repeated imaging studies and make decisions about continued therapy on the basis of both objective and symptomatic criteria. It is not intended that these RECIST guidelines play a role in that decision making, except if determined appropriate by the treating oncologist.

3. Measurability of Tumor at Baseline

3.1. Definitions

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

3.1.1. Measurable

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

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

3.1.2. Non-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified

by physical exam that is not measurable by reproducible imaging techniques.

3.1.3. 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 imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging 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 bone 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 no cystic 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 loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

3.2. Specifications by Methods of Measurements

3.2.1. Measurement of Lesions

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

3.2.2. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion 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 P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, 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, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in Appendix II.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). 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 of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must

normalize for a patient to be considered in 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 CA125 progression criteria which are to be integrated with objective tumor evaluation for use in first-line trials 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 lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). 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 criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

4. Tumor Response Evaluation

4.1. Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

4.2. Baseline Documentation of 'Target' and 'Non-target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those

that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ⩾15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm × 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ⩾10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

4.3. Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

4.3.1. Evaluation of Target Lesions

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, taking as reference the baseline sum diameters

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 to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered 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.

4.3.2. 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 <10mm. Case report forms 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 <10mm. 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. 2mm).

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 case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is

faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well).

This default value is derived from the 5mm 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 responses or progressions 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 on Treatment:

As noted in Appendix II, when non-nodal lesions 'fragment', 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'.

4.3.3. 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 nodes must be non-pathological in size (<10mm 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 (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

4.3.4. Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as

follows:

When the patient also has measurable disease， in this setting, 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, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. 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 entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. 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 burden 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: i.e. 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 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.

4.3.5. 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 new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not 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 may be simply healing or

flare 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 in an anatomical location 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 therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments 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 algorithm:

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

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

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

d. 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).

e. 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 anatomic images, this is not PD.

4.4. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The

patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see Section 4.6). Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

4.4.1. Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

4.4.2. Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.

If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

4.4.3. Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered

inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

4.4.4. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes 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 case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments 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 a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade 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.

Table 1 Time Point Response: Patients with Target (+/– Non-target) Disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time Point Response: Patients with Non-target Disease Only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note：‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

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 assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Table 3 Best Overall Response when Confirmation of CR and PR Required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PRa
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 = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

[a]: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even 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 was 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.

4.5. Frequency of Tumor Re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The

protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6~8 weeks on treatment or every 3~4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

4.6. Confirmatory Measurement/Duration of Response

4.6.1. Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or 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. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

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.

4.6.2. 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 measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.6.3. 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 on study (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 of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

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 periodicity 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.

4.7. Progression-free Survival/Proportion Progression-free

4.7.1. Phase II trials

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, response rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression-free survival' (PFS) or the 'proportion progression-free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behaviour patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomized trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion

progression-free in the absence of a treatment effect.

For the endpoints evaluation, independent assessment and result reporting concerning the Phase III trials, please see the English version.

Appendix 3 Restricted and Prohibited Drugs and Food

Restricted drugs and prohibited traditional Chinese medicine and food during the study are as follows:

1. Strong inhibitors and strong inducers of CYP3A4

The comparatively more common strong inhibitors of CYPA34 are listed as follows, which include but not limited to:

Ketoconazole	Saquinavir
Itraconazole	Erythromycin
Fluconazole	Clarithromycin
Voriconazole	Telithromycin
Nefazodone	Grapefruit
Indinavir	Grapefruit juice
Nelfinavir	

The comparatively more common strong inducers of CYPA34 are listed as follows, which include but not limited to:

Rifabutin	Phenobarbital
Rifampicin	Phenytoin
Rifapentine	Hypericum perforatum
Carbamazepine	

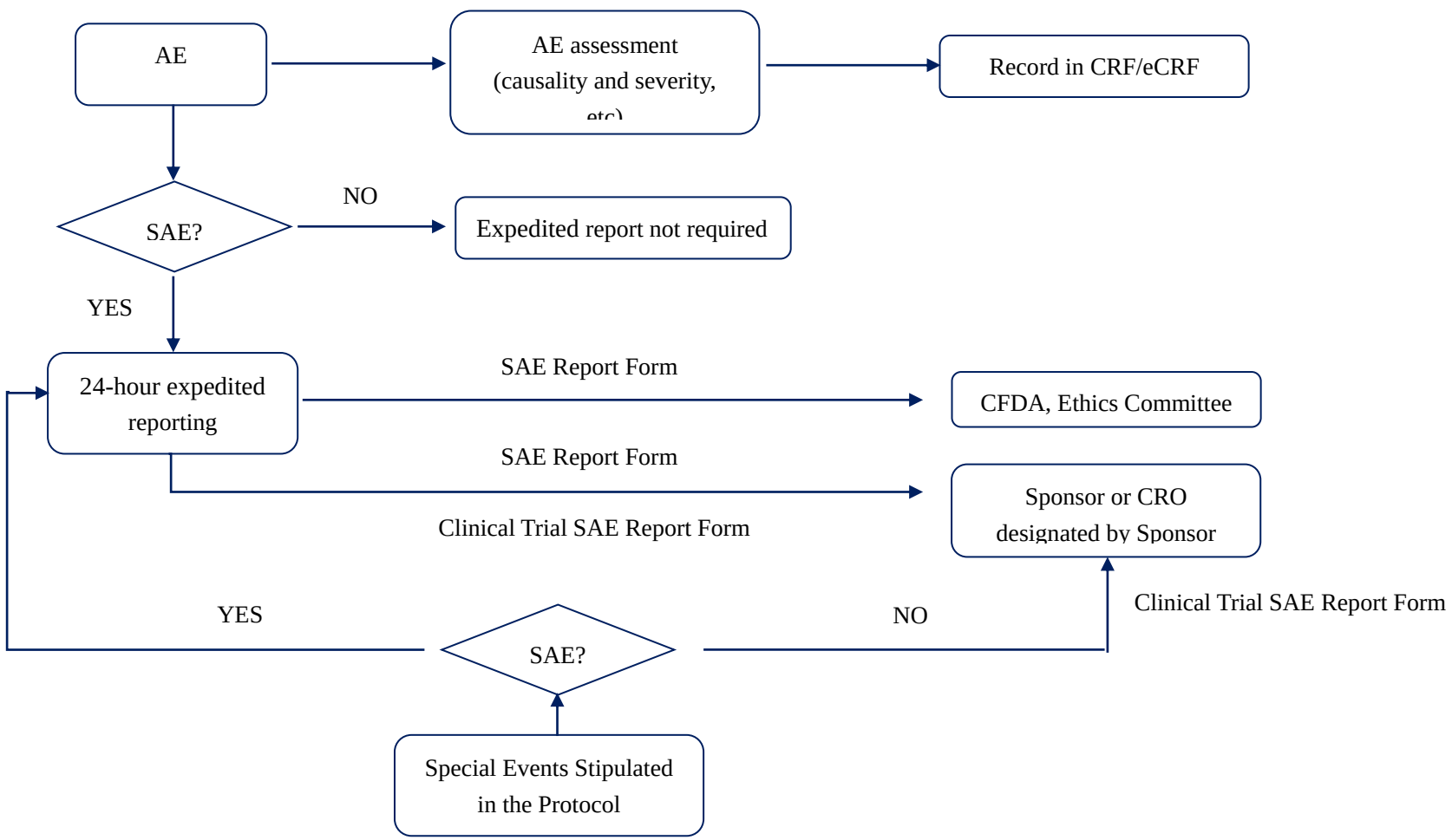
2. Traditional Chinese medicine: include all traditional Chinese medicine for anti-tumor indications

Huazhenghuisheng Pian	Fukang Capsules
Yadanziyou Ruanjiaonang	Xiaoaiping
Zhemu Tangjiang	Pingxiao Capsules
Ban’ao	Pingxiao
Huachansu	Shendan Sanjie Jiaonang
Kang’ai Zhusheye	Kanglixin Jiaonang
Kanglaite	Ankangxin Jiaonang
Zhongjiefeng Zhusheye	Bosheng Aining
Yadanzi Youru Zhusheye	Ezhuyou Putaotang Zhusheye
Aidi Zhusheye	Kanglixin Jiaonang

Awei Huapi Gao	Cidan Capsules
Kangaiping Wan	

3. Food: Fruits including grapefruit, pomelo or citrus maxima or any beverage containing the above-mentioned fruits should be avoided during the study.

