Clinical Study Protocol

Protocol Title:	**A Phase 1 Study of the Safety, Tolerability, Pharmacokinetics Profiles, and Preliminary Efficacy of 3D185 Monotherapy in Subjects with Advanced Solid Tumors**
Protocol Number:	**3D185-CN-001**
Protocol Date/Version:	**November 18, 2019 / Version 6.1**
US IND Number:	**142810**
Author	**3D Medicines (Beijing) Co., Ltd.**
Clinical Phase:	**Phase 1**
Sponsor:	**3D Medicines (Beijing) Co., Ltd.**
Name of Study Center	
Clinical Principal Investigator	

3D Medicines (Beijing) Co., Ltd.

Protocol Signature Page 01

Statement on behalf of the Sponsor

I have carefully read the protocol for this study and agree with the content of the final protocol currently provided for the clinical trial.

Name:	Silong Xiang	Title:	Medical Monitor
Signature:		Date:	

Protocol Signature Page 02

Statement of the Principal Investigator

I have read this protocol. I understand and agree with all the contents of this protocol. I will perform my responsibilities per the provisions of the "Good Clinical Practice (GCP)." I also will complete this work within the stipulated time.

I agree to provide a copy of the program and all relevant information to all staff responsible for assisting me in conducting this study and discuss with them to ensure that they are fully aware of the content of the protocol and follow the protocol.

Name: _____ Hospital: _____

Signature: _____ Date: _____

PROTOCOL REVISION HISTORY

Version Number	Version Date
1.0	Jul 09, 2018
2.0	Dec 19, 2018
3.0	Jan 30, 2019
4.0	Jul 31, 2019
5.0	Sep 9, 2019
5.1	Oct 17, 2019
6.0	Nov 06, 2019
6.1	Nov, 18, 2019

PROTOCOL SYNOPSIS

Name of Drug	3D185Tablets
Name of Active Ingredient:	Highly selective FGFR1-3 inhibitor
Title of Study:	A Phase 1 Study of the Safety, Tolerability, Pharmacokinetics Profiles, and Preliminary Efficacy of 3D185 Monotherapy in Subjects with Advanced Solid Tumors
Protocol No.:	3D185-CN-001
Name of Sponsor:	3D Medicines (Beijing) Co., Ltd.
Phase	Phase 1
Study Centers	Global multicenter in China and the United States of America
Leading Principal Investigator	Professor. Jin Li, MD
Study Population	Subjects with advanced solid tumors who have no available standard therapy or who have failed standard therapies
Estimated Participants	The maximum expected sample size is 42 subjects.
Estimated Study Period	From July 2018 to April 2020
Study Objectives	**Primary Objectives** ✧ To assess the safety and tolerability of 3D185 monotherapy in subjects with advanced solid tumors;

	✧ To explore the maximum tolerated dose (MTD) and the recommended dose for subsequent studies (RPTD) of 3D185 monotherapy in subject with advanced solid tumors.
	Secondary Objectives ✧ To preliminarily characterize the pharmacokinetics (PK) and the pharmacodynamics (PD) profiles of single and multiple-dose of 3D185 monotherapy in subjects with advanced solid tumors; ✧ To preliminarily evaluate the anti-tumor activity of 3D185 monotherapy in subjects with advanced solid tumors.
	Exploratory Objective ✧ To explore the relationship between the anti-tumor activity of 3D185 monotherapy and the tumor fibroblast growth factor receptor (FGFR) alterations in subjects with advanced solid tumors.
Study Design and Plan	**Study Design** This is an open-label, global multicenter, dose-escalation phase 1 study of safety, tolerability, preliminary PK profile, and preliminary efficacy of 3D185 monotherapy in subjects with advanced solid tumors. The starting dose in this dose-escalation study is 25 mg, and the preset 7 dose-escalation cohorts are 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg, respectively. This study adopts a combination of accelerated titration and i3+3[1] for dose escalation. All subjects in each cohort will receive a single oral dose of 3D185, followed by a 7-day washout period (i.e. single-dose PK study period). Then, subjects will receive consecutive daily doses (Once daily [QD], 28 days/cycle) until disease progression, death, unacceptable toxicity, or withdraw of informed consent, whichever comes first. The dose limiting toxicity (DLT) evaluation period includes the single-dose PK study period and the first treatment cycle (within 35 days after the first dose). The enrolled subjects will be sequentially assigned to the planned dose cohorts according to the protocol and receive 3D185 treatment to observe the occurrence of DLT.

