The Oncologist
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Supplemental Appendix for:
Anlotinib monotherapy for refractory metastatic colorectal cancer: A double-blinded, placebo controlled, randomized Phase III trial (ALTER0703)
Jianqiang Cai et al.

CHIA TAI TIANQING PHARMACEUTICAL GROUP CO., LTD (Confidential) Phase III clinical trial protocol of Anlotinib Hydrochloride Capsules (colorectal cancer)

SFDA approval number: 2015L00977/2015L00978 Chemicals 1.1

A randomized, double-blind, placebo-controlled, multicenter, phase III clinical trial comparing the efficacy and safety of the regimens of anlotinib hydrochloride capsules and placebo combined with best supportive care in patients with metastatic colorectal cancer who show deterioration after standard treatment

Protocol No.	ALTN-07- IIB
Version number	2.1
Version date	08-OCT-2015
Clinical Research Head	Prof. Cai Jianqiang, Prof. Yihebali Chi, Prof. Wang Jinwan
Clinical Research Statistical Unit	Department of Epidemiology and Health Statistics, Nanjing Medical University
Applicant	Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

(The following ranking is in no particular order)

Clinical Research Participating Units:

Department of Medical Oncology, National Cancer Center / National Clinical Research Center for Cancer / Cancer Hospital
Peking Union Medical College Hospital
307 Hospital of PLA
Tianjin Medical University Cancer Institute & Hospital
Harbin Medical University Cancer Hospital
Jilin Cancer Hospital
Liaoning Cancer Hospital & Institute
The Sixth Affiliated Hospital, Sun Yat-sen University
The First Affiliated Hospital of Nanchang University
Jiangxi Cancer Hospital
The Second Xiangya Hospital of Central South University
Fujian Cancer Hospital
Affiliated Tumor Hospital of Guangxi Medical University
Chongqing Cancer Hospital
Fudan University Shanghai Cancer Center
Zhongshan Hospital, Fudan University
Qinghai Provincial People's Hospital
Jilin Cancer Hospital
Qilu Hospital of Shandong University
Jiangsu Province Hospital
Jiangsu Cancer Hospital
The first affiliated hospital, Zhejiang University
Nantong Tumor Hospital
The Second Hospital of Anhui Medical University
First Affiliated Hospital of Bengbu Medical College
The First Affiliated Hospital of Xi'an Jiaotong University
Shaanxi Provincial Cancer Hospital
Tangdu Hospital, Air Force Medical University
Gansu Provincial Cancer Hospital
Yunnan Cancer Hospital
The fourth Hospital, Hebei Medical Hospital
Henan Cancer Hospital
The Affiliated Tumor Hospital of Xinjiang Medical University
Liuzhou Worker's Hospital

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Abbreviations

ACEI	:	angiotensin-converting enzyme inhibitors
AE	:	adverse event
AKP	:	alkaline phosphatase
ALT	:	alanine aminotransferase
ANC	:	absolute neutrophil count
APTT	:	activated partial thromboplastin time
ARB	:	angiotensin receptor blocker
AST	:	aspartate aminotransferase
bFGF	:	basic fibroblast growth factor
BSC	:	best supportive care
BUN	:	blood urea nitrogen
B ultrasound	:	B-type ultrasound examination
Ca	:	calcium
Cl	:	chlorine
Cr	:	creatinine
CR	:	complete remission
CRC	:	colorectal cancer
CRF	:	case report form
CT	:	computed X-ray tomography
DCR	:	disease control rate
DLT	:	dose-limited toxicity
DRQ	:	data request queue
ECOG PS	:	Eastern Cooperative Oncology Group Performance Status
EGFR	:	epidermal growth factor receptor
GCP	:	good clinical practice
FAS	:	full analysis set
FGFR	:	fibroblast growth factor receptor
FOLFIRI	:	Folinic acid, 5-fluorouracil and Irinotecan
FOLFOX4	:	Oxaliplatin, leukovorum, and 5-fluorouracil
Glu	:	glucose
Hb	:	hemoglobin
HFS	:	hand, foot and skin reactions
ITT	:	intent-to-treat analysis
K	:	potassium
LD_{50}	:	half lethal dose
LVEF	:	left ventricular ejection fraction
MI	:	myocardial infarction
MRI	:	magnetic resonance imaging
Na	:	sodium
NCCN	:	National Cancer Comprehensive Network
NCI-CTC	:	National Cancer Institute-Common Toxicity Criteria
NYHA	:	New York Heart Association
ORR	:	objective remission rate
OS	:	overall survival
PFS	:	progression-free survival
PD	:	progression of disease
PDGFR	:	platelet-derived growth factor receptor
PI	:	principal investigator
PLT	:	platelets
PR	:	partial response
PRO	:	protein
PPS	:	Per-protocol set
PT	:	prothrombin time
Qd	:	once a day
QoL	:	quality of life
RBC	:	red blood cells
RECIST	:	Response Evaluation Criteria in Solid Tumors
γ-GT	:	γ-glutamyltransferase
SAE	:	serious adverse events
SAS	:	safety analysis set
SD	:	stable disease
TT	:	thrombin time
TTP	:	time to progression
ULN	:	upper limit of normal
UA	:	uric acid

VEGFR : vascular endothelial growth factor receptor

WBC : white blood cells

WT : wild-type

Trial protocol Summary

Title	A randomized,double-blind, placebo-controlled, multicenter, phase III clinical trial comparing anlotinib hydrochloride capsules combined with the best supportive care and placebo combined with the best supportive care in patients with progressively metastatic colorectal cancer after the standard treatment
Program number	ALTN-07-IIB
Applicant	CHIA TAI TIANQING PHARMACEUTICAL GROUP III CO., LTD
Subjects	Patients with metastatic colorectal caner
Research purposes	Evaluation of the efficacy and safety of anlotinib hydrochloride capsules and placebo combined with the best supportive care in patients with advanced colorectal cancer Primary endpoint: Overall survival (OS) Secondary endpoint: progression-free survival (PFS), objective remission rate (ORR), disease control rate (DCR), quality of life score, biomarker evaluation, safety index
Adverse Reaction Criteria	NCI-CTC AE V4.02 was used to evaluate the adverse drug reactions
Study Design	Multicenter, randomized, double-blind, placebo-controlled design
Number of groups planned	2:1, 260 in the test group and 130 in the control group

Dosing regimen	Eligible colorectal cancer patients were treated with anlotinib Hydrochloride capsules/placebo. They were daily administered, each time 12 mg/0 mg dose, continuously for 2 weeks and 1 week off. The therapeutic effect was assessed every 6 weeks (42 days). Those patients with DCR (CR + PR + SD) who can tolerate adverse reactions were given sustained medication. Any other antineoplaston treatments cannot be administered before they show progression of disease (PD). The medication will be terminated when the investigators judged that the patients are not suitable for continued medication or when the therapeutic effect was evaluated as PD.
Principal investigator	Prof. Cai Jianqiang, Prof. Yihebali Chi, Prof. Wang Jinwan
Clinical Research Unit in-charge	Cancer Hospital Chinese Academy of Medical Sciences

Inclusion Criteria:

Those who fulfill all the following criteria are eligible for this trial:

1) Patients who voluntarily participate in this study and sign the informed consent;
2) Histologically or cytologically diagnosed as colon cancer or rectal cancer (Mucinous adenocarcinoma is excluded);
3) Metastatic colorectal cancer (stage IV) with measurable lesions (according to RECIST 1.1 criterion);
4) Patients had received previous second-line chemotherapy; PD or intolerance was noted during the standard treatment or within 3 months of last treatment. Fluorouracil or its ramification, oxaliplatin, and irinotecan are to be included in the standard treatment; patients who accepted oxaliplatin as adjuvant treatment present PD during the treatment or within 6 months after the termination of the treatment. Patients presented with PD after 6 months of completing the adjuvant treatment with oxaliplatin should join a another round of oxaliplation related treatment, and those with PD could join the study:
   [Intolerance: hematological toxicity is grade IV (Platelet level decreases to Level III or above, non-hematological toxicity reaches grade III or above)]
5) Age ≥ 18 years; ECOG PS score: 0–1; expected survival time: ≥3 months
6) Major organ functions meet the following criteria within 7 days before treatment:
   (1) Blood routine examination criteria (14 days without blood transfusion):
      a) hemoglobin (HB) ≥90g/L;
      b) absolute neutrophil count (ANC) ≥1.5 × 109/L;

c) platelet (PLT) $\geq 80 \times 10^9$/L

(2) Biochemical tests to meet the following criteria:

a) total bilirubin (TBIL) ≤ 1.5-fold of the upper limit of normal (ULN);

b) alanine aminotransferase (ALT) and aspartate aminotransferase AST ≤ 2.5 × ULN; in the case of liver metastasis, ALT and AST ≤ 5 × ULN;

c) serum creatinine (Cr) ≤ 1.5 × ULN, creatinine clearance (CCr) ≥ 60mL/min;

Doppler ultrasound evaluation: left ventricular ejection fraction (LVEF) ≥ normal low (50%).

7) Women of childbearing age should agree to the usage of contraceptive measures (such as intrauterine devices, birth control pills, or condoms) during the study period and for 6 months after the end of the study, the serum or urine test should be negative within 7 days before the study, and should be non-lactating. Males should agree to the usage of contraceptives during the study and within 6 months after the end of the study period.

Exclusion criteria: Patients with any of the following criteria will not be enrolled in this study:

1) Patients who had previously used anlotinib hydrochloride capsules;
2) Other malignancies within 5 years or simultaneously, cured cervical carcinoma in situ, non-melanoma skin cancer, and superficial bladder tumor except Ta (non-invasive tumor), Tis (carcinoma in situ), and T1 (tumor infiltration basement membrane);
3) Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, and immunotherapy (or Mitomycin C was used 6 weeks prior to administration of the test drug) was planned within 4 weeks before or during this study. Extended-field radiotherapy (EF-RT) was performed 4 weeks prior to grouping or restricted radiotherapy was performed on tumor lesions within 2 weeks before grouping;
4) Non-mitigated toxicity higher than CTC AE (4.0) level 1 owing to any previous treatment, except hair loss and neurotoxicity ≤ level 2 caused by oxaliplatin;
5) Patients with various factors that affect oral medication (such as inability to swallow and chronic diarrhea);
6) Patients with pleural effusion or ascites, causing respiratory syndrome (≥CTC AE level 2 dyspnea);
7) Patients with interstitial diseases and signs;
8) Patients with any severe and/or uncontrolled disease, including the following:
   a) Hypertensive patients and the blood pressure is not well controlled with single hypotensor (systolic blood pressure ≥ 150 mmHg, diastolic blood pressure ≥ 100

mmHg); patients who are on ≥2 types of antihypertensive drugs;

b) Myocardial ischemia of >grade I or myocardial infarction, arrhythmia (including QTC ≥ 480 ms), and ≥level 2 of congestive heart failure (NYHA classification);
c) Active or uncontrollable severe infection (≥CTC AE level 2 infection);
d) Liver cirrhosis, decompensated liver disease, active hepatitis, or chronic hepatitis to be treated with antiretroviral therapy;
e) Renal failure requires hemodialysis or peritoneal dialysis;
f) History of immunodeficiency, including HIV-positive or other acquired, congenital immune deficiency disease, or a history of organ transplantation;
g) Poor control of diabetes (fasting blood glucose (FBG) > 10 mmol/L);
h) Routine urine examination indicates protein ≥ ++, and confirmed 24 h urine protein > 1.0g;
i) Patients presenting with seizures and need treatment;

9) Patients with digestive tract disease such as duodenal ulcer, ulcerative colitis, or ileus (including incomplete intestinal obstruction) or the researcher judges that the patients might have digestive tract hemorrhage, perforation, or obstruction;
10) Imaging shows that the tumor has invaded crucial vasculature or the researchers determine that the tumor is likely to invade major blood vessels and cause fatal bleeding during the follow-up study;
11) Received major surgical treatment within 28 days prior to grouping, with a biopsy or a significant traumatic injury;
12) Irrespective of severity, patients show any signs of bleeding or medical history; in the first 4 weeks before the grouping, patients have any bleeding or bleeding events (≥CTCAE 3) with non-healing wounds, ulcers, or fractures;
13) Patients have arterial/venous thrombotic events, such as cerebrovascular accident (including temporary ischemic attack), deep vein thrombosis, and pulmonary embolism within 6 months;
14) Patients have a history of psychoactive substance abuse and cannot quit or have mental disorders;
15) Patients had any brain metastases or current brain metastases;
16) Patients participated in other antitumor drug clinical trials within 4 weeks;
17) Patients have concomitant diseases, which might be detrimental to the patient's safety or affect the patient's ability to complete the study according to the researcher's judgment.

1 Research background

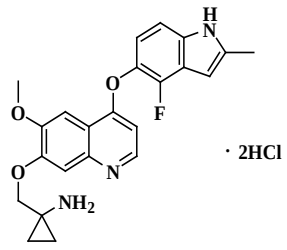
Protein tyrosine kinase (PTK) signaling pathway is associated with the proliferation, differentiation, and migration of tumor cells. Interference or blockade of tyrosine kinase pathway can be used to influence the growth of tumor cells. Thus, screening of PTK inhibitors could be a novel approach for the development of anti-neoplastic drugs.