Appendix 4 Safety Data Report



Appendix 5 Clinical Evaluation of Liver Damage

In accordance with the description of Section 7.1.3, repetitive blood biochemistry tests and increased frequency of monitoring are required for subjects with confirmed elevation of ALT/AST combined with increased total bilirubin (TBiL) (i.e. subjects with special events stipulated by the Protocol), so as to further describe the trend of biochemical indicators. In addition, it is necessary for investigators to exclude other causes leading to abnormalities by inquiry of medical history, physical examination and relevant auxiliary examinations.

Usual causes that may result in liver damage:

- Acute viral hepatitis
- Alcoholic and autoimmune hepatitis
- Biliary tract disease
- Cardiovascular reasons

Other less common causes may require consideration as well.

The investigator is recommended to obtain the following information, so as to further evaluate and follow up and complete the clinical data:

◆ Medical history of the subject

✧ Detailed history of current symptoms, diagnosis of complications and medical history

✧ Previous medical history (viral hepatitis, alcoholic hepatitis, autoimmune disease, biliary tract disease and cardiovascular disease, etc.)

✧ History of concomitant medication (including OTC and prescription drugs, herbal medicine and dietary supplements), alcohol consumption, recreational drugs and special diet

✧ History of exposure to chemicals

◆ Complete the following laboratory tests:

✧ Haematology

✧ Clinical biochemistry:

ALT, AST, bilirubin (including total bilirubin and direct bilirubin), alkaline phosphatase, albumin, PT or INR, amylase, fasting blood glucose, cholesterol and triglycerides.

✧ Serum test:

Hepatitis A (Anti-IgM and Anti-IgG), hepatitis B (HbsAg, Anti-HBs and

HBV DNA), hepatitis C (Anti-HCV, and HCV RNA test is required for any subject with positive test result), hepatitis D (Anti-IgM and Anti -IgG), hepatitis E (Anti-HEV and Anti-HEV IgM).

◆ Complete appropriate auxiliary examination:

✧ Subjects with confirmed elevation of ALT/AST combined with TBil are required to receive abdominal ultrasonography or other clinically applicable imaging examination within 48 hours (to exclude biliary tract, pancreas or intrahepatic causes, such as biliary calculi or tumor) and obtain the liver imaging result as soon as possible. If the causes (such as biliary tract, pancreas or intrahepatic causes) of abnormal hepatic result cannot be confirmed by imaging, paracentesis is recommended for pathological examination after obtaining consent of the subject;

✧ If suspected cardiovascular causes exist, cardiac ultrasonography is recommended to exclude cardiovascular dysfunction (including right heart failure, etc.);

Long-term follow-up: Perform close monitoring on the subject through repetitive tests of ALT, AST and bilirubin (including total bilirubin and direct bilirubin) for at least once a week till laboratory ALT and/or AST abnormality becomes stable or recovers, and then proceed according to the protocol. Report the data through the eCRF.

Appendix 6 Treatment of Hypertension (Extracted from Hypertension Treatment Guidelines)

6.1 Treatment Goal:

Two treatment goals, i.e. a standard goal and a basic goal are set in this guideline, since the nationwide unified health service and security system have not been established completely at present, and significant distances exist among the economic and social development of all provinces, municipalities and autonomous regions.

Standard goal: For patients with confirmed hypertension, initial and sustainable anti-hypertensive drugs (especially the antihypertensive medications that can control blood pressure for 24 hours by using once daily) recommended in this guide shall be used to achieve the blood pressure treatment goals on the basis of non-drug therapies. Meanwhile, other reversible risk factors shall be controlled, and the subclinical target organ damage and clinical disease detected should be effectively intervened.

Basic goal: For patients with confirmed hypertension, any safe and effective anti-hypertensive drugs (including short-acting drug at 2-3 times daily) reviewed and approved by China Food and Drug Administration (CFDA) can be used to achieve the blood pressure treatment goals on the basis of non-drug therapies. Meanwhile, other reversible risk factors shall be controlled, and the subclinical target organ damage and clinical disease detected shall be effectively intervened as far as possible.

The Basic Principles of Hypertension Treatment:

- Hypertension is an ongoing cardiovascular syndrome characterized by sustained elevation of arterial blood pressure, and it is often accompanied by other risk factors, target organ damage or clinical illness, so comprehensive intervention is required.
- Antihypertensive treatment includes non-drug and drug treatment. Most patients need long-term, even lifelong treatment.
- Regular measurement of blood pressure; treatment should be standardized and treatment compliance should be improved, so as to achieve blood pressure reduction and treatment goals as far as possible; keep long-term, stable and effective control of blood pressure.

The primary objective of hypertension treatment is to minimize the overall risks of cardiovascular complications and death to the greatest extent. Therefore, intervention in all other reversible cardiovascular risk factors (such as smoking, high blood

cholesterol disease or diabetes, etc.) and proper treatment of a variety of co-existed clinical conditions should be performed during the treatment of hypertension. Severity is getting worse when risk factors increase. If there are other clinical conditions accompanied, the absolute risk of cardiovascular disease will become higher, and the intervention on these risk factors shall also be reinforced.

There is a continuity relationship between the cardiovascular risk and blood pressure within a wide range, and no minimum danger threshold exist even when the blood pressure is lower than the so-called normal blood pressure range of 140/90 mmHg. Therefore, every effort should be spent in achieving the anti-hypertension goal.

It is found in the recent meta-analysis of previous antihypertensive clinical trials that the cardiovascular "residual risk" of patients at high risk is still high after the interventions of blood pressure, lipid and other risk factors, and the patient's long-term prognosis is difficult to fundamentally improve. More effective intervention in the earlier period is needed to change this situation, that is, providing more active treatment to patients at low and moderate risks, and effective treatment in various detected subclinical target organ damages to prevent or delay the progress of the disease in such patients into high-risk stage.

For population with high-normal blood pressure, antihypertensive therapy can be used to prevent or delay the occurrence of hypertension, but large-scale clinical trial studies are still needed to investigate whether antihypertensive therapy can reduce the risk of cardiovascular complications.

Point 7 Treatment Goals
□□ The primary objective of hypertension treatment is to minimize the overall risks of cardiovascular complications and death to the greatest extent. Treatment in all reversible cardiovascular risk factors, subclinical target organ damage and various of co-existing clinical diseases is required.
□□Anti-hypertension goal: For common hypertensive patients, blood pressure (systolic/diastolic) should be lowered to below 140/90mmHg; systolic blood pressure in the elder patients of 65 years or above should be controlled at below 150mmHg, which can be further reduced if tolerable; treatment for patients accompanied by kidney disease, diabetes, or patients with stable coronary heart disease or cerebrovascular disease should be individualized, and the blood pressure can be generally decreased to below 130/80mmHg. For patients with severe kidney disease, diabetes, coronary heart disease or cerebrovascular disease in the acute

phase, the management of blood pressure should comply with the applicable guidelines.

□□For the patients with coronary heart disease whose diastolic blood pressure are below 60mmHg, blood pressure should be gradually lowered to the goal under close monitoring.

Anti-hypertension goals for hypertensive patients: For common hypertensive patients, blood pressure (systolic/diastolic) should be lowered to below 140/90mmHg; systolic blood pressure in elder patients of 65 years or above should be controlled below 150mmHg, which can be further reduced if tolerable; the treatment for patients accompanied by kidney disease, diabetes, or patients with stable coronary heart disease or cerebrovascular disease should be individualized, the blood pressure can be generally decreased below 130/80mmHg. For the patients with severe kidney disease, diabetes, coronary heart disease or cerebrovascular disease in acute phase, the management of blood pressure should comply with the applicable guidelines. For patients with coronary heart disease whose diastolic blood pressures are below 60mmHg, blood pressure should be gradually lowered to the goal under the close monitoring.