	Accelerated titration dose-escalation phase: One subject is to be enrolled sequentially to 25 mg and 50 mg cohorts, respectively. If no Grade ≥ 2 drug-related adverse event (AE) occurs during DLT evaluation period, the study will escalate to the next dose level. Otherwise, 2 additional subjects will be enrolled, and the subsequent dose finding study will convert to i3+3 dose-escalation design from this dose cohort. In the accelerated titration phase, a subject may be replaced if he/she 1) does not reach to 75% of the total planned dose; 2) discontinued investigational product due to non-DLT reasons during the DLT evaluation period. ***i3+3 dose-escalation phase***: Starting at 100 mg cohort, 3 subjects are to be enrolled initially at each subsequent dose cohorts in accordance to i3+3 dose-escalation design. Each dose cohort should recruit at least one subject from each country after sites in both countries are activated. If a cohort requires ≥ 6 subjects, it must enroll at least 1 subject from each country and efforts will be made to ensure number of subjects enrolled from each country is similar. After 3 subjects in each cohort completed DLT evaluation, the safety monitoring committee (SMC) will review all available safety and PK/PD data from all treated subjects (DLT evaluable and non-DLT evaluable subjects), taking into consideration the dose-assignment recommendation based on i3+3 decision rule (Figure 1; Section 4.2), to make the recommendation on the conduct of the study including the dose level for subsequent subjects. In addition, the SMC will review and evaluate all available safety data if one of the following criteria is met: – More than 30% of all subjects who received 3D185 experienced serious adverse events (exclude unrelated events as assessed by investigator); – Any investigational product toxicity related death is reported. Enrollment will be paused while SMC is reviewing the data until a formal decision is made by SMC. The recommendations made by SMC include the following: • Recommend to start enrollment to the next higher dose level per protocol; • Recommend to enroll more subjects at a given dose level; • Recommend whether a lower dose or a different schedule should be evaluated; • Recommend whether the study should be terminated; • Recommend to modify the study design

Details of the safety monitoring process will be specified in a dedicated SMC charter.

If a Grade ≥ 2 drug-related AE occurs during the accelerated titration dose-escalation phase, the i3+3 dose-escalation phase will be initiated earlier. If the i3+3 dose-escalation phase starts from 100 mg, the maximum sample size in this phase will be 30 subjects; and, if i3+3 design starts at the dose of 50 mg or 25 mg, the maximum sample size will be 36 or 42, respectively.

If a subject terminates treatment due to non-DLT reasons during the first treatment cycle, there is no need to replace the subject. When the study has increased to a dose level (d) that is beyond the MTD, and according to the i3+3 decision table (Figure 1), the dose-assignment recommendations in cohorts of d and d-1 are dose de-escalation (D) and escalation (E), respectively, a new cohort may be added between the d and d-1 dose cohort after SMC review and evaluation on the available clinical data of PK/PD, safety, and efficacy, the new cohort can be an intermediate dose cohort (25 mg increment/decrement) or an intermittent schedule (such as 3 weeks on, 1 week off; 5 days on, 2 days off, etc.). The sample size will be increased by 6 subjects accordingly.