Anlotinib hydrochloride is a multi-target receptor tyrosine kinase inhibitor; it can ① inhibit vascular formation-related kinases such as VEGFR1/2/3, PDGFRα/β, FGFR1/2/3, c-Kit, Met, Ret, and Tie2; ② inhibit multiple tumor-related kinase targets, including EGFR, ALK, ABL, Aurora-A/B, DDR2, and EphB4; ③ exert inhibitory activity on various mutants; inhibitory activity against the mutant is more robust than that against WT, for instance, ABL (H396P), PDGFRα (V561D), c-Kit (D816V and V654A), Met (D1246H and Y1248C/D/H), EGFR (L861Q), FGFR2 (N549H), ABL (H396P), PDGFRα (V561D), c-Kit (D816V and V654A), Met (D1246H and Y1248C/D/H), EGFR (L861Q), and FGFR2 (N549H) activity against the mutant is more robust than that against WT.

Chia Tai Tianqing Pharmaceutical Group Co., Ltd. developed the anlotinib hydrochloride capsules, with independent intellectual property rights. In March 2011, the company obtained the State Food and Drug Administration clinical research approval (SFDA: 2011L00661) to perform clinical research and in May 2015, the company obtained phase III clinical research approval (SFDA: 2015L00978). Since May 2011, with the joint efforts of the expert group in Cancer Hospital of the Chinese Academy of Medical Sciences, the phase I tolerance and pharmacokinetic studies and the preliminary efficacy study of colorectal cancer have been completed. The study protocol used for phase III, advanced colorectal cancer is developed according to the national GCP, Provisions for Drugs Registration, Guiding Principles for Clinical Research of New Drugs and other relevant laws or regulations. Clinical studies will be conducted after approval by the Ethics Committee for approval.

1.1 Introduction to drugs

Anlotinib hydrochloride is produced as hard capsules. The structural formula of the main component anlotinib is as follows:



Molecular formula: $C_{23}H_{22}FN_3O_3 \cdot 2HCl$ Molecular weight: 480.36

1.2 Overview of general preclinical pharmacology

In the pharmacological study of anlotinib hydrochloride, mice were administered 2, 6, and 20 mg/kg for 24 h, and no significant effect was observed in the general behavior and spontaneous activity; different concentrations of anlotinib hydrochloride (0.3, 0.9, and 3 mg/kg dose) were administered to beagles via duodenum, and no significant effect was observed on the systolic blood pressure, diastolic blood pressure, and mean arterial pressure in the anesthetized dogs during the 240-min observation period. No arrhythmia was noted. No effect was noted on heart rate, electrocardiogram PR, QRS, and QTC intervals, neither on respiratory rate and respiratory depth.

1.3 Overview of preclinical pharmacodynamics

Anlotinib significantly inhibited the growth of transplanted tumor from colon cancer SW-620, ovarian cancer SK-OV-3, lung cancer Calu-3, and hepatocellular carcinoma SMMC-7721 in nude mice and led to partial shrinkage of the tumor. It exhibits optimal effect against renal cell carcinoma Caki-1 and glioma U87MG. The effect of anlotinib on the above tumor model is equivalent to that of sunitinib; however, it was significantly stronger than that of sorafenib. Whether it is administered orally at a relatively low dose once a day, continuously for 21 days or a high dose once a day, for 10 consecutive days, anlotinib hydrochloride exerted a significant effect, suggesting the flexibility of clinical medication program. The tumor-bearing mice adequately tolerated anlotinib hydrochloride; however, no significant reduction in body weight was observed when adequate effect of anlotinib hydrochloride was present. Anlotinib hydrochloride combined with 5-fluorouracil and oxaliplatin did not show any synergistic effect, at least in the colon cancer SW-620 model; no synergistic effect was noted between them and no obvious toxic superposition was observed.

1.4 Overview of preclinical toxicology

1.4.1 Animal acute toxicity test

ICR mice were intragastrically administered anlotinib once; the LD50 was 1735.9 mg/kg for 14 days with 95% confidential interval (CI) 1365.5–5474.6 mg/kg and LD50 was 982.8 mg/kg for continuous observation of 22 days, with 95% CI 657.28–1180.3 mg/kg. The potential target organs included liver, gallbladder, small intestine (mainly duodenum), kidney, spleen, and testis. Beagle dogs were intragastrically administered anlotinib and observed for 14 days after the drugs were discontinued. The maximum tolerable dose was 20 mg/kg, and the minimum lethal dose was 67.5 mg/kg. Drug-related toxic and side effects were similar to

those reported in the literature for the same drug.

1.4.2 Long-term animal toxicity test

SD rats were administered the drug in an intragastric manner for 13 weeks; then, drug administration was discontinued for 6 weeks. The dose of NOAEL was 0.25 mg/kg, and the toxic dose was ≥1 mg/kg. The toxicity was targeted to the organs such as teeth, liver, gallbladder system, duodenum, pancreas, adrenal gland, kidney, and blood system. Liver and gallbladder system as well as teeth and blood system lesions recovered significantly after stopping the treatment; the other organs were fully restored.

Beagle dogs were administered anlotinib in an intragastric manner for 13 weeks and recovered for 4 weeks after the treatment. The main toxicity of 0.40 mg/kg (AUC0→8h: 195ng/h/mL) included gastrointestinal reaction, slight slowing of the heart rate, and effects on the liver and kidney function. NOAEL was 0.12 mg/kg [51.7 ng/h/mL for area under the curve (AUC) 0–8 h]. After withdrawal, the recovery lasted for 4 weeks; the above toxicity recovered; and no delayed toxicity was observed.

1.4.3 Mutagenic test and literature

Anlotinib did not induce (1) mutagenicity in *Salmonella typhimurium* in the *S. typhimurium* response mutant test (Ames) and (2) chromosomal aberrations in Chinese hamster lung fibroblasts (CHL) cells in chromosome aberration tests. It did not increase the micronucleus rate of the bone marrow polychromatic erythrocytes in mice.

1.4.4 Reproductive toxicity test and literature

SD pregnant rats were administered anlotinib in an intragastric manner, and the no toxic reaction dose (NOAEL) of embryo development was <0.3 mg/kg.

1.5 Overview of preclinical pharmacokinetics

Pharmacokinetic parameters: Plasma pharmacokinetic studies in rats and dogs showed that anlotinib hydrochloride was slowly absorbed in the gastrointestinal tract after oral administration.

Bioavailability: Approximately 34% in rats and 67% in dogs.

Plasma protein binding rate: Anlotinib hydrochloride has high protein binding rates with rat, dog, and human plasma protein (97%, 96%, and 93%, respectively), which are independent of the drug concentration.

Tissue distribution: The concentration of drugs in the tissues was higher than that in blood at the same time point, and the distribution of the anlotinib in various tissues did not differ significantly by sex. Among them, the peak concentration in the lung tissue was

approximately 184- (male rats) and 331- (female) fold higher than the plasma concentration. The peak concentration in the spleen, adrenal glands, large intestine, small intestine, ovary, and kidney was 65–144-fold higher than the blood concentration; whereas that in the uterus, heart, liver, stomach, bladder, bone marrow, and fat tissues was 20–47-fold. The peak concentration in the skeletal muscle, pancreas, testis, and brain was 1.7–13-fold higher than the plasma concentration.

Tissue distribution of the tumor-bearing mice: After oral administration, the concentration of anlotinib in the tissue of nude mice was maximal at 4 h. The levels of AUC in the tissues were positively correlated with the dose; the AUC of the liver tissue was linearly related to the dose. The highest concentration of the drug was found in the lung and liver (approximately 10–14-fold as the plasma AUC), followed by kidney (approximately 5.9–8.6-fold as the plasma AUC). The AUC of the anlotinib tumor was approximately 2.4–2.6-fold as that of the plasma. The concentration in colon and plasma are similar (approximately 0.8–1.0-fold as plasma AUC).

Excretion: The cumulative excrement (Cum.Ae) of anlotinib hydrochloride excreted with urine (0–72 h), feces (0–72 h), and bile (0–24 h) was <5% dose of the injection (1.5mg/kg), suggesting that metabolic transformation is the primary elimination pathway for anlotinib.

Metabolites: A total of 23 metabolites were measured in the rat bile, 16 in rat urine, 12 in feces, and 8 in plasma. M16, M21, and M23 were the 3 most important plasma metabolites, and the cumulative excretion of M16 in urine and bile was the highest, whereas that of M18 was the highest in feces.

Metabolizing enzyme activity: Anlotinib had moderate and weak reversible inhibition of 7 CYP enzymes (8 substrates) in human liver microsomes with specific intensity (IC_{50})>100 μM (CYP1A2), 4.96 μM (CYP2B6), 3.71 μM (CYP2C8), 1.56 μM (CYP2C9), 1.67 μM (CYP2C19), 18.5 μM (CYP 2D6), 9.56 μM (CYP3A4-midazolam), and 2.09 μM(CYP3A4-testosterone). The in vitro effect of anlotinib on the induction of CYP1A2, CYP2B6, and CYP3A4, the 3 subtypes of CYP450 in human hepatocytes, suggested that the clinical application of anlotinib did not exert distinct effects on CYP1A2, CYP2B6, and CYP3A4.

1.6 Phase I tolerance and preliminary outcome

Phase I tolerance and preliminary efficacy was examined in clearly diagnosed patients. The tolerance of the use of anlotinib hydrochloride capsules was observed in patients with solid malignant tumors that failed with standard treatment or lack of standard treatment.

Two weeks of continuous medication and 1 week off, i.e., 3 weeks (21 days) is 1

treatment cycle. To study the tolerance, a minimum of 2 cycles (42 days) need to be administered. The results are as follows:

10 mg qd program of 2 weeks on treatment followed by 1 week off treatment:

This study observed a total of 3 patients' medication; adverse reactions in 2 cycles are as follows:

Item	N = 3	Severity
At least one adverse event	3	—
Fat and amylase increased	1	Level III
Fatigue	1	Level II
Increased blood pressure	1	Level I
Diarrhea, abdominal pain	1	Level I
Level I	2	Level I

One patient with abnormal amylase showed an abnormal increase in lipase and amylase, fluctuating in the range of level 1–3 after 5 cycles of treatment. The lipase increased to the highest level 4 and amylase increased to level 3. The patient self-administered anti-inflammatory gallbladder tablets until tumor progression (118 weeks) and was removed from the group.

After 2 cycles of medication, 1 patient had level 2 adverse reactions of diarrhea and leucopenia. Conversely, level 1 adverse reactions cases included 1 case of headache/dizziness, 1 case of hand and foot skin reaction, and 1 case of leukopenia, proteinuria, and elevated transaminase each.

16 mg qd 2 weeks on treatment followed by 1 week off treatment:

The medication program included 3 patients. One patient had level 3 hypertension (3rd week) and level 3 fatigue during 2 cycles of medication. The investigators considered 16 mg Anlotinib hydrochloride capsules as the dose-limiting tolerance (DLT). Other adverse events that occur in 2 cycles are listed the following table.

Item	N = 3	Severity
At least one adverse event	3	—
Fatigue (DLT)	*1*	*Level III*
Elevated blood pressure (DLT)	*1*	*Level III*
	1	Level II
Hypothyroid	2	Level II
Elevation of ALT, AST	1	Level II
Bleeding	1	Level II
Diarrhea, abdominal	1	Level I

pain		
Triglycerides increased	2	Level I
Level I	1	Level I

One case presented the following adverse reactions after 2 cycles of treatment, including level 2 adverse bleeding (dose was then decreased to 12 mg for continued observation), increased bilirubin, high blood pressure, elevated transaminase, hypothyroidism, level 1 adverse reaction of proteinuria, hoarseness, diarrhea, toothache, and tinnitus.

12 mg qd program of 2 weeks on treatment followed by 1 week off treatment:

Further investigation of the maximum tolerated dose: In total, 21 patients enrolled in succession. Medication-related adverse reactions that occurred during the study process (as of July 1, 2014, 8 patients were administering the medication), according to the previous 2 cycles and the entire process statistics, are shown as follows. In this dose group, 5 patients presented level 3 adverse reactions 7 times; specifically, the TG was higher in the 24th patient, hypertension and the hand and foot skin reactions were seen in the 29th patient, the lipase increased in the 31st patient, the bilirubin was elevated in the 32nd patients, and hypertension and elevated TGs were noted in the 34th patient.