5.2 Treatment Strategy

5.2.1 Stratification by Low Risk, Moderate Risk, High Risk and very High Risk

Comprehensive assessment of the overall risks of the patients should be performed, and the treatment decisions should be made based on risk stratification.

Patients with very high risks: Comprehensive treatment of hypertension with the co-existed risk factors and clinical conditions should be immediately started;

Patients with high risks: The drug treatment of hypertension with the co-existed risk factors and clinical conditions should be immediately started;

Patients with moderate risks: Firstly, the blood pressure and other risk factors of patients should be observed for several weeks to assess the damage of target organ, and then decide whether and when to start the drug treatment.

Patients with low risks: Observe the patients for a longer time, measure the blood pressure repeatedly, and try to perform 24-hour ambulatory blood pressure monitoring to assess the damage of target organ, and then decide whether and when to start the drug treatment.

5.3 Non-drug Therapies (lifestyle Intervention)

The non-drug therapies in this guideline mainly refer to lifestyle intervention, i.e. to

get rid of the behaviors and habits that may influence of the physical and mental health. It can not only prevent or delay the occurrence of high blood pressure, but also lower the blood pressure, improve the efficacy of antihypertensive drugs and then reduce cardiovascular risk. Specific contents are summarized as follows:

5.3.1 Reducing Sodium Intake

Sodium can significantly increase blood pressure and the risk of hypertension, while potassium can lower the increased blood pressure caused by sodium. The sodium intake of residents all over China is significantly higher than that current recommended amount by World Health Organization, which is less than 6 grams per day. However, potassium intake is of great deficiency, so all the patients with hypertension should take various measures to reduce the sodium intake and increase potassium intake in food. The main measures include:

- Minimizing cooking salt by using recommended quantitative salt spoon;
- Reducing the amount of condiments containing sodium such as aginomoto and soy;
- Eating less or avoid eating various types of processed foods containing high amounts of sodium, such as pickles, ham, sausage and all kinds of roasted seeds and nuts;
- Increasing the intake of vegetables and fruits;
- For patients with good renal function, using cooking salt containing potassium.

5.3.2 Weight Control

Overweight and obesity are among the important causes of high blood pressure, and the central obesity typically characterized by accumulation of abdominal fat will further increase the risks of hypertension and other cardiovascular and metabolic diseases. Blood pressure can be significantly reduced by decreasing the weight gain appropriately and reducing body fat.

The most effective measure to lose weight is to control energy intake and do more physical activities. The principle of a balanced diet should be followed, to control the intake of high-calorie foods (high-fat foods, sugared beverages and alcohol, etc.), and control staple food (carbohydrates) properly. Considering sports, regular aerobic exercise of moderate intensity is an effective way to control weight. Weight loss rate varies from person to person, and a rate of 0.5~1 kg per week is appropriate. For patients with severe obesity who failed to non-drug measures of weight loss, weight loss drugs can be used to control weight under the guidance of a doctor.

5.3.3 Avoid Smoking

As an unhealthy behavior, smoking is one of the main risk factors of cardiovascular disease and cancer. Passive smoking also significantly increases the risk of cardiovascular disease. Smoking can lead to vascular endothelial damage, significantly increase the risk of atherosclerotic disease in hypertension patients. It couldn't be surer for the benefits of quitting smoking, and people can benefit from smoking cessation at any age. Tobacco dependence is a chronic disease of addiction, it is difficult to quit and the recurrence rate is also high. Therefore, physicians should strongly recommend and urge the patients to quit smoking, and encourage patients to seek medication for smoking cessation (use of nicotine substitutes, Bupropion sustained-release tablets and varenicline, etc.), meanwhile patients who successfully quit smoking should be followed up and supervised to avoid to resume smoking.

5.3.4 Alcohol Restrictions

Long-term heavy drinking can lead to high blood pressure, and restrictions on alcohol consumption can significantly reduce the risk of hypertension. There are numbers of long-term heavy male drinkers in China, and also female drinkers in several other minority groups (such as the ethnic minority group). All investigators should control alcohol consumption of the patients. Daily alcohol intake should be no more than 25 grams for men and 15 grams for women. Patients with hypertension are not advocated of drinking, and it should be at small amount when drinking: the amount of liquor, wine (or rice wine) and beer should be less than 50ml, 100ml and 300ml, respectively.

5.3.5 Physical Activities

General physical activities can increase energy consumption and is good for health. Regular physical exercises can bring significant therapeutic effect in reducing blood pressure and improving glucose metabolism. Therefore, appropriate physical activities for about 30 minutes every day is recommend; and aerobic physical exercise of more than once per week should be done, such as walking, jogging, cycling, swimming, aerobics, dancing and non-competitive rowing and so on. Typical physical activity program includes 3 stages: ①mild warm-up activities of 5~10 minutes; ②aerobic exercise endurance activities of 20~30 minutes or; ③relaxation phase for about 5 minutes, gradually reducing the force, so that the reaction of cardiovascular and cerebrovascular system and body heat function can be gradually stabilized. The form and amount of exercise should be based on individual physical conditions.

5.3.6 Reduction of Mental Pressure and Maintenance of Psychological Balance

Psychological or mental pressure can cause psychological stress (response), which is the body response to the environment, psychological and physiological factors.

Long-term and excessive psychological reactions, especially negative psychological response can significantly increase cardiovascular risk. The main reasons for the increase in mental stress consist of excessive work and life pressures and morbid psychology, including depression, anxiety, A-type personality (a character featured with hostile, aggressive, jealous and time urgency), social isolation and lack of social support, etc. Various measures should be taken to help the patients to prevent and relieve stress as well as the correction and treatment of morbid psychology and, advise patients to seek professional psychological counseling or treatment if necessary.

5.4. Drug Therapies for Hypertension

5.4.1. Objectives of Anti-hypertension and Gradual Goals Achievement

1) Objectives of anti-hypertension treatment: The objectives of anti-hypertension treatment in patients with hypertension are: a) to effectively prevent or prolong the time to delay the occurrence of cardio-cerebrovascular complications, e.g. stroke, cardiac infarction, cardiac failure and renal deficiency by decreasing the blood pressure; b) to effectively control the disease progress and prevent the occurrence of severe hypertension, e.g. acute hypertension or sub-acute hypertension. The previously performed studies of anti-hypertension therapies which used diastolic pressure (>90 mmHg) as inclusion criteria indicated that, the risk of stroke and ischemic heart disease would be reduced by 40% and 14% respectively with the diastolic pressure decrease of 5 mmHg (systolic pressure decreased 10 mmHg); later studies of anti-hypertension therapy focused on systolic pressure (systolic pressure>160 mmHg, diastolic pressure <90 mmHg) indicated that, the risk of stroke and ischemic heart disease would be reduced by 30% and 23% respectively with the systolic pressure decrease of 10 mmHg (diastolic pressure decrease of 4 mmHg).

2) Ways of achieving standard blood pressure: The risk of cardio-cerebrovascular complications would be significantly reduced by lowering the blood pressure to the target levels of below 140/90 mmHg, 130/80 mm Hg for patients of high risks, systolic pressure of 150 mmHg for the seniors. But it is unknown whether the patients can still benefit from further anti-hypertension treatment after achieving the above target levels. Studies have shown that the risk of cardio-vascular events may be increased when the diastolic pressure of older patients with diabetes or coronary heart disease is reduced to below 60 mmHg.

Blood pressure should be lowered to the above target levels timely, but it is not the quicker the better. For most patients with hypertension, the blood pressure should be

lowered to the target level gradually within several weeks to several months (not several days) according to their disease condition. For patients with hypertension at younger age or with a shorter process, the lowering of blood pressure may take a shorter time; however, for patients with hypertension at older age, with longer process or with target organ damage or complications, the lowering of blood pressure should take a relatively longer time.