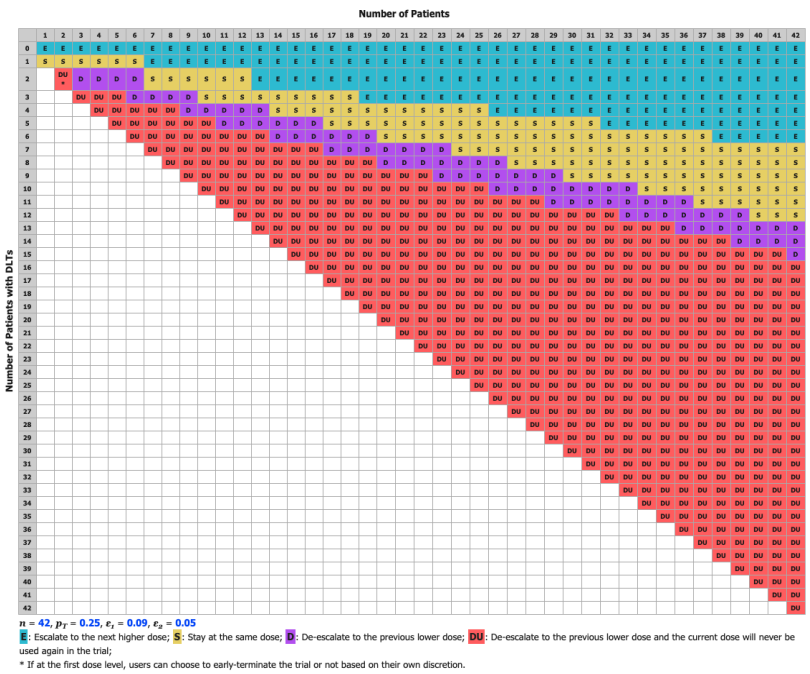


Figure 1 i3+3 Dose Escalation Decision Table

	This is a decision table for the 3D185 dose-finding study. The target toxicity probability (pT) is 25% and the equivalence interval (EI) is (16%, 30%) for 42 subjects. Each column represents (n) number of DLT evaluable subjects treated at the current dose and each row represents (x) number of subjects with DLTs at the dose level. Each cell in the table provides the dose-assignment recommendation based on the readouts from the corresponding row (x) and column (n). The letters in the decision table represent different dose-assignment recommendations. At the end of the study, the MTD will be inferred based on the DLT data and all safety data observed at all dose levels. The specific MTD estimation method is shown in Section 4.2. The RPTD will be established by taking into consideration of the PK and/or PD profiles and safety data from the dose escalation phase. The DLT evaluable subject is defined as the subject who received at least 75% of the planned doses of treatment and completed the safety assessment during DLT evaluation period. During the DLT evaluation period, subject can withhold 3D185 due to drug-related AEs. If the withholding time is more than 7 days, the AE will be considered as DLT. Subject's dose level of 3D185 will not be reduced during this period unless DLT occurs. **Study Plan and Process** ✧ **PK Sampling:** During the single dose PK study period, venous blood (3 mL each) will be collected within 1 h before the first dose, and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 48 h, 72 h, and 96 h after the first dose. During the first cycle treatment period, venous blood (3 mL each) will be collected within 1 h before dosing on C1D8, C1D15, and C1D28, and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h after dosing on C1D28. ✧ **Safety Evaluation:** The safety evaluation includes physical examinations, vital signs, laboratory evaluations, electrocardiogram (ECG), ophthalmological examination, and AE collection. Please refer to flow chat for detail safety visit schedules. ✧ **Efficacy Evaluation:**

	The anti-tumor activity will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Tumor imaging assessments will be performed every 8 weeks (±7 days) until disease progression, death, withdrawal of informed consent, or treatment discontinuation. Subjects who discontinue treatment for reasons other than disease progression or death should continue with imaging assessments per protocol-defined schedule until disease progression, death, or withdrawal of informed consent, whichever occurs first. If the imaging result shows a complete response (CR) or partial response (PR) for the first time, it is necessary to repeat the tumor imaging at least 4 weeks later to confirm the response. Imaging assessments will be performed according to the aforementioned schedule regardless of the efficacy confirmation scan. If subject discontinues 3D185 treatment due to symptomatic deterioration/disease progression, the Investigator should continue to perform imaging scan until documented radiographic disease progression. ✧ **Tumor Tissue Specimen:** For subjects with benefit from receiving 3D185 monotherapy (CR or PR or stable disease [SD]), it is recommended to obtain the disease-related archived tumor tissue or fresh tumor biopsy as much as possible with their consent to explore the relationship between the anti-tumor activity of 3D185 tablets and FGFR alterations in tumor tissue. ✧ **Safety Follow-up** Safety follow-up will be performed on Day 28 (±7 days) after the last dose. Subjects in this visit will receive safety assessments, including evaluation of AEs, vital signs, physical examinations, ECG, ophthalmological examination, laboratory tests, etc.
DLT	A DLT is defined as the occurrence of any of the following toxic reactions that are considered to be causally related to 3D185 by the PI within the first 35 days after the first dose. 1） Hematological toxicity: • Grade 4 hematologic toxicity; • Grade 3 febrile neutropenia (defined as absolute neutrophil count [ANC] < 1,000/mm^3, with fever, a single temperature of