Adverse reactions N = 21 n(%)	Cases of Level I/II		Cases of Level III	
	First 2 cycles	Full period of trial	First 2 cycles	Full period of trial
At least once	21(100%)	21(100%)	2(9.52%)	7(33.33%)
hand, foot and skin reactions	4(19.05%)	10(47.62%)	0	1(4.76%)
Rash	4(19.05%)	6(28.57%)	0	0
Increased blood pressure	5(23.81%)	5(23.81%)	0	2(9.52%)
Proteinuria	5(23.81%)	14(67%)	0	0
Triglycerides increased	6(28.57%)	11(52.38%)	1(4.76%)	2(9.52%)
Total cholesterol increased	6(28.57%)	13(62%)	0	0
Low-density lipoprotein increased	4(19.05%)	11(52.38%)	0	0
Hypothyroid	8(38.10%)	12(57 %)	0	0
Hyperthyroidism	2(9.52%)	2(9.52%)	0	0
Thyrotropin increased	2(9.52%)	4(19.05%)	0	0
ALT increased	6(28.57%)	10(47.62%)	0	0
AST increased	4(19.05%)	9(42.86%)	0	0
Creatinine increased	1(4.76%)	2(9.52%)	0	0
Total bilirubin	5(23.81%)	8(38.10%)	0	0

Adverse reactions N = 21 n(%)	Cases of Level I/II		Cases of Level III	
	First 2 cycles	Full period of trial	First 2 cycles	Full period of trial
increased				
Direct bilirubin increased	3(14.29%)	8(38.10%)	0	1(4.76%)
Indirect bilirubin increased	4(19.05%)	5(23.81%)	0	0
Lipase	1(4.76%)	5(23.81%)	1(4.76%)	1(4.76%)
Mylase	4(19.05%)	9(42.86%)	0	0
Myocardial zymogram abnormalities	2(9.52%)	3(14.29%)	0	0
Leukopenia	3(14.29%)	6(28.57%)	0	0
Neutrophils decreased	0	2(9.52%)	0	0
Platelet decreased	0	2(9.52%)	0	0
Bleeding	0	1(4.76%)	0	0
Urine occult blood	5(23.81%)	8(38.10%)	0	0
Fatigue	5(23.81%)	7(33.33%)	0	0
Diarrhea	6(28.57%)	7(33.33%)	0	0
Level I	3(14.29%)	5(23.81%)	0	0
Nausea	3(14.29%)	3(14.29%)	0	0
Loss of appetite	1(4.76%)	2(9.52%)	0	0
Toothache	1(4.76%)	4(19.05%)	0	0
Gingivitis	1(4.76%)	1(4.76%)	0	0
Pain	4(19.05%)	4(19.05%)	0	0
Sore throat	1(4.76%)	4(19.05%)	0	0
Dizziness/Headache	1(4.76%)	2(9.52%)	0	0
Fever	1(4.76%)	2(9.52%)	0	0
Oral mucositis	0	2(9.52%)	0	0
Tinnitus	1(4.76%)	1(4.76%)	0	0
Premature beat	0	1(4.76%)	0	0

1.7 Pharmacokinetic studies in human body

According to the phase I clinical trial program, all the subjects with solid tumor who participated in the tolerance study were monitored for plasma concentration. The LC-MS/MS technique was used to estimate the pharmacokinetic parameters of anlotinib hydrochloride capsules.

1.7.1 Pharmacokinetics of a single administration

Eligible Subjects administered anlotinib capsule once for a single pharmacokinetic study.

A total of 19 subjects in 3 dose groups (10 mg, 16 mg, and 12 mg) were tested for the plasma concentration. The average medication time curves for each dose group were shown in the left panel of Fig. 1. The estimated pharmacokinetic parameters are shown as follows:

Table 1 Pharmacokinetic study result of anlotinib hydrochloride capsules

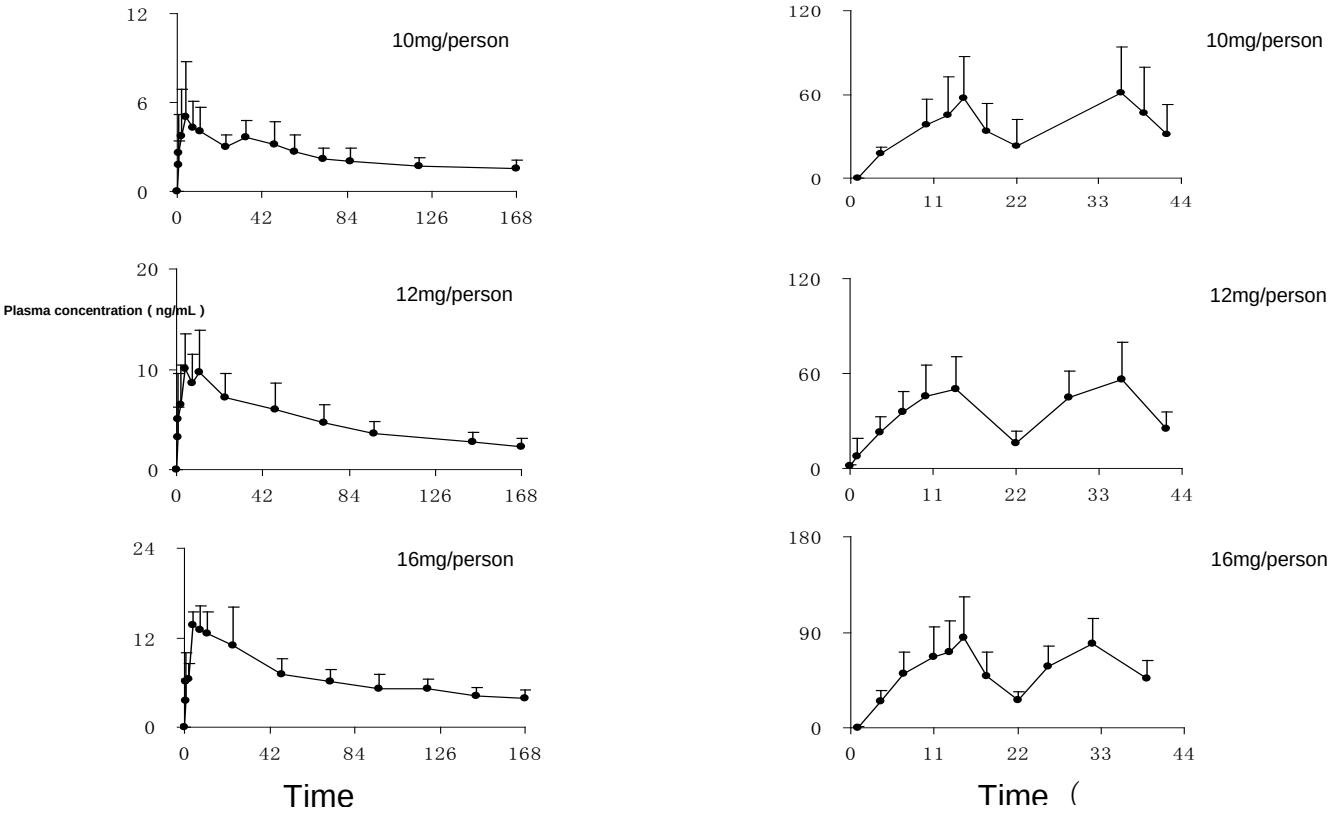
Pharmacokinetic parameters	Mean ± SD (RSD%)		
	10 mg/person(n=4)	12 mg/person(n=11)	16 mg/person(n=4)
C_{max} (ng/mL)	5.78 ± 2.76 (47.7)	10.5 ± 2.9（28.0）	15.8 ± 3.2 (20.1)
Body weight checked C_{max}	0.08 ± 0.05（58.2）	0.15 ± 0.05（34.0）	0.28 ± 0.09 (32.0)
T_{max} (h; p.o)	6.0 ± 4.4 (73.3)	7.3 ± 3.3（45.6）	11.0 ± 8.9 (80.6)
AUC_{0-t} (ng·h/mL)	385 ± 175 (45.7)	875 ± 240（27.5）	1290 ± 384 (29.7)
Body weight checked AUC	5.63 ± 3.37 (59.8)	12.8 ± 3.6（28.1）	23.2 ± 10.1 (43.7)
$AUC_{0-\infty}$ (ng·h/mL)	562 ± 328 (58.3)	1066 ± 263（24.6）	1585 ± 470 (29.6)
$t_{1/2}$ (h)	95.3 ± 21.7 (23)	116 ± 47（40.5）	97.9 ± 14.8 (15.1)

Body weight checked C_{max}: C_{max} /body weight; Body weight checked AUC: AUC/body weight

After a single oral administration of anlotinib hydrochloride, the concentration of the drug in the plasma reached a high level at 4–8 h, with an extremely long half-life. The levels of anlotinib ($AUC_{0–168\ h}$) were positively correlated with the administered dose; however, the linear correlation was uncertain at the dose range of 10, 12, and 16 mg/person. After single oral administration, the cumulative urinary excretion of anlotinib accounts for less than 4% of the oral dose.

1.7.2 Pharmacokinetics of continuous administration

Eligible subjects were administered medication once for a single pharmacokinetic monitoring, followed by at least 7 days clearance to the start of the pharmacokinetic studies for continuous medication. A treatment cycle included continuous medication for 2 weeks and 1-week withdrawal, and continuous monitoring lasted for at least 2 cycles. A total of 21 subjects in the 3 dose groups (10 mg, 16 mg, and 12 mg) received anlotinib hydrochloride capsules, and plasma concentrations were monitored. The average medication time curve for each dose group is shown in Fig. 1 right panel. The pharmacokinetic parameters estimated here are shown in Table 2.



Single medication curve 2 weeks on treatment followed by 1 week off treatment

Figure 1 Medication time curves for a single medication and 2 weeks on treatment followed by 1 week off treatment

Table 2 Estimated pharmacokinetic parameters of anlotinib for 2 weeks on treatment followed by 1 week off treatment

Pharmacokinetic parameters	Mean ± SD（RSD%）		
	10 mg/person/day (n = 3)	12 mg/person/day (n = 15)	16 mg/person/day (n = 3)
C_{max} (ng/mL)	65.2 ± 28.9 (44.3)	61.6 ± 16.3 (27)	93.7 ± 27.8 (30.0)
Body weight checked C_{max}	1.09 ± 0.48（44）	0.96 ± 0.31 (32)	1.84 ± 0.65 (35.4)
$AUC_{0\text{-}42days}$ (ng/h/mL)	1550 ± 864 (58)	1467 ± 395 (27)	2237 ± 814 (36.4)
Body weight checked $AUC_{0\text{-}42days}$	25.9 ± 14.3 (56)	22.7 ± 6.7 (31)	44.3 ± 18.1 (40.9)

Body weight checked C_{max}: Cmax/body weight; Body weight checked AUC: AUC/body weight

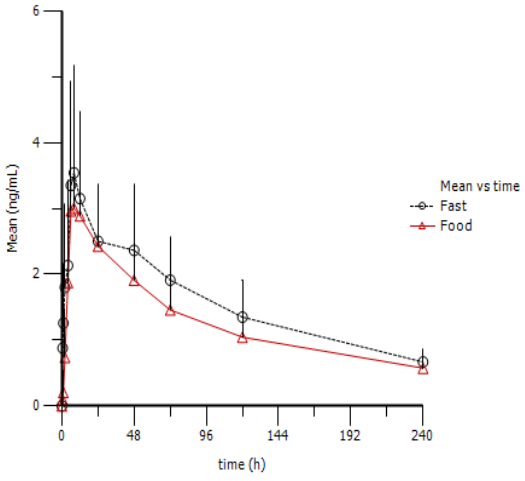
After continuous administration, owing to the prolonged half-life of anlotinib in the human body before being eliminated, the drug concentration in the plasma increases with the number of administrations. To control the anlotinib concentration in the plasma post-

administration, the program of 2 weeks on treatment followed by 1 week off treatment was employed. With the "2 continuous one withdrawal" mode of administration, the anlotinib concentration in the plasma peaked on day 14 post-administration. At the dosage of 10 and 12 mg/person/day, the anlotinib concentration in the plasma was controlled at ≤100 ng/mL.

1.7.3 Effects of diet on pharmacokinetic parameters for healthy subjects

A random, double-cycle, self-cross design was used. A total of 12 healthy subjects aged 18–40 years were randomly divided into 2 groups (fasting group and high-fat diet group), 6 in each group (equal number of men and women). The subjects were administered 5 mg anlotinib hydrochloride capsules with fasting for 10 hours, fasting, or postprandial. Patients were then eluted for 28 days, and patients from each group were swapped to another group and were administered 5 mg anlotinib hydrochloride capsules.

The pharmacokinetic parameters of fasting or postprandial medication are similar, as described in the following chart. The results of the study showed compared with that that in fasting group, the duration for which the concentration of anlotinib peaked in the human body was prolonged and the degree of drug absorption was slightly lower (approximately 80% in empty stomach group) in the high-fat diet group. Therefore, this medication is recommended to be taken under the fasting condition in the following clinical use.



Pharmacokinetic parameters	High-fat diet group	Fasting group
C_{max} (ng·mL^{-1})	3.35 ± 1.35	3.90 ± 1.60
T_{max} (h)	10.5 ± 6.7	9.3 ± 5.1
$AUC_{inf}/AUC_{0-\infty}$ (ng·h·mL-1)	392 ± 145	486 ± 158
$MRT_{inf}/MRT_{0-\infty}$ (h)	153.2 ± 43.7	161.7 ± 41.3
$t_{1/2}$ (h)	107.2 ± 27.4	113.2 ± 30.3

1.8 Current treatment status of colorectal cancer

According to the 2012 Global Cancer data updated at the end of 2013, colorectal cancer (CRC) is the third most common malignant tumor in the world (13.0% for lung cancer, 11.9% for breast cancer, and 9.7% for colorectal cancer). The mortality rate in developed countries almost reached 33%. China Cancer Registry Annual Report[1] published in 2012 shows that the incidence of colorectal cancer among malignant tumors at cancer-registered areas in China

was 29.44/100,000, ranking third; the mortality rate was 14.23/100,000, ranking fifth.

The latest grading standards for colorectal cancer has been developed by the Union for International Cancer Control together with the American Joint Committee on Cancer (AJCC). The treatment for colorectal cancer includes surgery, chemotherapy, and systemic chemotherapy according to the phases of the tumor.