3) Timing for anti-hypertension drug therapies: Patients with high risks, very high risks or grade 3 hypertension should start anti-hypertension drug therapy immediately. Patients with diagnosed grade 2 hypertension should consider to start anti-hypertension drug therapies; patients with diagnosed grade 1 hypertension can start anti-hypertension drug therapies when the blood pressure remains ⩾140/90 mmHg after several weeks of lifestyle intervention.

5.4.2. Clinical Trial Evidence of Anti-hypertension Therapies

The theoretical basis for the treatment and management of anti-hypertension has been established by a randomized, controlled, anti-hypertension treatment clinical trial which used the cardio-cerebrovascular complications as the primary study objective. Dozens of clinical trials in patients with hypertension have been conducted around the world since 1950s, and the trials were mainly divided into 4 types. In the earlier anti-hypertension treatment clinical trials, the primary objective was to find out if active anti-hypertension treatments could significantly reduce the risk of cardio-cerebrovascular complications compared to placebo or non-treatment. All the results of these trials showed that, anti-hypertension treatment could reduce the risk of cardio-cerebrovascular complications in patients with various types of hypertension by lowering the blood pressure, which turns out to be the most important theoretical basis for the treatment and management of various types of hypertension.

Several clinical trials have been conducted between different kinds of drugs based on this theory. The purpose of these trials was to investigate whether new anti-hypertensive drugs (e.g. calcium channel blocker [CCB], angiotensin-converting enzyme inhibitor (ACEI), Angiotensin receptor antagonist (ARB)) can prevent cardio-cerebrovascular complications more effectively compared with the traditional anti-hypertensive drugs (e.g. thiazine diuretic, Beta blockers). The results of these clinical trials have indicated that, the main reason for these drugs to reduce the cardio-cerebrovascular complications was lowering blood pressure, and the overall difference between drugs was very small, however, there was still significant difference when the drugs were used to treat specific complications, such as, CCB

was the most effective drug for treating stroke. Difference can be great between various combined therapies, e.g. the combined therapy of CCB and ACEI can prevent the cardio-cerebrovascular complications more effectively compared with the combined therapy of ACEI and thiazine diuretic and that of Beta blockers and thiazine diuretic. Compared to the monotherapy of ACEI or ARB, the ACEI+ARB combined therapy can increase the risk of complications such as adverse reactions and renal dysfunction instead of lowering the risks of cardio-cerebrovascular complications more effectively.

There are mainly two types of anti-hypertension therapy clinical trials in recent years. One type is to find out an optimal target hypertension level in hypertensive patients by comparing the patients with treatment intensification and patients without. The other type is to investigate whether the lower hypertension level can reduce the risks of cardio-cerebrovascular complications more efficiently in population at high risks of cardio-cerebrovascular complications. The blood pressure levels of the patients at enrollment were not considered usually, so there were hypertensive patients, patients with normal blood pressure and patients whose blood pressure had been controlled to normal included in the trials. In the group with lower blood pressure, significant decrease in the risk of some complications was observed, but with rising trend in the risk of some other complications. These results of the trials suggested that, after achieving the target level of below 140/90 mmHg, individualized anti-hypertension treatment should be used, and the disease conditions of the patients, the composition and conduction of the anti-hypertensive regimen should be fully considered.

Although most of the anti-hypertension treatment clinical trials have been performed in European countries and America, China has also independently conducted a series of clinical trials in this field and made contributions to many international multicenter trials. It was confirmed in the earlier anti-hypertension treatment clinical trial (Syst-China) conducted in the systole of the Chinese old people and the trials of Nifedipine conducted in Shanghai (STONE) and Chengdu (CNIT), that active anti-hypertensive regimen based on CCB (e.g. Nitrendipine, Nifedipine) may reduce the occurrence and mortality of strokes in Chinese hypertensive patients. According to this, the FEVER study (Felodipine decreases the risk of complications) showed that the combined therapy of Hydrochlorothiazide and Felodipine could decrease the occurrence of fetal and non-fetal strokes by 27% when compared to the monotherapy of Hydrochlorothiazide, though the blood pressure had been further decreased by 4/2 mmHg after adding Felodipine. It was discovered after the advanced conduction and

analysis of the FEVER study, that the risk of stroke, heart event and overall mortality were the lowest when the blood pressure was below 120/70mmHg after treatment. The interim report of the ongoing Chinese Hypertension Intervention Efficacy Study (CHIEF) shows that the combined therapy of the initial small dose of Amlodipine and Telmisartan or Compound Amiloride can apparently lower the blood pressure of hypertensive patients and achieve a control rate of 80%, which indicates that the combined therapy based on calcium channel blockers is one of the optimized anti-hypertensive therapies for the hypertensive patients in China.

In addition to the above primary prevention anti-hypertension clinical trials, China has contributed to the secondary prevention post-stroke anti-hypertension clinical trials. Post-Stroke Antihypertensive Treatment Study (PATS) conducted independently by China is the first international placebo-controlled secondary prevention post-stroke anti-hypertension clinical trial in a large scale. The results of the study showed that the blood pressure was lowered by 5/2 mmHg and the occurrence of stroke by 29% Indapamide-treated group (2.5mg/d) compared with placebo-treated group. China has also taken an active part in PROGRESS study later on, and recruited 1/4 patients of the whole study (6105 patients). The study results indicated that the combined therapy of Perindopril and Indapamide or the monotherapy of Perindopril reduced the overall recurrence of stroke by 28%, and the combined therapy turned out to be more effective than the monotherapy in reducing blood pressure. The analysis results of the subgroup indicated that there was a greater reduction in the risk of stroke in Asian population (e.g. China and Japan). The results of the post-hoc analysis indicated that the mean post-treatment blood pressure was lowered to 112/72mmHg but no J shaped curve was observed. The 1520 patients recruited by China were further followed up, and the mean data of 6-years'follow-up confirmed that hypertensive treatment reduced the recurrence of stroke obviously, and the overall mortality and risk of cardiac infarction were on a declining curve.

The scholars in China have also taken an active part in two important studies, HYVET study (HYVET, n=3845) and ADVANCE study (ADVANCE, n=11140), and help recruited about 40% and 30% patients respectively. The results of HYVET study showed that when the anti-hypertensive treatment was performed in hypertensive patients of advanced age (>80 yrs) whose systolic pressure was above 160 mmHg, the sustained release Indapamide (1.5mg/d) lowered the systolic pressure to 150 mmHg and the risk of stroke and death was lowered compared to placebo. However, ADVANCE study results showed that when anti-hypertensive treatment of Perindopril

(2-4mg)/Indapamide (0.625-1.25mg) in small dose was provided to patients with diabetes, the blood pressure was lowered by 5.6/2.2 mmHg to an average level of 135/75 mmHg compared to the conventional treatments. The endpoint events of great vessels combined with capillaries were lowered by 9%.

The results of ALLHAT study suggested that there was no significant difference in the effect of Amlodipine, Lisinopril and Chlortralidone on coronary events. VALUE study confirmed that earlier control of blood pressure may contribute in reducing the risks of cardiovascular events. It was demonstrated in the Cardiac Insufficiency Bisoprolol Study II (CIBIS-2) that Bisoprolol could obviously decrease cardiovascular death and the overall mortality in patients with congestive heart failure. The subgroup analysis of ACTION study showed that when Nifedipine controlled release tablets were used to treat hypertensive patients accompanied with coronary heart disease, the risk of cardiovascular events was significantly reduced.

The combination treatment trials provided clear evidence. In the LIFE study, the hypertensive patients with left ventricular hypertrophy were randomly treated, and the results showed Losartan±Hydrochlorothiazide group had better effect in reducing complex cardiovascular events compared with the Atenolol±Hydrochlorothiazide group. The results of ASCOT-BPLA study showed that the Amlodipine±Perindopril could lower the risk of cardiovascular events more effectively compared to the Atenolol±Bendrofluazide. The ACCOMPLISH study results showed that Benazepril+Amlodipine combination therapy had better results in reducing complex endpoint events compared with Benazepril+Hydrochlorothiazide. The ONTARGET study results indicated the monotherapy of Telmisartan or Ramipril could reduce the risk of cardiovascular events, but no difference was observed in main complex cardiovascular endpoint events when treated with the combination therapy of the two drugs. ONTARGET and HOPE study suggested that ARB or ACEI could prevent cardiovascular events of patients with high risks of cardiovascular disease (coronary heart disease, brain stroke, peripheral vascular disease, diabetes with target-organ damage).