	> 38.3 ℃ or a sustained temperature of ≥ 38 ℃ for more than 1 hour) or Grade 3 neutropenia lasts for more than 7 days with or without drug intervention; • Grade 3 thrombocytopenia with bleeding or require to platelet transfusion; 2） Non-hematologic toxicity: • Any Grade ≥ 3 non-hematologic toxicity (except the following conditions that can be controlled by symptomatic treatment within 48 hours: nausea, diarrhea, vomiting, and electrolyte imbalance [except serum phosphorus]; Grade 3 fatigue with duration ≤ 7 days; Grade 3 hypertension that can be self-resolved or controlled by drugs to below 140/90 mmHg or baseline level within 72 hours); • Serum phosphorus ≥ 7 mg/dL that is unable to recover to < 7 mg/dL within 14 days after phosphorus removal; • With liver metastasis or baseline transaminase abnormalities: ALT/AST > 8 × ULN; without liver metastasis or baseline transaminase abnormalities: ALT/AST > 5 ×ULN ; • 3D185-related AEs that resulted in dose interruption of 3D185 for ≥ 7 days in the first treatment cycle. If the DLT is clinically recovered to Grade 0-1 within 28 days, the subject can resume the treatment of 3D185. If the subject can resume treatment, the Investigator may refer to the provisions of Section 6.3 (Precautions and Dose Modifications) for dose modifications to the same dose or reduce by one dose level.

Specification and Administration	**3D185 Tablets:** specifications: 50 mg/tablet, 30 tablets/bottle **Administration:** Oral (fast), 28 days per treatment cycle
Inclusion Criteria	Subjects must meet all of the following criteria before they can be enrolled: 1. Age ≥ 18 years. 2. Subjects must have a histological diagnosis of locally advanced or metastatic malignant solid tumors. Subjects must have failed the established standard treatment, or the standard treatment does not exist; or subjects are intolerant of or have refused to receive standard treatment. All subjects must have received at least one previous line of systemic treatment. Subjects with known genomic alterations for which there are approved therapies (e.g., ALK mutated NSCLC, microsatellite instability high/mismatch repair deficient solid tumors, EGFR NSCLC, etc.,) will have received such therapies prior to the enrolling in this study. 3. Subjects must have measurable or evaluable disease (according to RECIST 1.1, see Appendix 1); 4. ECOG Performance Status ≤ 2. 5. Life expectancy ≥ 12 weeks. 6. Subjects must have normal levels of total serum calcium and total phosphate. 7. Subjects must have adequate organ and bone marrow function (subjects must not have received any hematopoietic growth factors, transfusion, or platelet within 1 week before the first dose). • CBC: neutrophils ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, hemoglobin ≥ 9.0 g/dL. • Liver function: total bilirubin ≤ 1.5 × ULN, unless known to have Gilbert's disease; ALT/AST ≤ 2.5 × ULN without liver metastasis; ALT/AST ≤ 5 × ULN with liver metastasis; • Coagulation: International normalized ratio (INR) ≤ 1.5 × ULN and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN (for subjects undergoing anticoagulant therapy, the Investigator should ensure that both INR and APTT are within the safe and effective treatment range).

	• Renal function: serum creatinine ≤ 1.5 × ULN, or creatinine clearance ≥ 60 mL/min/1.73 m^2 in the condition of creatinine level > ULN; urine protein analysis ≤ 1 + (if ≥ 2+, 24 hours of urine protein test is required, if 24 hours urine protein <1 g, then allowed to enroll); • Adequate cardiac function: left ventricular ejection fraction (LVEF) > 50% in two-dimensional echocardiography; 8. Subjects must have fully understood and voluntarily signed informed consent form (ICF) for this study.
Exclusion Criteria	Subjects who meet any of the following criteria should be excluded from the study: 1. Subjects who received other investigational products or devices in other clinical trials within 4 weeks before the first dose. 2. Subjects who received anti-tumor therapy (except for mitomycin, nitrosourea, and fluorouracil oral drugs) within 4 weeks before the first dose, including but not limited to chemotherapy, radiotherapy (palliative radiotherapy is completed at least 2 weeks before the first dose can enroll), targeted therapy or immunotherapy. Note: The last dose of mitomycin and nitrosourea should be at least 6 weeks before investigational product initiation; the last dose of oral fluorouracil such as tegafur and capecitabine should be at least 2 weeks before investigational product initiation. 3. Subjects who previously received selective FGFR1-3 inhibitor therapy. 4. Subjects who require the use of concomitant medications that prolong the QT/QTc interval. 5. Subjects who have previous toxicity of anti-tumor therapy that has not recovered to Grade 0 or 1. (alopecia, chemotherapy-induced peripheral neurotoxicity, and ototoxicity ≤ Grade 2 can enroll). 6. Subjects who received CYP3A4 and/or CYP2C8 strong inhibitors or CYP3A4 strong inducers (see Appendix 6) within 14 days prior to the first dose and the subjects who need to continue using these drugs. 7. Subjects who have any of the following eye diseases/conditions: 1) history of retinal pigment epithelial detachment (RPED); 2) history of laser treatment or intraocular injection for macular degeneration; 3)