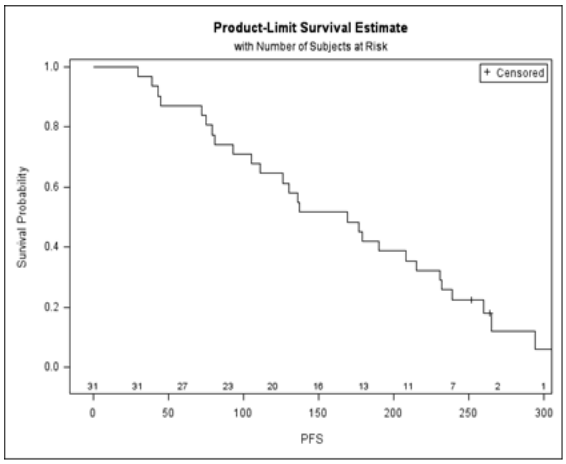
Approximately 50%–60% of patients diagnosed with colorectal cancer were in the advanced phase with metastasis, and 80%–90% of these patients had liver metastasis which cannot be resected by surgery. Grade IV colorectal cancer included the distant metastasis. The treatment of recurrent colorectal cancer is supposed to be administered according to recurrence site; the treatment options include the following: surgical resection could be performed for local recurrent tumor; for selective patients with metastasis, surgical resection could be performed to remove primary lesion with coloproctostomy or bypass operation could be performed at the obstruction site or hemorrhagic primary focus; liver metastases could be resected (the 5-year cure rate of surgical resection for isolated or combined metastasis is >20%) or treated by ablation. Surgical resection of isolated lung or ovarian metastatic lesions in selective patients; palliative reduction radiotherapy; palliative reduction chemotherapy; participation in clinical trials evaluating new drugs or biological treatments; participation in clinical trials to compare multiple chemotherapy regimens or biological treatments used alone or in combination.

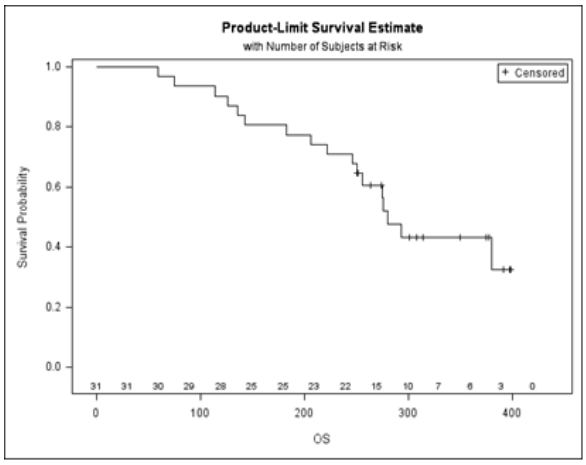
Drugs approved for the treatment of metastatic colorectal cancer in China and abroad include 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab, and Georgini (regorafenib). The choice of treatment depends mainly on the target of treatment, the type and duration of previous treatments, and the different toxicity effects of the various drugs in the treatment regimen. Regorafenib is a small molecule tyrosine kinase (VEGFR, FGFR, PDGFR, BRAF, KIT, and RET) inhibitor. Phase III clinical CORRECT study showed that 760 patients with colorectal disease who progressed after standard treatment were treated with regorafenib or placebo in combination with best supportive treatment, the primary end point was achieved [OS (6.4 months vs. 5.0 months; HR = 0.77; 95% CI, 0.64–0.94; p = 0.005). PFS (1.9 vs. 1.7 months; HR = 0.49; 95%CI, 0.42–0.58; p < 0.000001)].

1.9 Preliminary data of patients treated with anlotinib hydrochloride for colorectal cancer

Anlotinib is a multi-targeted small molecule receptor tyrosine kinase inhibitor; several of

its targets are consistent with those of regorafenib, and it has more effective targets. From the second half of 2013, 31 patients with advanced colorectal cancer were observed in the clinical study of the treatment of advanced tumors with anlotinib hydrochloride capsules used in a program of 2 weeks on treatment followed by 1 week off treatment. As of March 31, 2015, safety and preliminary efficacy statistics were studied, suggesting that there is a certain therapeutic effect of anlotinib hydrochloride capsule on advanced colorectal cancer and it is well tolerated. The patient's mPFS was 5.63 months and mOS were 9.33 months.





Adverse reactions included common adverse reactions observed in phase I study, such as elevated blood pressure, hand–foot syndrome, and dyslipidemia.

Based on the above data, a phase III clinical study protocol was to be designed to further confirm the efficacy and safety of anlotinib hydrochloride capsules in patients with advanced colorectal cancer.

2 Research purposes

This study aimed to evaluate the efficacy and safety of anlotinib hydrochloride capsules and placebo combined with the best supportive care in patients with advanced colorectal cancer.

The efficacy indicators include OS, PFS, ORR = CR + PR, DCR = CR + PR + SD, QoL score, and biomarker assessment results.

3 Study population

Patients with advanced colorectal cancer have to sign the informed consent form before participating in the clinical trial.

3.1 Selection criteria

1) Patients who voluntarily participate in this study and sign the informed consent;
2) Histologically or cytologically diagnosed as colon cancer or rectal cancer (Mucinous adenocarcinoma is excluded);
3) Metastatic colorectal cancer (stage IV) with measurable lesions (as RECIST 1.1 standard);
4) Patients had received previous ≥ second-line chemotherapy, PD or intolerance was on during the standard treatment or within 3 months of last treatment. Fluorouracil or its ramification, oxaliplatin, and irinotecan are to be included in the standard treatment; patients accepted oxaliplatin as supportive treatment may present with PD during the supportive treatment or within 6 months after the supportive treatment finished. Patients with PD 6 months after completing the adjuvant therapy with oxaliplatin and failed the oxaliplatin-based second treatment or could not tolerate the drug toxicity can join the study;

   [Intolerance: hematological toxicity is grade IV (Platelet level decrease to Level III or above, non-hematological toxicity reaches grade III or above)]
5) Age ≥ 18 years; ECOG PS score: 0–1; expected survival time ≥ 3 months;
6) Major organ functions meet the following criteria within 7 days prior to treatment:

   （1） Blood routine examination criteria (14 days without blood transfusion):
   a) hemoglobin (HB) ≥90g/L;
   b) absolute neutrophil count (ANC) ≥1.5 × 10^9/L;
   c) platelet (PLT) ≥ 80 × 10^9/L.

   (2) Biochemical tests to meet the following criteria:
   a) total bilirubin (TBIL) ≤ 1.5-fold of the ULN;
   b) alanine aminotransferase (ALT) and aspartate aminotransferase AST ≤ 2.5 × ULN; in the case of liver metastasis, ALT and AST ≤ 5 × ULN;
   c) serum creatinine (Cr) ≤ 1.5×ULN, creatinine clearance (CCr) ≥ 60mL/min;

   (3) Doppler ultrasound evaluation: left ventricular ejection fraction (LVEF) ≥ normal low (50%).
7) Women of childbearing age should agree to the usage of contraceptive measures (such as intrauterine devices, birth control pills, or condoms) during the study period and for 6 months after the end of the study, the serum or urine test is negative within 7 days before the study, and should be non-lactating patients. Males should agree to the usage of contraceptives during the study and within 6 months after the end of the study period.

3.2 Exclusion criteria

Patients with any of the following criteria will not be enrolled in this study:

1) Patients who had previously used anlotinib hydrochloride capsules;
2) Other malignancies within 5 years or simultaneously, cured cervical carcinoma in situ, non-melanoma skin cancer, and superficial bladder tumor except [Ta (non-invasive tumor), Tis (carcinoma in situ), and T1 (tumor infiltration basement membrane)];
3) Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, and immunotherapy (or use of Mitomycin C 6 weeks prior to administration of the test drug), was planned within 4 weeks prior to or during this study. Extended-field radiotherapy (EF-RT) was performed 4 weeks before grouping or restricted radiotherapy was performed on tumor lesions within 2 weeks before grouping;
4) Non-mitigated toxicity higher than CTC AE (4.0) level 1 owing to any previous treatment, except hair loss and neurotoxicity ≤ level 2 caused by oxaliplatin;
5) Patients with various factors that affect oral medication (such as inability to swallow and chronic diarrhea);
6) Patients with pleural effusion or ascites, causing respiratory syndrome (≥CTC AE level 2 dyspnea);
7) Patients with interstitial diseases and signs;
8) Patients with any severe and/or uncontrolled disease, including the following:
    a) Hypertensive patients and the blood pressure is not well controlled with single hypotensor (systolic blood pressure ≥ 150 mmHg, diastolic blood pressure ≥ 100 mmHg); patients who are on 2 or more types of antihypertensive drugs;
    b) Myocardial ischemia of >Grade I or myocardial infarction, arrhythmia (including QTC ≥ 480 ms), and ≥level 2 of congestive heart failure (NYHA classification);
    c) Active or uncontrollable severe infection (≥CTC AE level 2 infection);
    d) Liver cirrhosis, decompensated liver disease, active hepatitis, or chronic hepatitis to be treated with antiretroviral therapy;
    e) Renal failure requires hemodialysis or peritoneal dialysis;
    f) History of immunodeficiency, including HIV-positive or other acquired, congenital immune deficiency disease, or a history of organ transplantation;

g) Poor control of diabetes (fasting blood glucose (FBG) > 10 mmol/L);

h) Routine urine examination indicates protein ≥ ++, and confirmed 24 h urine protein > 1.0g;

i) Patients presenting seizure and need treatment;

9) Patients have digestive tract disease such as duodenal ulcer, ulcerative colitis or ileus (including incomplete intestinal obstruction), or the researcher judges that patient might have digestive tract hemorrhage, perforation, or obstruction;
10) Imaging shows that the tumor has invaded crucial vasculature or the researchers determine that the tumor is likely to invade major blood vessels and cause fatal bleeding during the follow-up study;
11) Received major surgical treatment within 28 days prior to grouping, with a biopsy or a substantial traumatic injury;
12) Irrespective of severity, patients show any signs of bleeding or medical history; in the first 4 weeks before the grouping, patients have any bleeding or bleeding events (≥CTCAE 3) with non-healing wounds, ulcers, or fractures;
13) Patients have arterial/venous thrombotic events, such as cerebrovascular accident (including temporary ischemic attack), deep vein thrombosis, and pulmonary embolism within 6 months;
14) Patients have a history of psychoactive substance abuse and cannot quit or have mental disorders;
15) Patients had any brain metastases or current brain metastases;
16) Patients participated in other antitumor drug clinical trials within 4 weeks;
17) Patients have concomitant diseases, which might be detrimental to the patient's safety or affect the patient's ability to complete the study according to the researcher's judgment.

3.3 Standards for termination of the subject's medication

1) Determine the PD or clinically consider PD based on efficacy evaluation criteria;
2) Patients present malignant pleural effusion which is ≥Level III or pneumothorax according to NCI-CTC AE4.0;
3) Interim analysis shows lack of therapeutic effect of drug to terminate the trial;
4) The study physician had to necessarily terminate the treatment for the patient's benefit;
5) The occurrence of intolerable adverse reactions or serious adverse events confirmed

by the researchers;

6) Patients with poor compliance, and the use of drugs should range in 80%–120% of the patients;
7) Patient's withdrawal of the informed consent;
8) Use of other antitumor drug treatments (such as chemotherapy, targeted therapy, or biological agents) that affect the determination of efficacy;
9) Accidental pregnancy;
10) Death.

3.4 Elimination criteria

1) Dosage and method error;
2) During the trial period, other chemotherapy, surgical treatment, or trial drug therapy, other than the current program is used;
3) Patient does not fulfill the standards and is erroneously included;
4) Patient without medication.

4 Test drug

Test Drugs: Anlotinib hydrochloride capsules: produced and provided by Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Specifications: 12 mg/tablet, 10 mg/tablet, 8 mg/tablet;

Placebo: Blank capsules substituting the anlotinib hydrochloride capsule: produced by Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Storage conditions: sealed, dark, room temperature, valid for 24 months.

According to the requirements of GCP, the research medication is governed by the hospital custody; the drug is regularly released and recycled. Both issuance and recycling require a complete record. The recycled drug is submitted to the sponsor after completion of the trial. Inspectors regularly check the usage and record of the drugs as well as monitor the recycle situation at any time.

5. Experimental design

A randomized, double-blind, placebo-controlled, multicenter, phase III clinical trial was designed using anlotinib hydrochloride combined with the best supportive care and placebo-controlled therapy combined with the best supportive care in patients with progressively metastatic colorectal cancer after standard treatment. All centers competed to include patients.

5.1 Sample size estimation

Regarding the fact that no OS values have been observed in patients with colorectal cancer using anlotinib hydrochloride capsules, based on the clinical data of similar drugs [5], the phase III clinical study sample size is estimated according to the main efficacy index, i.e., overall survival.

The primary objective of this study was to compare the OS of patients with advanced colorectal cancer who were treated with anlotinib hydrochloride and placebo combined with best supportive care. Assuming that the hazard ratio of the OS was 0.70, the median OS time in the anlotinib group was 43% higher than that in the placebo group. Assuming that the actual median OS of the anlotinib group was 9.0 months and the placebo group was 6.3 months, the unilateral test level was $\alpha = 0.025$, the power was 0.85, and control ratio was 2:1. Furthermore, 291 (194 in the anlotinib group and 97 in the control group) cases of OS events occurred in the 2 groups, thereby revealing statistically significant difference in the 2 groups. Assuming 12 months for enrolling patients and 12 months follow-up, the study planned to enroll 390 patients, including 260 in the trial group and 130 in the control group.