Dispute about the target blood pressure level for some hypertensive patients at high risk arose in their hypertensive treatment. The ACCORD and INVEST studies showed that for older diabetic patients mainly with coronary heart disease, when the systolic pressure was reduced to below 115-120mmHg through anti-hypertension treatment, the risk of cardiovascular events was increased. However, the HOT study results suggested that cardiovascular events could be reduced when the diastolic pressure was

lowered to below 80mmHg.

In short, anti-hypertension therapies can reduce the risks of cardio-cerebrovascular complications efficiently in various types of hypertensive patients. The overall difference was small in CCB, ACEI, ARB, thiazide-type diuretics and Beta blockers, however, there may be significant difference when the drugs or their combination therapies were used to treat specific complications. CCB or diuretics was the most effective drug among them when preventing stroke. ACEI or ARB had better effect in protecting target organ. And Beta blockers were better in preventing heart disease.

According to the above statements, the risk of hypertensive patients depends not only on BP level, but also on the complications, co-existing conditions and other cardiovascular risk factors. Hyperhomocysteinemia is the most common risk factor for Chinese hypertensive patients apart from diabetes and dyslipidemia, and it has significant positive correlation with the risk of brain stroke, whose risks can be increased by it. It is showed in multivitamin treatment trials independently conducted by China and the meta analysis of folic acid treatment trials that supplement of folic acid can significantly reduce the risk of brain stroke (-18%). However, larger scale clinical trials about the prevention of brain stroke in Chinese hypertensive patients by supplement of folic acid are still needed.

With the rapid development of the hypertension target organ subclinical lesion detection technique in recent years, such as ultrasound cardiogram in detecting left ventricular hypertrophy, and vascular ultrasound in detecting intima-media thickness (IMT), proteinuria and new onset diabetes mellitus ,etc., as well as the extensive clinical trials with the primary objective of intermediate vascular detection indicator, subgroup analysis and post-hoc analysis aiming at intermediate detection indicator are increasing in recent years. These studies play an important role in probing the damage mechanism of hypertension and the protection mechanism of anti-hypertension treatment due to the small sample size required and the availability of obvious observation results within one year. But due to the complexity of the detection technique, many risk factors, the uncertainty of the correlation of cardio-cerebrovascular complications and the inconsistency of the study results at times, that whether the intermediate measurement indicators clinical trials can take place of those with big sample size, long period, aiming at cardio-cerebrovascular complications still deserves further investigation.

5.4.3. Basic Principle for the Use of Anti-hypertensive Drugs

The use of anti-hypertensive drugs should follow 4 principles, i.e. starting with small

dose, preference for long-acting drugs, combined use and individualized treatment.

1) Small dose：Small therapeutic dose should be selected at initial treatment, and the dose can be gradually increased as required. Since long-term or even life-time use of anti-hypertensive drugs is needed, and the safety and tolerability of the drugs are considered of more importance than the efficacy.

2) Preference for long-acting drugs: Long-acting drugs with 24-hour anti-hypertension effect are preferred so as to control the nighttime BP and morning surge, thus effectively preventing of cardio-cerebrovascular complications. If the intermediate or short-acting drugs are taken, it needs to be taken 2-3 times daily in order to achieve stable BP.

3) Combined use: It has better anti-hypertensive effect and less adverse reactions. The combination therapy of two or more anti-hypertensive drugs can be used when the monotherapy of drug at low dose is not satisfying. In fact, combined therapy is often required for patients with grade 2 or above hypertension to achieve stable BP. For patients with BP≥160/100mmHg or at intermediate or higher risks, combined therapy at low dose or fixed compound preparation at low dose can be used.

4) Individualized treatment: Anti-hypertensive drugs should be selected according to the patient's condition, individual willingness or long-term tolerability.

5.4.4. Types and Characteristics of Common Anti-hypertensive Drugs

Common anti-hypertensive drugs include calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), Angiotensin receptor antagonist (ARB), diuretics, β blockers (Table 5-1) and the compound preparations of fixed ratio of the above drugs. In addition, α-receptor blocker or anti-hypertensive drugs of other types can be applied to some hypertensive population.

CCB, ACEI, ARB, diuretics, Beta blockers and compound preparations of fixed ratio at low dose can be used as initial medication or long-term medication, monotherapy or combination therapy (Table 5-1). Though the above anti-hypertensive drugs are all recommended as initial medication or long-term medication, it cannot be taken for granted that the drugs can be used at one's will or that the drugs have the same chance to be selected for initial medication. However, certain type of anti-hypertensive drug should be prioritized based on the patients' risk factors, subclinical target organ damage and the co-existing medical conditions (which are sometimes referred to as compelling Indication).

1) Calcium channel blocker: vessel dilation and blood pressure reduction are achieved when the calcium channel blocker blocks the calcium channel on the vascular smooth

muscles. Calcium channel blocker includes dihyyridin type of calcium antagonists and non-dihyyridin type of calcium antagonists. The former comprises of Nifedipine, Nitrendipine, lacidipine, Amlodipine and Felodipine. Previous anti-hypertensive treatment clinical trials with big sample size conducted in China were mainly using the dihyyridin type of calcium antagonists as study drug, and it was confirmed that anti-hypertensive treatment based on dihyyridin type of calcium antagonists could reduce the risk of brain stroke in hypertensive patients significantly. This type of drug can be combined with the other 4 types, especially for elderly hypertension patients, patients with isolated systolic hypertension, hypertensive patients accompanied with stable angina pectoris, coronary sclerosis, artery atherosclerosis or peripheral vascular disease. Common adverse effects include tachycardia caused by reflexive sympathetic activation, flushing, edema in ankles, and gingival hyperplasia, etc. There are no absolute contraindications for dihyyridin type of CCB, but patients with tachycardia or cardiac failure should use them with caution. If the patients must be treated with this type of drugs, then certain preparation such as molecular long-acting drug Amlodipine should be selected cautiously. Usually, the short-acting Nifedipine is not recommended for patients with acute coronary syndromes.

Clinically common non-dihyyridin type of calcium antagonists include Verpamil and Diltiazem, both of which can be used for anti-hypertensive treatment. While the common adverse effects are inhibition of cardiac systolic function and conduction, and sometimes gingival hyperplasia. Patients with II or III atrioventricular block or cardiac failure are prohibited to use. Therefore, questioning of detailed medical history and ECG examination should be performed before taking non-dihyyridin type of CCB, and re-examination within 2-6 weeks after starting the medication is required.

2) ACEI: ACEI can reduce blood pressure by inhibiting the Angiotensin-converting enzyme inhibitors' reducing the activity of the renin-angiotensin-aldosterone system (RAAS). Frequently prescribed ACE inhibitors include captopril, enalapril, Benazepril, Ramipril and Perindopril, etc. A large number of clinical trials with big sample size have been conducted in European and American populations, whose results have showed that this type of drug can protect the target organ and prevent the cardiovascular endpoint events of hypertensive patients. ACEI demonstrates good anti-hypertensive effect when used alone, and it has no adverse effect in glucolipid metabolism. Lowering salt assumption or adding diuretics may help increase the anti-hypertensive effect, especially for patients with chronic heart failure, myocardial

infarction accompanied with cardiac insufficiency, diabetic nephropathy, non-diabetic nephropathy, metabolic syndrome, proteinuria, or microalbunminuria. Persistent dry cough is a relatively common adverse effect in the early period of administration, and patients with mild symptoms can continue the medication, but for patients who are intolerable, ARB is often used instead. Other adverse reactions include hypotension, rash, occasional seen angioneurotic edema and dysgeusia. And long-term use of ACEi may result in increased serum potassium, therefore, regular examination of the serum potassium and serum creatinine should be performed. The ACE inhibitors are contraindicated in patients with bilateral renal artery stenosis, hyperkalemia and pregnant women.