	history of dry or wet age-related macular degeneration; 4) history of retinal vein occlusion (RVO); 5) history of retinal degenerative diseases; 6) history of chorioretinal lesions. 8. Subjects who received clinical intervention for biliary obstruction 14 days prior to the first dose or the Investigator judges that the symptoms have not resolved or require anti-infective treatment. 9. Subjects who have gastrointestinal disorders that will affect oral administration or the Investigator judges that the absorption of 3D185 will be interfered. 10. Subjects underwent major surgery (except biopsy) within 4 weeks, or the surgical incision has not completely healed prior to the first dose. 11. Subjects who had clinically uncontrollable pleural effusion, ascites, or pericardial effusion within 2 weeks prior to the first dose. 12. Subjects who have symptomatic brain metastases or spinal cord compression. For the subjects, who have previously treated for brain metastases, if the clinical condition is stable and imaging evidence does not show disease progression within 4 weeks prior to the first dose, and do not need corticosteroid treatment within 2 weeks prior to the first dose, can enroll. 13. Subjects who have active bacterial or fungal infections (Common Terminology Criteria for Adverse Events [CTCAE]) Grade ≥ 2) that required systemic treatment within 14 days prior to the first dose. 14. Subjects who have active HBV infection (HBV DNA ≥ 1,000 copies/mL) and/or HCV antibody testing positive; 15. Subjects who have clinically significant cardiovascular diseases that occurred 6 months prior to first dose. Cardiovascular diseases include, but not limited to follows: acute myocardial infarction; severe/unstable angina; cerebrovascular accident or transient ischemic attack; congestive heart failure (New York Heart Association [NYHA] > Class II, see Appendix 3); arrhythmias that require antiarrhythmic treatment except for beta blockers or digoxin; repeated ECG with QTc interval > 450 ms; high blood pressure that cannot be controlled by antihypertensive drugs (systolic blood pressure > 150 mm Hg, diastolic blood pressure > 100 mmHg).

	16. Subjects who have clinically significant abnormal serum electrolyte levels. 17. Subjects who are receiving warfarin (low-dose warfarin up to 2 mg/day is allowed); or receiving antiplatelet anticoagulant therapy (aspirin at dose ≥ 300 mg/day, clopidogrel at dose ≥ 75 mg/day). 18. Female subjects in pregnancy or lactation. Male subjects or female subjects at reproductive ages who are unwilling to receive effective contraceptive measures. 19. Subjects who are judged by the Investigator to be unsuitable for this study.
Study Termination Criteria	• The study objectives have been achieved; • The incidence and severity of AEs in this study suggest that it is not appropriate to continue this clinical trial.
Criteria of treatment Discontinuation	**Study treatment Completion Criteria** (Eligible for any of the following criteria)**:** ✧ Progressive disease (RECIST 1.1); ✧ Death. **Early treatment discontinuation criteria** meeting any of the following criteria)**:** 1) Subject withdrew informed consent; 2) Unacceptable treatment toxicity; 3) Receive other anti-cancer therapies; 4) The Investigator determines it is in the best interest of the subject to discontinue the investigational product treatment; 5) Poor compliance or severe protocol violations, and have an impact on drug tolerance, safety, or PK evaluation; 6) Pregnancy during the study period; 7) Lost to follow-up; 8) Others.

Primary endpoint:

The safety and tolerability of 3D185:

The safety and tolerability of 3D185 will be evaluated based on the frequency and attribute of DLT in the first 35 days after the first dose and the incidence of all AEs and serious adverse events (SAEs) during study period (including screening period, treatment period, and safety follow-up period) (according to NCI CTCAE v4.03).

Secondary Endpoints：

1. PK evaluation: including but not limited to, C_{max}, T_{max}, $AUC_{0\text{-}24\ h}$, $AUC_{0\text{-}96\ h}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, CL and Vd.
2. PD evaluation: PD parameters will be assessed by analyzing the change in serum phosphate levels relative to baseline level over time (Serum biochemistry test)
3. Efficacy evaluations: CR, PR, SD, and disease progression will be evaluated, and objective response rate (ORR) (CR+PR) and disease control rate (DCR) (CR+PR+SD) will be determined according to RECIST version 1.1 criteria.