5.2 Interim analysis

An independent data monitoring committee was established to conduct mid-term data analysis for assessing the patients' risks/benefits. The independent data committee comprised 3 independent oncologists and an independent statistician to work independently of the sponsor and investigator.

One interim analysis will be performed during this study, when about 150 events of OS will be performed (approximately half of the total number of OS events required for this study). If the analysis of results provides a risk ratio of ≥0.9134 (the corresponding OS increased by ≤9% compared with placebo), it can be considered to be ineffective and the trial is stopped; if the risk ratio is ≤0.7740 (corresponding OS increased by ≥33.3% compared with placebo), the summary can be submitted in advance because the drug is effective, and the data could be supplemented after the trial is finished.

In this study, the mid-term validity analysis was performed according to O'Brien–Fleming's method, $\alpha_1 = 0.005$ for mid-term analysis and $\alpha_2=0.048$ for final analysis.

5.3 Randomization method

In this study, centralized randomized grouping method is used. The centralized randomized grouping program utilizes the centralized randomized grouping system provided by the Department of Epidemiology and Health Statistics, Nanjing Medical University. The participants in the test center of this trial logs in to the random system after screening for

every qualified subject by the researchers in all centers, fills in the screening information, obtains the random number, and the corresponding drug number information. The appropriate research drugs were issued according to the random number and drug number.

During the study, if the patient needs to adjust the dose, the reasons for adjustment are recorded, and the specialized statistical staff is notified in writing. After confirmation of the same number, different doses of drugs will be issued to the research center.

To ensure the balance between the test and control groups, the following factors affecting the efficacy of indicators are controlled:

- Previous history of receiving VEGF targeting therapy (yes/no)
- The duration from diagnosis of the disease to metastatic disease (≥18 months vs. <18 months)

5.4 Dosage regimen

(1) Administration method:

Before breakfast, anlotinib hydrochloride capsules/placebo is taken, 1 tablet/once/day, 12/0 mg (1 tablet); the drug administration is continued for 2 weeks and stopped for 1 week, thus 3 weeks (21 days) for a treatment cycle. If medication is missed and the interval from the next medication is <12 h, no medication is supplemented.

Patients with disease control (CR + PR + SD) and those who can tolerate adverse reactions continue the medication. When the investigators confirm that the patient cannot tolerate continued medication based on RECIST 1.1 standard evaluation for the PD, the treatment is ended.

For patients who are evaluated as PD but with tumor center necrosis or reduced density, if they can get clinical benefits by continuing the use of study drug and they proactively submit a written request to continue using the drug, they can continue to use the study drug with the original number if the request is signed and approved by the principal investigator of each sub-center and another senior physician and agreed upon by the sponsor. According to RECIST1.1 standard, the patient was still evaluated as PD.

(2) Principle of dose adjustment

During the medication, the dose was adjusted by the investigator based on the degree of drug-related toxicity (according to NCI-CTC AE 4.0) and the potential benefit to the patient. This study was designed in 2 levels of dose adjustment. If >2 dose levels need to be reduced, the treatment should be terminated.

Dose level	Dosage	Specific amount of drugs

1–Standard dose	12 mg oral, once a day	12 mg anlotinib hydrochloride capsules, 1 pill
2–Reduction 1	10 mg oral, once a day	10 mg anlotinib hydrochloride capsules, 1 pill,
3–Reduction 2	8 mg oral, once a day	8 mg anlotinib hydrochloride capsules, 1 pill

(3) Delayed administration and dose level adjustment

The following table shows the delayed delivery time and/or change in the dosage regimen recommended when a drug-related toxic response occurs with the study drug (When the patient present abnormal liver function, bleeding, proteinuria, and decline in the platelet count, please refer to the sequential isolated table).

Adverse reaction level	Time of administration	Dose adjustment
Level 0–2	Administration on time	No change
Level 3	Delayed administration until the extent of recovery to < Level 2 #	Reduce one dose level
Level 4	Delayed administration until the extent of recovery to < Level 2 #	Reduce one dose level. The treatment can be permanently terminated according to the researcher's judgment.

If it has not been restored after 3 weeks of delay, the treatment should be permanently terminated.

The following Table shows delayed administration time and/or change in the dosage regimen in case of a liver function abnormality occurs (elevated ALT, AST, or total bilirubin)

AE Levels	Dose adjustment program	Recommendations
Level 1	Maintain the original dose	Follow-up as the original plan
Level 2 (normal baseline)	Delay administration and reduce the dose level if the AE level is restored to <2 within 2 weeks	Active liver protection and strict monitoring of liver function once a week
Level 2 (normal baseline)	Maintain the original dose	Active liver protection and strict monitoring of liver function once a week
Level 3	Delay administration and	Active liver protection and strict

	reduce the dose level if the AE level is restored to <2 within 2 weeks	monitoring of liver function twice a week until the toxicity is restored to <2 or there is an explanation
Level 4	Permanent termination of treatment	Active liver protection and strict monitoring of liver function 1–2 times a week until the toxicity is restored to <2 or there is an explanation

The following table shows the delayed administration time and/or change in the dosage procedure recommended for proteinuria

AE Levels	Dose adjustment program	Recommendations
Level 1: Routine urine examination showed urine protein+ or quantitative detection of 24 h urine protein is <1.0g	Maintain the original dose	Follow-up as the original plan
Level 2: Routine urine examination showed urine protein++ but quantitative detection of 24 h urine protein is 1.0g–2.0g (not included)	Maintain the original dose	Active treatment and urine monitoring (once a week); if necessary, consult renal clinicians
Level 2: Routine urine examination showed urine protein++ or above, quantitative detection of 24 h urine protein is 2.0–3.5g (not included)	Delay administration; reduce the dose level for follow-up medication if the AE level is restored to <2 within 2 weeks	Active treatment; if necessary, consult renal clinicians, terminate the treatment at the third occurrence
Level 3: Quantitative detection of 24 h urine protein is ≥3.5 g	Delay administration. Reduce the dose level for follow-up medication if the AE level is restored to <2 within 2 weeks	Active treatment; if necessary, consult renal clinicians, terminate the treatment at the third occurrence

The following table shows the delayed delivery time and/or change in the dosage level recommended after a bleeding event

AE Levels	Dose adjustment program	Recommendations
Level 1	Maintain the original dose	Follow-up as the original plan

Level 2	Delay administration and reduce the dose level if the AE level is restored to <2 within 2 weeks	Deal with it actively
Level ≥3	Permanent termination of treatment	Emergency medical intervention

The following table shows the delayed delivery time and/or change in the dosage level recommended when thrombocytopenia happened

AE Levels	Dose adjustment program	Recommendations
Level 1: Platelet count 100–75 × 10^9/L	Maintain the original dose	Follow-up as the original plan
Level 2: Platelet count 75–50 × 10^9/L	Delay administration and maintain the original dose if the AE level is restored to <2 within 1 week	Routine blood checks once every 2–3 days. In the follow-up visit, blood routine should be reviewed weekly
	Delay administration and reduce the dose level if the AE level is restored to <2 within 2 weeks	Routine blood checkup once every 2–3 days. In the follow-up visit, blood routine should be reviewed weekly
Level 3: Platelet count 50–25 × 10^9/L	Delay administration and reduce the dose level if the AE level is restored to <2 within 2 weeks	Routine blood checkup once every 2–3 days. In the follow-up visit, blood routine should be reviewed weekly
Level 4: Platelet count <25 × 10^9/L	Permanent termination of treatment	Daily review of blood routine until the recovery to ≤2; active infusion of single platelets and active treatment

6 Efficacy evaluations

Primary efficacy indicators: OS

Secondary efficacy indicators: (1) PFS

(2) ORR (CR + PR),

(3) DCR (CR + PR + SD),

(4) Quality of life score.

The objective efficacy index was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

PFS is defined as the time from randomization to tumor progression or death.

DCR is defined as the percentage of patients with complete remission, partial remission, and disease stabilization and maintaining the number of evaluable patients over 4 weeks.

OS is defined as the time from randomization to death for any reason. It is presented as

number of days. For subjects lost for follow-up, the last follow-up time is usually considered as the death time.

For patients who discontinued the study without PD, follow-up to obtain the results of tumor evaluation should be recorded on CRF until the PD. Any of these antitumor treatments must also be recorded in the CRF. In the analysis, the censor time of these patients was set as the date of last follow-up visit. A long-term follow-up (including telephone follow-up) was performed on patients (including outpatients); in addition, they were followed up every 8 weeks to obtain OS, followed by anticancer treatment information and survival status during major follow-up.

Quality of Life Score: QLQ-C30 is a specific questionnaire for cancer patients and is used to determine health-related quality of life. QLQ-C30 questionnaire includes 5 functional domains (physical, responsible, emotional, social, and cognitive), 3 symptoms score (fatigue, pain, and nausea/vomiting), health score, and other individual items (dyspnea, sleep disorders, constipation, and diarrhea) with clinical symptoms as well as economic pressures.

Most of the QLQ-C30 questionnaires were analyzed by a 4-point Likert scale. A 7-point Likert scale analysis was used only for health status/quality of life. All the scaling and individual items should be converted to 0–100 scales for convenience of illustration and description In the Functional and Quality of Life Scale, the higher the score, the better the functional status. However, regarding clinical symptom scales and individual items, high scores represent a high degree of symptomology.

The EQ-5D is a questionnaire used to measure a patient’s health status/quality of life. This questionnaire comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels to indicate the extent of problems experienced by a patient: no problems (Level 1), some problems (Level 2), and extreme problems (Level 3). The results for the 5 dimensions can be combined into a single EQ-5D value. This value differs from 0 to 1; 0 represents worst imaginable health state or death and 1 represents best imaginable health state. The questionnaire also included a visual analog scale (EQ-VAS) that records the patient’s self-assessed health on a vertical scaled visual analog scale ranging from 0 (Worst imaginable health state) to 100 (Best imaginable health state).

7 Exploratory study

7.1 Biomarker

To explore the possible mechanisms underlying the effect of anlotinib hydrochloride capsules in the treatment of patients with metastatic colorectal cancer and to develop more targeted treatment strategies for patients with colorectal cancer, the following exploratory studies were conducted. Patients were enrolled in this trial under informed and voluntary terms.

It is planned to use the tumor tissue specimens, cancerous pleural effusion, plasma, and/or serum. The tumor tissue can be retained from the previous withdrawal or collected before or during the study. The analysis results of plasma and/or serum samples can be obtained when the patient visits the outpatient department or when other exams are performed. Patients who refuse to provide biomarker specimens or biomarker specimens cannot be used for biomarker analysis can also be enrolled in the study.

Patients signed informed consent to use their specimens for genetic analysis and protein analysis. Protein analysis, primarily to detect the expression levels of cytokines (such as VEGF and FGF) associated with tumor angiogenesis, is an attempt to determine whether there is a relationship between the level of a certain cytokine and the efficacy of the drug. Genetic analysis is mainly to evaluate the mutation status of specific genes in different treatment stages, including the mutation status of KRAS/NRAS, BRAF, and PIK3CA. It is planned to investigate where the mutation status of a certain gene is associated with the efficacy of anlotinib hydrochloride capsules or with the possible resistance. In the process of biomarker analysis, the patient’s personal information should be protected to the greatest extent if possible.

The collection, handling, and transport of specimens are listed in Appendix V.

7.2 Studies on population pharmacokinetics

To further study the changes in plasma concentration in the body after long-term usage of the drug and explore the relationship between plasma concentration and efficacy as well as adverse reactions, some patients in conditional centers should be selected to conduct the group pharmacokinetic study.

The patient signed the informed consent for the pharmacokinetic study, according to the Appendix “Anlotinib hydrochloride capsules system exposure level and efficacy and safety of the relevant research program” requirements for blood collection and transportation.

If the patients exited the trial, the medication was stopped and follow-up was no longer studied.

8 Observation items

8.1 Before the trial

The following criteria should be observed and evaluated 1 week before the start of the trial:

- Collection of medical history and basic information, including patient ID, sex, age, mailing address, and contact number;
- Detailed history, treatment history, gene mutation status, QoL score, and comprehensive physical examination, including ECOG PS score, height, weight, vital signs, and physical examination of the organs;
- Collection of 10–20 tissue slices;
- 12 electrocardiogram (with special attention to QTc), echocardiography and myocardial enzymes (CK, CK-MB);
- routine blood, urine, and stool analysis (including fecal occult blood);
- Liver function (TP, A, G, ALT, AST, LDH, ALP, TBil, DBil, and IBil), renal function (BUN, Cr, and UA), blood lipids (TC, TG, HDL, and LDL), electrolyte (K^+, Na^+, CL^-, Ca^{2+}, Mg^{2+}, P), lipase, amylase, fasting blood glucose, etc.;
- Verify the HCG in women of childbearing age except in the case of pregnancy;
- Coagulation function test (PT, APTT, TT, Fbg, D-Dimer, and INR);
- Thyroid function (T3,T4, FT3, FT4, and TSH);
- examination of CEA, CA199, or HIV-related indicators;
- Imaging (CT/MRI) can be completed within 14 days before medication. PET examination is not evaluated as a conventional radiographic examination. Evaluation of the assessment site before medication must include chest, abdomen, and pelvic CT or MRI. All suspicious lesions should be examined by radiography. In case of suspected patients with brain metastasis or clinical symptoms, brain MRI examination should be performed.