3) ARB: ARB can lower the BP by blocking the activation of angiotensin II AT1 receptors. Common ARB inhibitors include Losartan, Valsartan, Irbesartan, and Telmisartan, etc. A large number of clinical trials with big sample size have been conducted in European and American population, whose results have showed that ARB can lower the risk of cardiovascular events of hypertensive patients, and proteinuria, or microalbunminuria of the diabetic patients or nephritic patients, and especially for patients with left ventricular hypertrophy, cardiac failure, atrial fibrillation (for prevention), diabetic nephropathy, metabolic syndrome, proteinuria, or microalbunminuria and patients who are intolerant to ACEI. Adverse reactions are rare, except for occasional diarrhea. Serum potassium may be increased by long-term use, therefore, regular examination of the serum potassium and serum creatinine should be performed. The ARB inhibitors are contraindicated in patients with bilateral renal artery stenosis, hyperkalemia and pregnant women.

4) Diuretics: the anti-hypertension is realized by promoting urine output and lowering high blood volume load. Diuretics include Thiazide-type diuretics, loop diuretic, potassium-sparing diuretics and aldosterone antagonists. Thiazide-type diuretics are mainly used to control BP. In China, common Thiazide-type diuretics are Hydrochlorothiazide and Indapamide. PATS study has confirmed that Indapamide treatment could apparently reduce the relapse of stroke. Thiazide-type diuretics at low dose (e.g. Hydrochlorothiazide 6.25-25mg) have little effect on metabolism, and its anti-hypertensive reaction (of the other type) can be significantly enhanced when combined with other anti-hypertensive drugs (especially ACEI or ARB). Diuretics are particularly fit for old and elderly patients with hypertension, isolated systolic hypertension or cardiac failure, and it is one of the fundamental drugs for refractory hypertension. Due to the close relationship between adverse reactions and dose, low

dose is usually adopted. Thiazide-type diuretics can result in hypokaliemia, therefore, regular examination of the serum potassium and supplement of potassium should be performed for long-term users. Diuretics are contraindicated in patients with gout. And patients with hyperuricemia or obvious renal deficiency should use Diuretics with caution, and when required, loop diuretic, such as Furosemide should be considered.

Potassium-sparing diuretics (e.g. Amiloride) and Aldosterone antagonists (e.g. Spironolactone) may be applied to control BP at times. Thiazide-type diuretics will not increase the discharge of potassium while promoting urine output. The risks of hyperkalemia should be noticed when combined with potassium-sparing anti-hypertension drugs (e.g. ACEI or ARB). Long-term use of Spironolactone may result in adverse reactions such as gynecomasty.

5) β-receptor blocker: Beta blockers can lower BP by suppressing the activities of over-activated sympathetic nerve system, myocardial contraction and slowing down heart rate. Common β-receptor blockers include Metoprolol, Bisoprolol, Carvedilol and Atenolol. Metoprolol and Bisoprolol have high selectivity for β1 receptor, and they can block β2 receptor with less adverse reactions. They can lower BP, protect target organ and reduce the cardiovascular events. β blocker is particularly applicable for hypertensive patients with tachyarrhythmia, coronary angina pectoris, chronic heart failure, enhanced sympathetic nerve system activity and hyperdynamic status. Common adverse reactions include fatigue, cold extremities, unrest, upset stomach, and it may also influence glucose and lipid metabolism. β blocker is contraindicated in patients with advanced heart block and asthma. Patients with chronic obstructive pulmonary disease, Peripheral vascular disease or abnormal glucose tolerance and athletes should use with caution. β blocker with high selectivity can be selected with caution as necessary. Rebound reaction (i.e. worsening of the existing symptoms or occurring of new symptoms) may happen due to a sudden interruption during long-term use, and the common rebound reactions include rebound elevated BP, headache, anxiety, which are called withdrawal syndrome.

6) α-receptor blocker: It is not used as the first choice for treatment of hypertention, and it applies for hypertensive patients with prostatic hyperplasia, and refractory hypertension. The initial dose should be taken before bedtime, so as to avoid postural hypotension. Sitting BP should be measured during medication and the controlled-release preparation should be used. α-receptor blocker is contraindicated for patients with postural hypotension. Patients with cardiac failure should use with

caution.

7) Renin Inhibitors: a new type of anti-hypertensive drugs, represented by Aliskiren, and it can significantly reduce BP of the hypertensive patients, but clinical trials with big sample size to assess the effect on cardiovascular events are still needed.

5.4.5. Combined Use of Anti-hypertensive Drugs

1) Purpose of combined medication: combined use of anti-hypertensive drugs has become a fundamental method for anti-hypertensive treatment. At least 2 types of anti-hypertensive drugs are required for many hypertensive patients to achieve the goal of BP lowering.

2) Indications of combined medication: for high-risk patients with grade Ⅱ hypertension and (or) with many risk factors, target organ damage or clinical conditions, the initial therapy generally require 2 anti-hypertensive drugs at low dose. Dose increase base on the initial therapy or 3 or 4 anti-hypertensive drugs are acceptable if the BP level couldn't be achieved.

3) Methods of combined medication: the mechanism of the 2 drugs should be complementary for each other when used in combination. Therefore, the adverse reactions would be cancelled or relieved by the combination. For example, adding Thiazide-type diuretics at low dose in the combination of ACEI or ARB will achieve or exceed 2 times of the original anti-hypertensive effect of ACEI or ARB. Similarly, adding Dihydropyridines CCB would have the same effects. For detailed information of combination regimen, see Table 5-2:

(1) ACEI or ARB+Thiazide-type diuretics: the adverse reaction of diuretics is to activate RAAS, imposing bad effects on lowering BP. While used in combination with ACEI or ARB, the bad effects can be cancelled. In addition, since ACEI and ARB can increase the serum potassium level, the adverse reactions such as Hypokalemia lead by long-term use of Thiazide-type diuretics can be prevented. ARB or ACEI+ Thiazide-type diuretics combination has good anti-hypertensive effects due to its synergistic effect.

(2) Dihydropyridines CCB+ACEI or ARB: as the former has direct effect of dilating artery, and the latter blocks RAAS, the combination can dilate both artery and vein, so the two drugs have synergistic effect. The commonly seen edema in ankles caused by Dihydropyridines CCB can be removed by ACEI or ARB. CHIEF study showed that long-acting Dihydropyridines calcium antagonist channel blockers at low dose plus ARB as initial treatment for hypertensive patients could remarkably increase the control rate of hypertension. Moreover, ACEI or ARB could partially block the

adverse reactions of reflexive increased Sympathetic nervous tension and rapid heart rate resulting from BBC.

(3) CCB+Thiazide-type diuretics: FEVER study showed that Dihydropyridines CCB + Thiazide-type diuretics treatment could reduce the occurrence of stroke in hypertensive patients.

(4) Dihydropyridines CCB (D-CCB) + β blockers: the effect of dilating vein and increasing heart rate in the former can counteract the shrinking and lowering heart rate effect of β blockers. Adverse reactions can be reduced by the combination therapy.

Mainly recommended optimized combination regimens include: D-CCB+ARB, D-CCB+ACEI, ARB+Thiazide-type diuretics, ACEI+Thiazide-type diuretics, D-CCB Thiazide-type diuretics, and D-CCB+ β blockers.

Secondly recommended optimized combination regimens: diuretics+β blockers, α-blockers+β-blockers, D-CCB+potassium-sparing diuretics, and Thiazide-type diuretics + potassium-sparing diuretics.

Combination regimens that are non-conventionally recommended but used with caution when necessary include ACEI+β-blockers, ARB+β-blockers, ACEI+ARB, and centrally acting antihypertensive drugs +β-blockers.