Exploratory Endpoint:

4. The relationship between the anti-tumor activity of 3D185 and the tumor FGFR alterations.

Statistical analysis

The final sample size for the dose escalation study will depend on the number of dose levels evaluated and the occurrence of DLT at each dose cohort. The maximum sample size is expected to be 42 subjects.

Analysis Population:

1. Full Analysis Set (FAS)

   The FAS will include all subjects who received 3D185 treatment in this study. The FAS will be the primary population for evaluating all efficacy, safety and subject characteristics.

2. DLT Analysis Set (DLT set)

The DLT set will include all subjects who received at least ≥ 75% of the planned doses of treatment and completed the safety assessment during DLT evaluation period. The frequency and severity of DLT will be analyzed.

3. PK Analysis Set (PK set)

The PK set will include subjects who have received at least one dose and have at least once evaluable PK sample collection after administration.

4. PD Analysis Set (PD set)

The PD set will include subjects who have received at least one dose and have at least once serum phosphate level measurement (serum biochemistry) after administration.

Statistical analysis

Data will be listed and summarized using SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina) according to Sponsor agreed reporting standards, where applicable. Complete details will be documented in the statistical analysis plan (SAP).

The following statistical analysis is performed based on the nature of the parameters:

- Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum.
- Categorical variables: frequencies and percentages.
- Time-to-event variables: number of non-missing observations (N), median, minimum, and maximum. Kaplan-Meier event rates may also be provided if applicable for specific time-to-event variables.

Further description of the statistical methods and analyses will be provided in the SAP.

TABLE OF CONTENTS

List of Tables

List of Figures

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations and Terminology	Definition
AE	Adverse Events
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CL	Clearance
CR	Compete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose Limiting Toxicity
DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

FAS	Full Analysis Set
FDG-PET	Fluorodeoxyglucose - Positron Emission Tomography
FGF	Full analysis set
FGFR	Fibroblast Growth Factor Receptors
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
IB	Investigator's Brochure
IC_{50}	The half maximal inhibitory concentration
ICF	Informed Consent Form
IEC/IRB	Institutional Review Board /Independent Ethics Committee
INR	International Normalized Ratio
LDH	Lactic Acid Dehydrogenase
LDL	Low density lipoprotein
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NE	Not Evaluated
NTL	Non-Target Lesions
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free survival

PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin Time
QD	Once Daily
QTc	QT Interval
RECIST	Response Evaluation Criteria in Solid Tumors
RD	Recommanded Dose
SAE	Serious Adverse Event
SD	Stable Disease
SMC	Safety Monitoring Committee
TL	Target Lesions
T_{max}	Time of Maximum Concentration Observed
ULN	upper limit of normal
V_{ss}	Volume of Distribution at Steady State
WBC	White Blood Cell

2. STUDY BACKGROUND

2.1. Disease Background

Cancer is a significant public health problem worldwide. It is the second leading cause of death in the United States (US). The American Cancer Society (ACS) estimates that 1,762,450 new cancer cases and 606,880 cancer deaths will occur in 2019 in the US[2]. The top five most common tumors in the US are breast cancer, lung cancer, prostate cancer, colorectal cancer, and melanoma[2]. China has a significant cancer burden in the world. According to the latest data from the National Central Cancer Registry of China, it was estimated that there were about 4,292,000 new cancer cases and 2,814,000 cancer deaths in China in 2015. More importantly, the cancer profile in China is markedly different from those of developed countries. The four most common cancers diagnosed in China were lung, stomach, liver, and esophageal cancer. These cancers account for 57% of cancers diagnosed in China, compared with 18% in the United States[3]. Also, these cancers diagnosed in China account for between 1/3 and 1/2 of the global incidence burden[3]. At present, diagnosis of cancers at an early stage is uncommon in China, and majority of cancer were diagnosed at locally advanced or advanced stage. which is one of the reasons for the generally low cancer survival rate in China[4-6]. Globally, advanced cancers are generally insensitive to chemotherapy and associated with poor prognosis.

FGFRs are members of the receptor tyrosine kinases (RTKs) superfamily[7-9]. Evolutionarily, FGFRs are relatively conserved, with high homology among subtypes. Fibroblast growth factors (FGFs) act as ligands, have high-affinities for FGFRs and can regulate a wide range of physiologic processes, including embryonic development, organ differentiation, angiogenesis, cell proliferation, migration, and survival, etc., by the transduction of multiple levels signaling pathway[7-9]. More and more evidence indicates that FGFR/FGF pathway abnormalities have a close relationship with many malignant tumors[7-9].