8.2 Medication period

- Monitor blood pressure and record the adverse reactions during the period of medication;
- a comprehensive physical examination, including weight, vital signs, and physical examination of the organs is undertaken at least once a week;
- record the adverse reactions of the treatment and clinical manifestations;

- Check ECG (with particular attention to QTc) once at every visit. In the event of chest pain, palpitations, echocardiography, myocardial enzymes (CK, CK-MB), and troponin were also assessed.
- Efficacy assessment was performed once per 2 cycles (imaging examination CT/MRI). ECOG PS score, QoL score, and serum CEA or CA199 examination time is supposed to be consistent with imaging time;
- Check blood routine every week in the first cycle, and check once every 1–3 weeks in the follow-up cycle. After 8 cycles, check once every 2 cycles (42 days). If the neutrophils were $\leq 1 \times 10^9$/L or platelets $\leq 50 \times 10^9$/L, the frequency of review should be increased (1 time /2–3 days). The blood routine should be rechecked every week if hematologic events cause delayed toxicity or dose adjustment.
- Check urine routine once every weekend. After 8 cycles, check once every 2 cycles (42 days). If urinary protein in urine routine during the medication is ≥++, the 24-h urine protein quantification is conducted once a week.
- Check blood biochemistry on the 7th day of the first cycle and at the end of the first cycle, followed by checks at the end of each subsequent cycle. Next, the blood biochemistry is checked once every 2 cycles after 8 cycles. During the medication, before the discovery of blood biochemical abnormalities, if early symptoms such as liver damage (loss of appetite, nausea, vomiting, right upper abdominal discomfort, and fatigue) occur, blood biochemical should be immediately tested. If ALT or AST increases 3-fold of ULN or baseline values and total bilirubin increases by 2-fold of ULN or baseline values, the frequency of the test should be increased (recommended 1–2 times/week).
- Blood coagulation function, thyroid function (T3, T4, FT3, FT4, and TSH), lipase, and amylase are verified every 2 cycles.

8.3 End of medication and follow-up

Follow-up period starts after the last administration of the trial drug. The treatment and follow-up of unadjusted adverse reactions are continued until recovery to NCI-CTC AE V4 Grade 1 or complete recovery.

- comprehensive physical examination: QoL score, PS score, weight, vital signs, and physical examination of the organs;
- ECG, routine blood check, blood biochemistry, fasting blood glucose, urine routine, stool examination, and electrolyte levels;

- Coagulation function test (PT, APTT, TT, Fbg, D-Dimer, and INR);
- serum CEA or SCC199 examination.
- Imaging (CT/MRI): the excluded patients underwent tumor imaging assessment (patients with an examination that is conducted at <21 days from the last imaging assessment time are excluded).

The long-term follow-up of patients was conducted every 8 weeks (including telephone follow-up). Before collecting results, whether the patient was treated with other anticancer treatments, the treatment plan, number of cycles, and outcomes were recorded if the patient was treated with other anticancer treatments. The follow-up was continued until the patient died; the cause of death and the specific duration of OS are recorded.

9. Adjoint medication

9.1 Best supportive care

Patients may receive best supportive care. This treatment can be combined with the following medications or related treatments: antibiotics, analgesics, hormones, transfusion, radiotherapy for pain control (only limited to bone metastasis), psychotherapy, palliative surgery, or any other essential symptomatic treatment used to provide the best supportive care. Other investigational antitumor drugs or antitumor chemotherapy/endocrine/immunotherapy is not defined within the scope of the supportive care.

If the investigators confirm that there is no impact on the outcome of the study, the application of unconventional treatment (for example, herbal or acupuncture) and vitamin/mineral supplement therapy is allowed. Patients can receive bisphosphonates for bone metastases during the treatment.

If systemic pain or local analgesia cannot be used to effectively control the pain of bone metastases, a palliative small area (radiotherapy area must be <5% of the bone marrow region) can be subjected to radiotherapy, considering that the target lesion does not include radiation field.

During treatment, the granulocyte colony stimulating factor (G-CSF) and other hematopoietic growth factors can be employed if the clinical presentation suggests or if the investigator determines the need to treat acute toxicity such as neutropenic fever. In such cases, the long-term usage of erythropoietin is permitted.

9.2 Drugs banned or cautiously used during the trial

- Caution with anticoagulant and antithrombotic drugs

Anticoagulant and antithrombotic drugs should be cautiously used during the treatment to avoid the increased risk of potential bleeding, mainly including but not limited to the following list of several types of drugs: salicylic acid derivatives such as aspirin, heparin anticoagulant drugs such as low molecular weight heparin, enoxaparin, heparin, and ardeparin), prophylactic anticoagulant drugs such as clopidogrel and ticagrelor after cardiovascular events.

- Drugs that interfere with liver P450 enzymes

During the treatment, caution should be exercised while using CYP3A inducers (carbimazole, rifampicin, and phenobarbital) and inhibitors (ketoconazole, itraconazole, erythromycin, and clarithromycin), CYP3A4 substrate (simvastatin, cyclosporine, and pimidine), drugs metabolized by CYP3A4 [benzodiazepines, dihydropyridine calcium antagonists [for hypertension that cannot be controlled by angiotensin-converting enzyme inhibitors (ACEI)], selected calcium antagonists), and HMG-COA reductase inhibitors]. Caution should be exercised while using CYP2C9 substrates (diclofenac, phenytoin sodium, piroxicam, S- warfarin, and Tolbutamide) and CYP2C19 substrates (diazepam, imipramine, lansoprazole, and S-meperfen).

- Drugs that prolong QT interval

As tinidazole drugs in clinical use can cause toxic side effects, i.e., prolong QT interval, caution should be exercised during the trial period while using the categories of drugs that could prolong QT, mainly including but not limited to the following list:

Antimicrobials (clarithromycin, azithromycin, erythromycin, roxithromycin, metronidazole, and moxifloxacin);

Antiarrhythmic drugs (quinidine, sotalol, amiodarone, propiramine, and procainamide);

Antipsychotics (risperidone, fluphenazine, droperidol, haloperidol, thioridazine, pimozide, olanzapine, and clozapine);

Antifungals (fluconazole and ketoconazole);

Antimalarials (mefloquine and chloroquine);

Antidepressants (amitriptyline, imipramine, clomipramine, thiazepine and doxepin).

- Chinese medicine and immunizing agents with anticancer effect

During the trial period, it is forbidden to use the CFDA approved modern Chinese medicine preparations and immunomodulators (such as Lentinan, Eddie, compound Sophora, cinobufagin, Kanglaite, Ginseng polysaccharide, Xiaoganping, Shenqi Fuzheng, Brucea javanica Oil emulsion, Kang Ai, thymosin, interferon, IL-2, BCG, transfer factor, and

levamisole).

Citrus, carambola, grapefruit, and grapefruit juice can affect the cytochrome P450 activity and thus, should be avoided.

10. Safety assessment

10.1 Adverse events

Adverse events are adverse medical events that occur after a patient is admitted to a clinical trial. This period lasts from when the patient signed informed consent and accepted the test drug treatment to 1 month after the ending of treatment. Any adverse medical events were recorded, irrespective of the causal relationship with the test drug.

The researcher should record in detail any adverse events that occur in the patient. The record of adverse events includes description of adverse events and all related symptoms, time of occurrence, severity, duration, measures taken, final results, and outcome.

10.2 Evaluation of adverse events

The criteria for assessing the nature and severity of adverse events were in accordance with the National Cancer Institute's Common Toxicity Criteria [CTC AE 4.0].

10.3 Criteria for judging the relevance of drugs to adverse events

	1	2	3	4	5
Definitely Related	+	+	+	+	+
Probably Related	+	+	+	+	?
Possibly Related	+	+	±	±	?
Unlikely Related	+	--	±	±	?
Unrelated	--	--	--	--	--

Note: + affirmative, - negative, ± difficult to affirm or negative, ? indicating that the situation is unknown

Researchers should assess the potential association between adverse events and test drugs. Specific criteria can be determined by referring to the 5 categories of criteria as listed. 1) the occurrence time of adverse events matches the time of medication administration; 2) adverse events are related to the confirmed adverse reactions of this drug; 3) adverse events that cannot be explained by other reasons; 4) adverse events disappeared after stopping the medication; and 5) adverse events reproduced after administration of the drug.

Results that are affirmed as these 3 items that are definitively related, probably related, possibly related will be counted as treatment related adverse event; the incidence of treatment

related adverse event will be calculated according to this.

10.4 Serious adverse events (SAEs)

SAEs are classified as those according to one or more of the following criteria: death, life risk (for example, immediate danger of death), hospitalization or prolonged hospitalization, permanent or severe disability, congenital malformations, or defects. Medical events that do not cause death, life risk, or hospitalization are considered as a SAE by a physician who thinks that they might cause danger, and uses medication or surgeries to avoid the above situations.

Death due to progression of the disease is reported as SAE, and during the study period, the patient must report to the sponsor when a pregnancy event occurs in the patient or his/her partner. Although pregnancy is not a SAE, it is still reported in the form recording SAEs.

10.5 SAE handling

Any SAEs in the clinical trial must be immediately informed to the Ethics Committee and the sponsor (below). The investigator should complete and submit the report of SAEs within 24 h to the Ethics Committee, upstream authorities, and the sponsor. The contents of the written report include the time of SAEs, severity, duration, measures, and outcome.

Reporting unit	Contact person	Contact number
Chia Tai Tianqing Pharmaceutical Group Co., Ltd.	Dai Jie	18168112813
Cancer Hospital Chinese Academy of Medical Sciences	Ethics Committee	010-87788495
National Food and Drug Administration Registration Division	--	010-68586295

The researchers and the main investigators at each center decide whether the patient with SAE should be unblinded. The emergency letter is prepared by a specialist in the Statistics Department and distributed to the main investigators of each research center for record purposes. If unblinding is necessary, the project manager of sponsor and inspectors from each center should be informed. Once unblinded, the case should be removed from the trial.

10.6 Suggestions for symptomatic treatment of common adverse reactions

10.6.1 Palmar–plantar erythrodysesthesia syndrome

Hand–foot syndrome is defined by an uncomfortable feeling in the palms and foot or acral red, with swelling, tingling. The compressed or stressed area is more significant. Tumor patients may present with such symptoms in the course of chemotherapy or molecular

targeted therapy.

Grade 1 is characterized by painless, slight change in skin, or dermatitis (erythema, edema, and hyperkeratosis); grade 2 is characterized by painful changes in the skin (such as peeling, blisters, bleeding, swelling, and hyperkeratosis); instrumental daily activities are affected; and grade 3 is characterized by severe changes in the skin (peeling, blisters, bleeding, edema, and hyperkeratosis) with pain, thereby affecting the personal daily activities.

For patients with level 1 toxicity, support treatment is not required. Patients with level 2 or more toxicity consider the following symptomatic supportive treatment, including strengthening skin care, keeping the skin clean, avoiding secondary infection, avoiding stress or friction, using moisturizer or lubrication agents, topical use of urea and corticosteroid ingredients of the emulsion or lubricant, and the use of local anti-fungal or antibiotic treatment if necessary.

10.6.2 Pleural effusion and pneumothorax

Pleural effusion refers to the increase in the amount of liquid inside the chest, leading to shortness of breath, cough, and substantial chest discomfort. The presence of malignant pleural effusion indicates that the tumor has spread or has progressed to a later stage, and the patient’s life expectancy will be significantly shorter.

Most patients with malignant pleural effusion (MPE) present clinical symptoms, whereas approximately 25% of the patients are asymptomatic; physical examination or X-ray examination detected MPE accidentally. Breathing difficulties are the most common symptoms. Once the diagnosis of MPE is clear, palliative care should be considered at the earliest. The patient’s symptoms, general situation, and the expected survival time are comprehensively assessed to develop a treatment program primarily to reduce the symptoms of dyspnea. Pleural effusion severity is rated according to the following criteria:

Level 1: asymptomatic; only clinical examination or diagnosis; no intervention required.

Level 2: symptomatic; need treatment (diuretics or thoracic puncture).

Level 3: respiratory distress and hypoxia symptoms; surgery includes intubation or pleural fixation.

Level 4: life-threatening breathing disorders or hemodynamic disorders; need intubation or emergency treatment.

Specific recommendations include the following [7]:

Clinical observation: primary tumor has been clear; however, patients with asymptomatic

MPE do not require any treatment intervention; patients with symptomatic MPE need to consult the respiratory specialist and decide whether just to avail a simple observation.

Treatment of thoracic puncture: MPE recurrence rate is higher at 1 month after chest puncture; thus, in patients with life expectancy of >1 month, thoracic puncture is not recommended. Repeated treatment of thoracic puncture can temporarily alleviate the breathing difficulties; consequently, patients with short expected survival time and those in poor physical condition will be avoided to be hospitalized and it is suitable for patients with physical weakness as well as end stage patients.