Combination of more than 2 types of drugs: (1) Combination of 3 types of drugs: the combination is formed by adding another type of anti-hypertensive drug based on one of the above combination therapy consisted of 2 types, and the combination therapy of Dihydropyridines CCB+ACEI (or ARB)+Thiazide-type diuretics is the most frequently used. (2) Combination of 4 types of drugs: it is mainly applied for patients with refractory hypertension. The combination can be formed by adding another type of anti-hypertensive drug based on one of the above combination therapy consisted of 3 types, such as β blockers, Spironolactone, Clonidine or α blockers.

4) Fixed compound preparation: it is a group of commonly used anti-hypertensive drugs. It is usually comprised of 2 types of low dose anti-hypertensive drugs with different mechanisms, and it is also called single tablet fixed compound preparation. Different from the separately prescribed anti-hypertensive combination therapy, it is easy to use and improves patient compliance, and it is becoming the new trend for the combination therapy. Fixed compound preparation can be used as one of the initial drug treatment for some patients with grade 2 or 3 hypertension or patients at high risk. Contraindications for the corresponding composition and potential adverse effect should be noticed in use.

1. Traditional fixed compound preparation includes: (1) Compound Reserpine Tablets

(Compound anti-hypertension tablet), (2) Compound Hypotensive Tablets Compound Reserpine And Hydrochlorthiazide Tablets (Beijing Hypotensive No.0), (3) Zhenju Jiangya Tablet, main ingredients include Reserpine Tablets, Hydrochlorothiazide, and Dihydralazine Hydrochloride or Clonidine. Despite the disputation about rationality of the composition of the compound preparation, it is widely used in the grass roots.

2. New type of fixed compound preparation includes: It is usually comprised of 2 types of anti-hypertensive drugs with different mechanism. Most of this kind of drug is orally taken, 1 tablet/d. It is easy to use and improves patient compliance. Principal types of fixed compound preparation on Chinese market include: ACEI+ Thiazide-type diuretics, ARB+ Thiazide-type diuretics, Dihydropyridines CCB+ARB, Dihydropyridines CCB+β blockers; Thiazide-type diuretics+potassium-sparing diuretics.

3. Fixed compound preparation comprised of anti-hypertensive drugs and other cardiovascular drugs: Dihydropyridines CCB+Statin, and ACEI+folic acid. The medication of this kind of drugs should be based on the coexisting risk factors or medical conditions, and the indications and contraindications of anti-hypertensive drugs and non- anti-hypertensive drugs should be considered.

5.5. Management of Relative Risk Factors

5.5.1. Lipid Regulation Treatment

Dyslipidemia is an important risk factor of atherosclerosis. The risk of cardiovascular disease will be significantly increased for hypertension with dyslipidemia. Hypertension is the most dangerous pathogenic factor for Chinese population compared with other cardiovascular diseases. *Guidelines on Prevention and Treatment of Blood Lipid Abnormality in Chinese Adults* emphasizes the importance of stratification of cardiovascular risks imposed on patients with dyslipidemia by hypertension in Chinese population.

The efficacy of combination therapy with Statins in the treatment of hypertension was evaluated in ALLHAT and ASCOT trials. ASCOT study results showed that lipid regulation treatment was helpful, which reduced the risk of stroke by 15% and 30% as primary prevention and secondary prevention. The series of international trials about Statins in coronary disease and the study of Xuezhikang conducted in China indicated that secondary prevention could be of significant benefit for patients with coronary disease and hypertension, since it could reduce the coronary events and overall mortality remarkably. Similar effect could be achieved by lipid regulation treatment of Statins for patients with or without hypertension in preventing cardiovascular events,

i.e. it could effectively reduce the risks of cardiovascular events. Low dose of Statins was safe and effective when used in patients with hypertension and dyslipidemia as primary prevention. Drug treatment of Statins is not required for all the patients with hypertension as primary prevention. Lipid regulation treatment of Statins could be of significant benefit for patients with moderate and high risks of cardiovascular disease, but not for patients with low risks. Based on the consideration of safety and benefit/cost ratio, treatment of Statins for patients with low risks as primary prevention should be used with caution.

Patients with hypertension and dyslipidemia should adopt active anti-hypertensive treatment and appropriate lipid regulation treatment. Recommendations for lipid regulation treatment are as follows: firstly, change to curative lifestyle. Statins should be the first choice of drug therapy when the lipid level can't reach the goal after strict implementation of curative lifestyle for 3-4 months (Table 2). The dispute about the relationship between blood TC level and cerebral hemorrhage is still ongoing and needs further investigation. Adverse reactions such as abnormal liver function and myalgia should be noted, and regular examination of hematology, ALT, AST and CK should be performed during the treatment of Statins.

5.5.2 Anti-platelet Therapy

Supported by numerous clinical study evidences, the effect of aspirin in secondary prevention of cardio-cerebrovascular diseases is well recognized. Aspirin can effectively reduce the risks of serious cardiovascular disease by 25%, among which, non-fetal myocardial infarction is reduced by 1/3, non-fetal brain stroke is reduced by 1/4, and tall the vascular events are reduced by 1/6. (1) Aspirin of low dose (100 mg/d) should be used in the secondary prevention for patients with hypertension accompanied by co-existing stable coronary heart disease, myocardial infarction, ischemic stroke or history of TIA and co-existing peripheral arthrosclerosis. (2) Administration of aspirin should be based on recommendation of applicable guidelines for patients with co-existing thrombosis accompanied with acute coronary syndrome, ischemic stroke or TIA, and peripheral arteriosclerosis obliterans. Aspirin of loading dose (300 mg/d) could be administered in acute period for secondary prevention and then low dose (100 mg/d) should be used. (3) Anticoagulants such as Warfarin are preferred for hypertensive patients with atrial fibrillation. For patients at moderate or low risks and that cannot administer oral anticoagulants, aspirin can be given according to the applicable guidelines. (4) Aspirin of low dose (75mg～100mg/d) can be used in the primary prevention for patients with hypertension

accompanied by co-existing diabetes or patients at high risk of cardiovascular events. (5) Clopidogrel (75 mg/d) can be used for patients who cannot tolerate aspirin.

The followings should be paid attention to long-term use of aspirin for patients with hypertension: (1) aspirin should be initiated when BP is stable (<150/90 mmHg), and it might increase the risk of cerebral hemorrhage for patients with poor-controlled BP. (2) high risk factors such as disease of digestive tract (peptic ulcers and its complications), age >65 yrs, concomitant medication of corticosteroids or other anticoagulants or nonsteroidal anti-inflammatory drugs should be screened before administration. Prevention actions (screening and treatment of Helicobacter pylori infection, preventive use of proton pump inhibitor and application of proper combination therapy of antithrombotic drugs) should be taken if high risk factors exist. (3) Patients with co-existing active gastric ulcer, severe hepatopathy, and hemorrhagic disease should use aspirin with caution or discontinue aspirin treatment.

5.5.3. Blood Glucose Control

The risk of cardiovascular disease is higher in hypertensive patients with diabetes. The increasing risk of cardiovascular disease is associated with FBG or glycosylated hemoglobin (HbA1c) above normal level. UKPDS study indicates enhancement of blood glucose control has little prevention effect in major vascular events, but has significant lowering effect in microvascular complications compared to conventional blood glucose control. The ideal target of diabetes treatment is: FBG ≤6.1 mmol/L or HbA1c ⩽6.5%. For old people, especially for those live alone, with long course of disease, many complications, diabetic patients with poor self-control, blood glucose control shouldn't be too strict, the target level is FBG ≤7.0 mmol/L or HbA1c ≤7.0%, PBG≤10.0 mmol/L. For diabetic patients at middle or young age, blood glucose should be controlled within normal limit, i.e. FBG ≤6.1 mmol/L, 2hPBG ≤8.10mmol/L, HbA1c ≤6.5%.