Aberrations in FGFR are widespread in the development of various tumors. There are three major forms of FGFR aberrations including: 1) gene fusion; 2) activation mutation; 3) gene amplification/protein overexpression[7-9]. Aberrant FGFR signaling contributes to carcinogenesis by serving as "driver mutations," where the acquisition of somatic molecular alterations directly stimulates cancer cell proliferation and survival; or driving neoangiogenesis; or resulting in resistance to anticancer agents[9].

2.1.1. FGFR gene fusions

FGFR gene fusions occur in several malignancies, such as glioblastoma, bladder cancer, non-small cell lung cancer, and cholangiocarcinoma, etc. Fusions have been described in the FGFR1-3 genes with multiple partners, including TACC1, TACC3, BAIAP2L1, BICC1, and AHCYL1. Among them, fusions involving FGFR3 and TACC3 are found in 3% to 7% of glioblastomas and 3% to 6% of urothelial bladder carcinomas[9]. In vivo, both FGFR3–TACC3–initiated bladder carcinoma and glioblastoma were sensitive to specific FGFR inhibitors, suggesting oncogenic addiction to the FGFR gene fusion.

2.1.2. FGFR Activating Mutations

FGFR gene mutations are widespread in tumors. It was reported that urothelial bladder carcinoma has the most established association with altered FGFR signaling, with up to 80% of poorly differentiated tumors harboring FGFR mutations[9]. The most common activating mutations affect either the extracellular (R248C, S249C) or the transmembrane (G370C, S371C, Y373C, G380R, A391E) domains of the protein. FGFR2 mutations have been found in 12% to 14% of endometrial cancer. And, the activating mutations of FGFR4 are found in 6% to 8% of subjects with rhabdomyosarcoma[9].

2.1.3. FGFR gene amplification / protein overexpression

Unlike some receptor tyrosine kinases (such as c-Met), overexpression of FGFRs may lead to ligand-independent FGFR signaling and is mainly caused by gene amplifications. FGFR1 amplification has been found in approximately 7% to 20% of squamous non–small cell lung carcinoma, 18% of osteosarcoma, and 6% of small cell lung carcinoma[9]. In breast cancer, amplification of FGFR1 have been observed in 23% of HR-positive, 27% of HER2-amplified, and 7% of triple-negative cases. FGFR2 amplification has been found in 4% of triple-negative breast cancer and 4%–9% of gastric cancers[9]. FGFR gene amplification/protein overexpression is thought to be closely related to early tumor recurrence, efficacy prediction and prognosis, and high sensitivity to FGFR inhibitors.

2.1.4. Development status of FGFR inhibitors

The FGFR inhibitors currently under investigation mainly include small molecule FGFR tyrosine kinase inhibitors (non-selective and selective) and FGFR monoclonal antibodies.

Up to now, only one selective FGFR inhibitor- Balversa™ erdafitinib received accelerated approval by FDA for the treatment of adult patients who had progressed during or following at least one line of prior platinum-containing chemotherapy with locally advanced or metastatic urothelial carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations[10]. The approval

was based on a single arm phase 2 study where erdafitinib was associated with an ORR of 32.2% in patients with locally advanced or metastatic urothelial carcinoma with specific FGFR alterations identified based on a clinical trial assay performed at a central lab[10]. Erdafinitib was associated with significant toxicities in the pivotal phase 2 study with grade 3-4 adverse drug reactions in 67% of subjects, dose interruptions in 68% of patients, dose reductions in 53% of patients, and permanent discontinuations in 13% of patients[10]. Therefore, more FGFR inhibitors with improved tolerability and/or efficacy are still needed.