Intercostal catheter drainage and pleural fixation: For patients with extremely short life expectancy, repeated thoracic puncture are not recommended. A small diameter drainage tube can be intercostally placed for pleural effusion to ease the symptoms of dyspnea. If there is no obvious collapse of the lungs, pleural fixation (injection of hardening agent) should be performed after intercostal catheter drainage to prevent the recurrence of MPE. Patients with isolated intercostal catheter drainage without the implementation of pleural fixation revealed a high rate of MPE recurrence; thus, isolated intercostal catheter drainage should be avoided. It is recommended to insert drainage tube with a small diameter intercostally to perform pleural effusion drainage and pleural fixation under ultrasound guidance.

Outpatient long-term retention of the chest drainage tube: retention of the chest drainage tube is an effective way to control recurrent MPE, particularly for lung collapse or for patients who want to shorten the hospital stay. At regular intervals, the catheter is connected to the vacuum bottle for drainage that can promote pulmonary re-expansion and thoracic atresia. Most drainage tubes can be removed after a short-term retention.

Pneumothorax refers to the chest experiencing abnormal gas, resulting in lung compression. The condition is usually a sudden onset with typical symptoms of sudden chest pain, followed by chest tightness or difficulty in breathing and may have irritating dry cough. Onset of the disease is slow, even without symptoms in some patients.

Clinical signs: depending on the amount of gas. A small amount of pneumothorax might not show obvious body signs; however, when there is a large amount of gas, the patient exhibits chest fullness, weakened respiratory movement, weakened or disappeared tactile chatter; moreover, percussion drum sound is heard, and auscultation breath sounds are weakened or disappeared. Although both sides of the breath sounds are weakened in patients with emphysema and pneumothorax, the weakening is rather obvious in pneumothorax, which will also be present even if there is not a lot gas; therefore, pay more attention on the

comparison of left and right sides and upper and lower sides of the chest when percussion is performed. A large number of pneumothorax is seen to be associated with contralateral shift. When a large number of pneumothorax is present on the right side, the hepatic dullness descend; when there is pneumothorax on the left or mediastinal emphysema, click sound or high-profile metal tone (Ham-levy) is heard at the left sternal edge which is consistent with the sound of heartbeat. When patients exhibit cyanosis, sweating, severe shortness of breath, tachycardia, and hypotension, tension pneumothorax should be considered.

X-ray examination is a major approach for the diagnosis of pneumothorax. If there is high possibility of pneumothorax clinically, but with normal postero-anterior chest X-ray, a lateral or lateral decubitus view X-ray should be performed. Pneumatic chest X-ray shows a clear line of the pneumothorax, which is a junction line of the atrophy of lung tissue and pleural cavity gas and showed a convex line on the film. Outside the pneumothorax line was the non-lung texture of the light transmission area, and the compressed lung tissue inside the line was also noted. If a large number of pneumothorax was present, the mediastinum and the heart would shift to the contralateral side, when combined with pleural effusion, gas–liquid surface can be visualized. When the localized pneumothorax in the antero-posterior part or X-ray examination is easily missed, lateral chest radiograph can help with the diagnosis; it can also be found when rotational X-ray is performed. If there is a light band around the edge of the heart, it should be considered as mediastinal emphysema. X-ray imaging is the most commonly used method for the diagnosis of pneumothorax. CT might be more sensitive and accurate for the differential diagnosis of a small amount of pneumothorax, localized pneumothorax, and bullae than X-ray. The basic CT manifestations of pneumothorax comprise extremely low-density gas in the pleural cavity, accompanied by varying degrees of compression and collapse of the lung tissue. Notably, pneumothorax is different from the following: pulmonary bullae, acute myocardial infarction, pulmonary embolism, chronic obstructive pulmonary disease, and bronchial asthma. Pneumatic severity and treatment recommendations are as follows:

Level 1: Asymptomatic; only found by clinical examination or diagnosis; no intervention required;

Level 2: Symptomatic; need intervention (for example, placement of catheter, no hardening agent);

Level 3: Hardening agent treatment and/or surgical treatment; need hospitalization;

Level 4: Life-threatening; need emergency treatment.

Treatment measures include conservative treatment, exhaustion therapy, prevention of relapse, surgical treatment, and prevention of complications.

10.6.3 Hypertension

Blood pressure should be monitored daily in the first 6 weeks of this study since the start of drug administration.. In the case of an increase in blood pressure, it should be actively communicated to the doctor. In the event of increased blood pressure, most can be controlled with conventional antihypertensive therapy. If blood pressure is difficult to control, it can be released by reducing or withdrawing the target drug dose.

Hypertension staging and routine treatment recommendations

Hypertension refers to pathological increased blood pressure, with repeated measurement giving values of >140/90 mmHg.

Severity Rating:

Level 1: early stage of high blood pressure: (systolic blood pressure 120–139, diastolic blood pressure 80–89 mmHg) with no indications for the use of antihypertensive drugs only to monitor the blood pressure.

Level 2: first stage of hypertension (systolic blood pressure 140–159 mmHg, diastolic blood pressure 90–99 mmHg), requires medical intervention, repeated or lasting (≥24 h) symptomatic systolic blood pressure increased by >20 mmHg or the past normal range >140/90 mmHg; monotherapy is required to monitor the blood pressure at the same time; thiazide diuretics are mostly used; however, the use of ACEIs, angiotensin receptor blockers (ARB), β-blockers, and calcium channel blockers are also considered.

Level 3: stage 2 hypertension (systolic blood pressure ≥ 160 mmHg, diastolic blood pressure ≥ 100 mmHg); requires medical intervention; requires multiple medications, usually hiazide diuretics with ACEI or β-blockers or calcium channel blockers.

Level 4: life-threatening (such as malignant hypertension, transient or persistent nerve damage, and high blood pressure crisis) conditions require emergency treatment. Presently, there is no uniform classification worldwide; however, based on the recent perspective of clinical treatment, hypertension can be divided into 2 types:

（1）Hypertension emergencies, diastolic blood pressure of >120 mmHg, with acute or progressive target organ damage, such as cerebral infarction, intracranial or subarachnoid hemorrhage, and hypertensive encephalopathy, of which, progressive or acute hypertension based on chronic primary hypertension is the most common (approximately 40%–50%);(2) Hypertension urgencies (hypertension urgencies), diastolic blood pressure of >120 mmHg

with or exhibits only minor organ damage.

Sodium nitroprusside or nifedipine are used to rapidly decrease blood pressure. Diazepam and phenobarbital are used to stop convulsions. Furosemide and mannitol are used to hydrate, reduce the sodium and reduce the intracranial pressure;

Once the patient has a high blood pressure crisis, the medication should be terminated and the patient should quit the clinical study.

10.6.4 Proteinuria

During the entire treatment period, all patients were closely monitored for proteinuria, particularly those with a history of hypertension, and 24 h urinary protein was measured for 2 consecutive urine proteins ≥++. After the appearance of proteinuria, the principle of dose adjustment is followed based on the relevant information in the dosing regimen.

10.6.5 Diarrhea

The supportive care can be given for the presence of level 1–2 diarrhea, such as the use of loradine in the earliest episode (for example, oral administration of 4 mg and 2 mg orally every 2 hour until diarrhea is relieved).

10.6.6 Hyperlipidemia

The treatment of hyperlipidemia should consider the patient's pre-treatment state and eating habits. In addition to diet control, high levels of hypercholesterolemia (≥7.75 mmol/L) at ≥grade 2 or hypertriglyceridemia of ≥level 2 (≥2.5-fold of normal upper limit), HMG-CoA reductase inhibitors (atorvastatin), or appropriate lipid lowering drugs are administered.

10.6.7 Suggestions of gastrointestinal bleeding

In the case of gastrointestinal bleeding, including fecal occult blood (++) or hematemesis, symptomatic treatment should be administered. In the case of upper gastrointestinal bleeding, fasting should be performed; acid suppression, gastric mucosa protection, hemostasis (Acidum Tranexamicum and Batroxobin), blood transfusion, and supportive treatment are administered. If necessary, octreotide could be used. In the case of lower gastrointestinal bleeding, hemostasis, blood transfusion, and supportive care are given. If the bleeding cannot be controlled, surgery is essential.

10.6.8 Hypothyroidism

Thyroid function is closely monitored in all patients throughout the treatment period. When TSH ≥ 20 mU/L or any value of T3, T4, FT3, and FT4 is lower than normal, levothyroxine treatment should be used.

11 Data management and statistical analysis

11.1 Electronic case report form

Researchers should record the related information in a timely and true manner; Researchers or their authorized personnel use the Electronic Input System (EDC) within a specified period of time to complete the relevant information in the electronic case report Table. The contents of the entry are ensured to be consistent with that of the study of medical records. To protect patient's privacy, code should be used instead of the patient's name. After completing the study, the electronic case report form is copied and maintained by the sponsor and the research unit.

11.2 Database setup

Statistical experts specify the data administrator in advance to make the electronic case entries and query data; the system prompts the researcher or the authorized personnel to verify the changes. The database is audited and the data locked through key by investigators, data managers, statisticians, and auditors. To ensure data security, unrelated personnel cannot enter and modify the data. Electronic case report data must also be backed up. Any changes in data require the principal investigator, statistician, and data administrator to sign the consent form before proceeding.

11.3 Data lock

After all the concerns are resolved and the database is confirmed to accurate correct, the data management audit report is prepared by the data manager and the analysis dataset is determined in the presence of the principal investigator, sponsor, statistical analyst, and data manager simultaneously. Then, the data files are locked and in principle, no changes are permitted.

11.4 Choice of statistical analysis data

Full Analysis Set: Analyze all cases who received at least one dose in accordance with the intent-to-treat analysis (ITT) principle.

Per-protocol Set: All treatments are completed for >6 weeks (including 6 weeks), the test plan fulfilled, compliance is good, the trial did not use the banned medication, and the case report form is completed to fill the contents of the case. No imputation will be done for missing data. The efficacy of the drug is determined at the same time by FAS and PPS statistical analysis.

Safety Analysis Set: All patients enrolled in the study receive at least one trial medication, and all patients with safety records were classified as safety analysis. This data set is used for security analysis.

11.5 Statistical analysis plan

According to the above sample size estimates, when there are 291 OS events, the statistical data are reported as follows.

All statistical analyses will be conducted using SAS 9.2 statistical analysis software. All statistical tests were conducted on both sides of the test; *P*-value of ≤0.05 will be considered statistically significant with 95% confidence interval.

The baseline data are analyzed by the whole analysis set. All the validity indexes are analyzed according to the full analysis set and per-protocol set. The safety analysis is based on the safety analysis set.

The measurement data of each treatment group in different treatment groups will be described by mean ± standard deviation or median (minimum, maximum). Compared with the base value of the screening period, the paired *t*-test was used to compare the differences between the 2 groups. Changes were made before and after treatment in each group using ANOVA or rank. The enumeration data of each treatment group were statistically described by frequency (composition ratio). Changes in each group before and after treatment were evaluated by χ^2 test accuracy or nonparametric test.

Shedding analysis: descriptive analysis, if necessary, was estimated for the 2 groups based on the total rate of shedding and loss due to AE by χ^2 test or the *Fisher's* exact probability.

Quantitative analysis of basal values: *t*-test or χ^2 test compared the demographic data and other baseline values to estimate the balance between the 2 groups.

Efficiency Analysis: Kaplan–Meier method was used to determine the main indicators of OS; 25%, 50% (median), and 75% OS were calculated according to the actual situation of the 2 groups. The log-rank test was used to compare the 2 groups. For comparing the secondary indicators of ORR and DCR, central stratification of the CMH-χ^2 test was used to compare the efficacy of the 2 groups and calculate the 95% CI between the groups. For the index PFS, the multiplication limit was used, 25%, 50% (median), and 75% PFS and PFS at different time points after the start of treatment were calculated according to the actual situation of the data; the 2 groups were compared by log-rank test.

Safety analysis: mainly descriptive statistical analysis was performed by making a list of AEs occurring in this study; if necessary, Fisher's exact probability method compared the incidence of AEs in each group. The laboratory test results describe the abnormal post-trial conditions and the relationship between the medications and abnormal changes.

(See Statistical Analysis Plan Book)

12 Applicant and investigator's responsibilities

12.1 Applicant

1) Provides information and other support to the researchers, explains the program to the researchers, and fills in a variety of information before starting the clinical trial; and
2) Sends a clinical inspector, visits regularly; inspectors ensure the use of telephone, fax, and email, at any time to maintain contact with the researchers.
3) Inspectors supervise the investigators to follow the approved program to carry out clinical studies, check the release and recovery of drugs in accordance with the relevant provisions, and ensure that the test records of clinical trial are consistent with the original report data.

12.2 Investigator

1) After the GCP and the training of this trial program, the investigators have sufficient time to carry out the test according to the research program.
2) Patients should be explained relevant information of this study before recruitment and sign the informed consent.
3) The investigator is obliged to take the necessary measures to ensure the safety of the patient. In the event of adverse reactions, the investigator immediately followed the relevant regulations, reported the principal investigator, and followed up the serious adverse reactions. Patients with severe adverse reactions should be provided consultation at any time.
4) Actively cooperate with the clinical inspector for the regular visit;
5) Maintain all the laboratory records, clinical records, and the patient’s original medical records;
6) To ensure the evaluation and supervision of clinical trials by the State Food and Drug Administration, the research hospitals shall maintain all the research materials uniformly, including confirmation of all patients (for effective verification of the different records), effective signature of the informed consent, and detailed distribution of the drug records. The preservation period is 5 years. The ownership of all the information in this clinical trial belongs to the sponsor. The investigators cannot provide any information to a third party without the written consent of the sponsor in addition to the national drug regulatory authorities.