5.5.4. Comprehensive Intervention of Various Dangerous Factors

Hypertensive patients often have many coexisting cardiovascular risk compositions, including risk factors, coexisting target organ damage and concurrent medical conditions. In addition to intervention in certain risk composition, comprehensive intervention of various dangerous factors should be emphasized. Comprehensive intervention is good for overall control of cardiovascular risk factors and prevention of cardiovascular disease in the early period. There are many aspects involved in the comprehensive intervention of hypertensive patients, e.g. anti-hypertension, lipid regulation, antithrombus treatment. Data suggests hyperhomocysteinemia is

associated with risk of brain stroke, while the risk can be lowered by adding folic acid. Thus, supplement of folic acid in population who has deficiency of folic acid can be one of the comprehensive intervention measures. The goal of prevention of cardiovascular disease can be achieved by managing various risk factors, protecting target organs and treating the diagnosed diabetic patients.

Inexpensive, low dose fixed compound preparation (Polypill) is beneficial in improving the compliance and effect of comprehensive intervention. At present, the Polypill that is available on the market includes anti-hypertensive drugs/lipid regulating agents (Amlodipine/Atorvastatin) fixed compound preparation; anti-hypertensive drugs/folic acid (Enalapril/folic acid) fixed compound preparation. The ongoing international Polypill intervention study (TIPS) will evaluate pilypill (ACEI, Hydrochlorothiazide of low dose, Atenolol, Simvastatin) as primary prevention in population at moderate or severe risk and susceptible to cardiovascular disease.

5.6. Periodic Checkups and Recording in Hypertension Treatment

5.6.1. Objectives and Details: in the period after the treatment initiation, in order to assess the treatment response and maintain the BP at target level, periodic checkups should be enhanced, and intervals between periodic checkups should be shorter.

The relationship with patients should be well established in the periodic checkups, except close monitoring of patients' BP, other risk factors and improvement of medical conditions and observing the efficacy. The patients should be given lectures about healthcare, they should know the condition of their diseases, including hypertension, risk factors and co-existing clinical conditions, they should know the importance of controlling BP, and the necessity of lifelong treatment. On time administration should be stressed at periodic checkups to get a satisfying efficacy, and patients should get acquainted with potential adverse effect of the drug therapy, and once they experience the adverse effect, they should report as soon as possible. The importance of changing lifestyle should be explained to patients in a simple way to let them know the objective of treatment and stick to the plan for a long term.

Intervals between periodic checkups: intervals should be determined according to the patients' stratification of overall cardiovascular risk and BP level in discretion of doctors. If the current BP level of hypertensive patient is high-normal BP or grade1, and the risk stratification of the patient is in low grade or the patient is taking only one drug, the periodic checkup can be arranged once every 1-3months. For those newly-diagnosed case with high risk and complex diseases, the intervals should be

shorter, for those with high risk and BP not attained to standard level, periodic checkup should be at least once every two weeks; for those with stable BP attained to standard level, follow-up should be once a month. If the BP is reduced to the target level and other risk factors are controlled after treatment, follow-up can be reduced. Transferring patients to the specialized clinics of hypertension or specialized clinics of hospital at higher level should be considered if the patient's BP level is still not reaching the target level after 6 months' treatment and use of at least 3 types of drugs.

Specialized clinics of hypertension should be set up in qualified hospitals at different levels, intensified follow-up should be done to improve the treatment rate and control rate of hypertension.

Special emphasis is: for patient who decided not to receive treatment temporarily, regular follow-up and monitoring should be performed, and in case of delay the decision about whether or not to give the patient anti-hypertensive drugs should be made based on the follow-up results.

Dose reduction: lifelong treatment is always needed for hypertensive patients. If the patient discontinues the drug on his/her own will after the diagnosis, his/her BP level will return to the pretreatment level (sooner or later). However, if the BP level of the patient is under control for a long time, administration frequency or dose could be carefully and gradually reduced, especially for those patients who receive the treatment seriously, observe the lifestyle changing progress and results closely. The BP level should be cautiously monitored when the patient is trying this gradual reduction.

Medical record: It usually takes a hypertensive decade to receive the treatment, and there are many changes in the regimen, including choice of drugs. It is better for doctors to recommend patients to keep a detailed recording of drugs he/she received and the efficacy. Doctors should maintain the complete record for the patients he/she treated for availability at any time.

BP level at clinics of hypertension: the BP value measured by the doctor at clinics.

BP level at admission: the BP value measured by the doctor at admission.

Diagnosis of hypertension (example):

- For newly found elevated BP, if the BP is between 140-179/90-109mmHg, then patient needs a reexamination (usually arranged after 2 weeks), if the 3 BP levels which are not measured within 1 day meet the hypertension criteria, then a hypertension should be diagnosed.
- For patient who was diagnosed as primary hypertension and is receiving

anti-hypertensive treatment, if the BP level for this time is <140/90mmHg, then a primary hypertension should be diagnosed (with treatment of anti-hypertensive drugs).

- If the mean BP value is 152/96mmHg, then a grade 1 primary hypertension should be diagnosed.
- If the hypertensive patient has coexisting risk factors or target organ damage, then the risk factors or target organ damage can be listed, such as hypertension, hypercholesterolemia, left ventricular hypertrophy.
- If the hypertensive patient has coexisting clinical conditions, then clinical conditions could be listed, such as hypertension, coronary heart disease, angina pectoris, sequel of cerebral infarction and diabetes.

Writing about the hypertension risk stratification in the clinic medical record or in-patient case history: risk stratification provides reference mainly for prognosis and medical decision-making. Risk stratification (such as high risk) is not recommended to be included in the hypertension diagnosis of clinic medical record. There is no explicit provision about whether to include the risk stratification in the hypertension diagnosis of in-patient case history. However, exclusion of risk stratification in the hypertension diagnosis of in-patient case history is preferred. And the severity can be narrated in the case analysis.

5.6.2. Dose Adjustment

For most patients with non-acute hypertension or acute hypertension, the anti-hypertensive treatment should be performed gradually to find the minimum effective dose. Thus, treatment should be initiated with low dose, dose can be increased if there is insufficient efficacy and few adverse reactions or the reactions are tolerable after 2-4 weeks of treatment. If the adverse reactions are intolerable, then treatment can be switched to another drug. BP measurement should be performed at the same time during follow-up period. For patient with severe hypertension, early control of BP should be done to increase dose and combined medication. During the follow-up period, necessary examinations are required as well as subjects' subjective feeling to understand the target organ condition and adverse reactions. For patients with non-acute hypertension or acute hypertension, if the BP is controlled and maintained stable for over 1 year after treatment, under the premise of not affecting efficacy, dose reduction can be attempted to reduce the potential adverse reactions.

5.6.3. Annual Assessment of Risk Stratification and Adjustment of Stratification and Management Level

For patients who are clearly diagnosed as hypertension in early period, risk stratification should be based on BP level, co-existing risk factors, target organ damage, clinical conditions. For patients who were diagnosed as hypertension previously but the previous conditions could not be determined at present, risk stratification should be based on current conditions. Try to use the mean value of several BP values measured not in 1 day to be the BP value for risk stratification and BP classification, or use the mean value of the BP measured in the latter 6 days of 7 continuous days (e.g. home blood pressure). The hypertensive patients should be evaluated annually. An annual evaluation of patients who are under risk stratification and classification should be conducted by the physician in charge. New management level is determined in compliance with follow-up recording (BP recording for the whole year, change of risk factors). Clinical assessment, reconfirmation of management level, follow-up management according to the new level management should be conducted when the hypertensive patients under management experience condition change and diseases related to hypertension. In general, for patients with co-existing heart, brain and kidney diseases and diabetes and pertaining to the high risk or very high risk population, risk stratification and management level remain unchanged for long term; for patients with co-existing target organ damage and pertaining to the high risk population, the level remains unchanged; for patients who are classified as moderate risk level or high risk level only based on BP level and/or 1-2 changeable risk factors, the management level can be adjusted after 1 year’s management according to the practical condition; for patients with well-controlled BP for long time (6 continuous months), risk stratification and management level can be lowered with caution; for patients with newly occurred cardio-cerebrovascular disease or nephropathy and diabetes, assessment should be changed: e.g. previous assessed as low risk or moderate risk should be changed to high risk or very high risk, and the management level should be increased meanwhile.