13 Ethical norms and informed consent

This clinical trial must follow the Helsinki Declaration (2013) and the relevant Chinese clinical trials research norms and regulations. Before the start of the clinical trial, the test plan shall be formulated by the researcher and the sponsor, and shall be submitted to the Hospital Ethics Committee for examination and approval. During the actual implementation of the trial, if the program needs to be revised, the revised trial will be submitted to the Ethics Committee for approval. If critical new information concerning the test drug is found, informed consent form must be revised and approved by the Ethics Committee, followed by the patient's agreement.

Before the start of the clinical trial, the investigator must provide the patient with detailed information about the clinical trial, including the nature of the trial, the purpose of the trial, the possible benefits and risks, and the patient's rights and obligations. Clinical trials cannot start unless the patient is fully aware of all prospects of the trial and has signed the form of informed consent.

14 Summary of trial

The person in-charge of the trial will summarize the results of the statistical analysis objectively and in detail, and actively complete the summary report of the clinical trial to meet the CFDA standard review of the clinical new drugs, whereas the participating hospitals will complete the sub-unit summary.

15 Clinical trial progress

Proposed start time: September 2014 (after the approval of the Ethics Committee); proposed end date: December 2016;

16 References

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Appendix one: Clinical trial flow-chart of anlotinib hydrochloride capsules

Item	Screening Enrolled	The first cycle (day)			The second-n^{th} cycle	Out of group
		D7	D15	D21	D42~	
Informed consent	×					
Medical history and past history of treatment	×					
Pregnancy test	×					
Tumor biomarker, HIV check	×					
Thyroid function	×				×	×
Lipase, amylase	×				×	×
Coagulation function	×				×	×
QoL, PS score	×				×	×
Blood biochemistry	×	×		×	×	×
Urine, stool routine test	×			×	×	×
Electrocardiogram, blood routine[#]	×	×	×	×	×	×
Echocardiography	×					
Imaging examination[a]	×				×	×
Physical signs physical examination	×	×	×	×	×	×
Release the recovered drug		×	×	×	×	×
Recorded adjoint medication, adverse events		×	×	×	×	×

- The visit window period for the first cycle is ±2 days, follow-up visit window period is ±3 days, and OS follow-up window period is ±7 days when off the group.
- Efficacy assessment was performed once per 2 cycles (imaging examination CT/MRI). Time point of the PS QoL score and serum CEA and CA199 examination is the same as that of the imaging examination.
- Check blood routine every week in the first cycle, and check once every 1–3 weeks in the follow-up cycle. After 8 cycles, check once every 2 cycles (42 days). If the neutrophils are $\leq 1 \times 10^9$/L or platelets $\leq 50 \times 10^9$/L, the frequency of review should be increased (1 time /2–3 days). The blood routine should be rechecked every week if hematologic events cause delayed toxicity or dose adjustment. Urine and stool routine test should be performed once at the end of each cycle. After 8 cycles, check once every 2 cycles (42 days). If urinary protein in urine routine during the medication is ≥++, the 24-h urine protein quantification is conducted once a week.
- Check blood biochemistry on the 7th day of the first cycle and at the end of the first cycle, followed by checks at the end of each subsequent cycle. Then, the blood biochemistry is checked once every 2 cycles after 8 cycles. During the medication, before the discovery of blood biochemical abnormalities,

if early symptoms such as liver damage (loss of appetite, nausea, vomiting, right upper abdominal discomfort, and fatigue) occur, blood biochemical should be immediately tested. If ALT or AST increased 3-fold of ULN or baseline values, total bilirubin increased by 2-fold of ULN or baseline values, the frequency of the test should be increased (recommended 1–2 times/week).

- Check ECG (with particular attention to QTc) once at every visit. In the event of chest pain, palpitations, echocardiography, myocardial enzymes (CK and CK-MB), and troponin were also assessed.
- Blood coagulation function, thyroid function (T3, T4, FT3, FT4, and TSH), lipase, and amylase are verified every 2 cycles.

Appendix two: AJCC Colorectal Cancer Version 7 TNM staging system

T: Primary tumor

Tx: Primary tumor cannot be assessed

T_0: No evidence of primary tumor

Tis: Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria[a]

T_1: Tumor invades submucosa

T_2: Tumor invades lamina propria

T_3: Tumor invades through the muscularis propria into pericolorectal tissues

T_{4a}: Tumor penetrates to the surface of the visceral peritoneum[b]

T_{4b}: Tumor directly invades or is adherent to other organs or structures [b.c]

N：**Regional lymph node(s)**

Nx：Regional lymph node(s) cannot be assessed

N_0：No regional lymph node metastasis

N_1：Metastasis in 1–3 regional lymph nodes

N_{1a}：Metastasis in 1 regional lymph node

N_{1b}：Metastasis in 2–3 regional lymph nodes

N_{1c}：Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis

N_2：Metastasis in ≥4 regional lymph nodes

N_{2a}：Metastasis in 4–6 regional lymph nodes;

N_{2b}：Metastasis in ≥7 regional lymph nodes

M: Distant Metastasis [b]

M_x: Distant metastasis cannot be assessed

M_0:： no distant metastasis.

M_1: distant metastasis

M_{1a}: Metastasis confined to one organ or site (e.g., liver, lung, ovary, and nonregional node)

M_{1b}: Metastasis in more than one organ/site or the peritoneum

[a]Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into submucosa.

Direct invasion in [b]T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confined on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of cecum) or for cancers in a retroperitoneal or subperitoneal location, invasion of other organs or structures by virtue of extension beyond the muscularis propria (a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall or a mid or distal rectal cancer with invasion of prostate, seminal, vesicles, cervix, or vagina).

[c]Tumor that is adherent to other organs or structures is grossly classified as cT4b; however, if no tumor is present in the adhesion microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classification should be used to determine the presence or absence of vascular or lymphatic invasion, whereas the PN site-specific factor should be used to determine the presence of perineural invasion.

A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histological evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or a totally replaced lymph node (N1/2). Replaced nodes should be separately enumerated as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the site-specific factor category tumor deposits.

Staging	T	N	M	Dukes*	MAC[e]
Anatomical staging/Prognostic grouping					
0	Tis	N0	M0	—	—
Ⅰ	T1	N0	M0	A	A
	T2	N0	M0	A	B1
ⅡA	T3	N0	M0	B	B2
ⅡB	T4a	N0	M0	B	B2
ⅡC	T4b	N0	M0	B	B3
ⅢA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
ⅢB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
ⅢC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
ⅣA	Any T	Any N	M1a	—	-
ⅣB	Any T	Any N	M1b	-	-

Note: * Dukes B stage includes 2 types of patients, i.e., patients with better prognosis(T3N0M0) and those with worse prognosis (T4N0M0), the same as Dukes C stage (any TN1M0 and any TN2M0).
eMAC is modified Astler–coller staging.

Appendix three: Quality of life score ECOG PS standard (ZP S 5 points)

0	Normal activity
1	Mild symptoms, and able to perform activity of light or sedentary nature
2	Tolerated tumor symptoms, capable of self-care but confined to bed for >50% of waking hours during daytime
3	Severe tumor symptoms, confined to bed for >50% of waking hours during daytime but able to stand, and capable of part self-care
4	Completely disabled
5	Death

KARNOFSKY Performance Status Scale (KPS%) Criteria

Physical status	points
Normal, no symptoms or signs	100
Able to perform normal activity, minor signs or symptoms of disease	90
Normal activity with effort, some signs or symptoms of disease	80
Capable of self-care, unable to perform normal activity or to do work	70
Able to care for most needs, requires occasional assistance	60
Requires assistance from others	50
Unable to perform self-care, requires special care and assistance	40
Severely disabled	30
Very sick, hospital admission and active supportive treatment necessary	20
Moribund, fatal processes progressing rapidly	10
Death	0

Appendix four: New York Heart Association (NYHA) cardiac function classification

Classification	NYHA Heart function classification
Class I	Physical activity is not limited, daily activities do not cause excessive fatigue, difficulty breathing or palpitations; cardiac function is compensatory
Class II	Physical activity is slightly limited. Asymptomatic at rest, daily activities can cause fatigue, palpitations, difficulty in breathing, or angina. Also known as degree I or mild heart failure

Class III	Physical activity was limited; asymptomatic at rest, lighter than the daily activities can cause the above symptoms; also known as degree Ⅱ or moderate heart failure
Class IV	Patient cannot engage in any physical activity, patient at rest also exhibit congestive heart failure or angina symptoms, any physical activity will worsen the condition; also known as degree Ⅲ or severe heart failure

Heart function is divided into 4 classes; heart failure is divided into three degrees (slightly added byNYHA classification).

Appendix five: Biological sample collection SOP

Part I: pathological tissue slice

Collection of 10–20 pieces of pathological tissue slices at 5–10-μm thickness (area > 1 cm × 1 cm) after enrollment.

Part II: Retrospective study of tumor biomarkers

Serum

Objective: To detect the expression of related cytokines in blood.

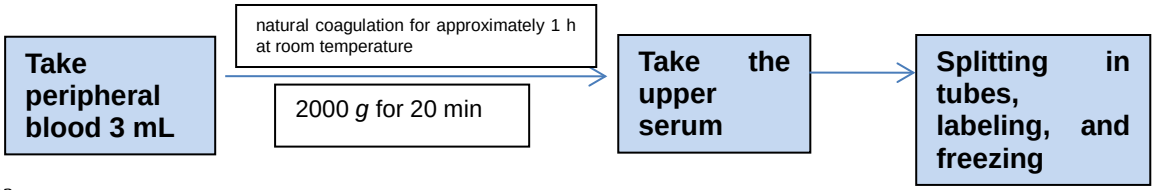
Number of acquisitions: This study was conducted in qualified hospitals for a total of 3 times; the first time was before medication (within the first 3 days), the second time for the second cycle at the end of the drug administration (imaging assessment day, 42th day), and the third time for observing the presence of disease progression (within 3 days after imaging assessment).

Collection volume: A total of 3 mL whole blood was collected in the blood tubes each time (without anticoagulants), stored at room temperature, and natural coagulation was allowed for approximately 1 h, followed by centrifugation at 2000 *g* for 20 min. The upper serum was immediately collected (do not absorb the lower layer of precipitation) and transferred into two 1.5 mL tubes and then to centrifuge tube of approximately 0.5 mL/tube.

Storage shipping: Preservation at −20°C or lower to prevent repeated freezing and thawing. Use dry ice to transport to the company in stages.

Number Principle: N-Drug No. -X1-CHJM-Collection Date (For example: N034X1-CHJM20150305), C represents CRC cancer research; X, Y, Z indicate the first 1, 2, 3 times of serum collection, followed by 1, 2 indicates tube 1 or 2 different tubes. If the patient has no drug number, the sample number is supposed to be underlined, as C X1-CHJM-20150305, followed by CRA supplement)

Schematic:

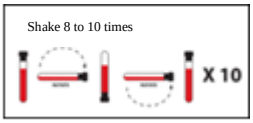


Plasma

OBJECTIVE: To extract free tumor DNA from plasma and detect the gene mutation status.

Number of acquisitions: Sample from each patient was collected twice, first before the medication (within the first 3 days) and second during the disease progression.

Collection volume: Use the blood collection tube provided by Amoy Dx specifically; each blood sample should be ≥8 mL, thoroughly mixed by shaking up and down 10 times (gentle action, mild).

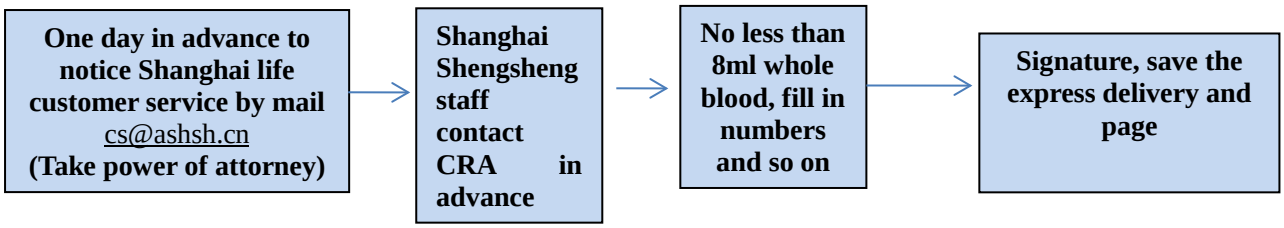


Storage shipping: Shanghai Shengsheng staff is appointed. Before transport, the collection tube is stored at room temperature. Shanghai Shengsheng staff will fill out the express delivery forms. CRA will fill the

blood bank bar code, stick the bar code on the blood collection tube, fill in the checklist, and send them together, and save the shipper's copy.

Numbering Principle: C-drug number -P1- Pinyin abbreviation - Sample date; for example (C034P1-CHJM-20150305), C for colorectal cancer study, P1 for the first acquisition, P2 for the second acquisition. If the patient has no drug number, the sample number is supposed to be underlined. For example, C_P1-CHJM-20150305, then email to lhy@amooydx.com as a supplement.

Schematic:



Appendix six: Pharmacokinetics of blood sample collection criteria

Another article is attached with "The program of the relevance between anlotinib hydrochloride capsule system exposure level and efficacy and safety."