Ongoing clinical research with several investigational FGFR inhibitors showed preliminary evidence of efficacy in patients with FGFR alterations across several tumor types including biliary tract cancer, urothelial cancer, lung cancer, gastrointestinal cancer, and breast cancer. For example, in the first in human (FIH) study of BGJ398, 32.9% (28/85) of patients with advanced solid tumors at the dose ≥ 100 mg had reduced tumor burden after treatment with BGJ398[11]. Among them, the disease control rate (DCR) in patients with FGFR3-mutated bladder/urothelial cancer treated was 75%, and the DCR in patients with FGFR1-amplified sqNSCLC was 50%[12]. In a further phase 2 study of BGJ398, the DCR was as high as 82% in patients with cholangiocarcinoma containing FGFR2 fusions[13]. In addition, in the study of the selective FGFR inhibitor AZD4547, the DCR reached to 55.5% in patients with FGFR2-amplified gastric/esophageal cancer, and, in patients with FGFR1-amplified breast cancer, the DCR was 37.5%[14, 15]. Previous clinical studies have indicated that the toxicity profile of non-selective FGFR inhibitors is similar to vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI), whereas selective FGFR inhibitors have specific toxicity types associated with FGFR pathway inhibition. So far, the major drug-related AEs observed in the clinical studies of FGFR selective inhibitors are mostly mild to moderate and reversible, including hyperphosphatemia, nail, and mucosal disorders, fatigue, reversible RPED, etc.[10-17], while VEGFR-related cardiovascular toxicity such as high blood pressure has not been noted. Considering the multiple physiological functions of FGFRs, the feasibility of long-term use of FGFR inhibitors in cancer patients remains to be defined.

2.2. 3D185 Overview

The 3D185 (original development code: HH185) tablets is a novel oral selective FGFR inhibitor developed by 3D Medicines and Haihe Biopharma. 3D Medicines has the rights for clinical development, production and commercialization of 3D185 for the treatment of advanced solid tumors.

The selective inhibition of FGFRs, pharmacodynamic effects, and mechanisms of actions of 3D185 have been systemically studied at molecular, cellular, and in vivo animal levels preclinically using another clinical stage FGFR selective inhibitor AZD4547 as the control. 3D185

is a potent inhibitor of FGFR1-3 and a weak inhibitor of FGFR4 and over 300 other receptor tyrosine kinases. 3D185 also showed FGFR selectivity at the cellular level.

As a selective inhibitor of FGFR1-3, 3D185 has the potential advantages of reduced toxicity, easier patient selection, and amenable to combination therapy. 3D185 has the potential to become a new effective treatment for cancer subjects.

2.2.1. Summary of 3D185 Preclinical Studies

2.2.1.1. Pharmacokinetics

The pharmacokinetics of 3D185 were studied in Sprague Dawley rats and Beagle dogs after single and multiple dose administration. The results are as shown below:

Clearance of 3D185 was low both in rats (15.0 mL/min/kg) and dogs (7.35 mL/min/kg). The steady-state volume of distribution (Vdss) was 5.70 L/kg and 5.82 L/kg in rats and dogs, respectively. Both exceed the total volume of fluid in the body, suggesting that it can be widely distributed into tissues. After intragastric administration, the absolute bioavailability of 3D185 ranged from 10% to 17% in both rats (6~24 mg/kg) and dogs (2~8 mg/kg). The exposure of individual differences was large. In the dosage range of 6-24 mg/kg (rats) and 2-8 mg/kg (dogs), the increase in AUC of 3D185 was basically proportional to the dosage. Elimination half-lives were 6.78 and 12.8 hours in rats and dogs, respectively. After continuous administration, there was no significant accumulation in the dogs.

After intragastric administration of 3D185 in rats, the concentration in most tissues was higher than plasma concentration. It was mainly distributed to the gastrointestinal (GI) tract, adrenal glands, spleen, liver, pancreas, kidneys and lung, with approximately 20 folds higher exposure than in the plasma. The exposure in brain and testis were low, which indicated low risk of blood-brain barrier and the blood-testis barrier penetration. The maximum mean concentration in most tissues were detected at 2 to 6 hours post dose, with apparent individual variations. After 36 hours post dose, the mean concentrations were less than 15% of the maximum concentration in most tissues and organs. The blood and plasma concentration ratio were 0.95. Plasma protein binding (PPB) for 3D185 was observed to be 99.9%, 99.5%, and 99.8% in rat, dog and human plasma, respectively.

After intragastric administration of 3D185 in rats, the detected main form in the body was the parent drug. Three metabolites were detected. Speculated metabolic pathways included O-demethylation and sulfation. It was mainly excreted via feces in the unchanged form (parent drug) with a total cumulative recovery of 97.6% up to 96 hours. The detected main form in rat and dog plasma after single oral dose was the parent drug.

Parent drug was detected in the incubation system of 3D185 with human, monkey, dog, rat, and mouse hepatocytes. Major metabolic pathways in human hepatocytes included O-demethylation (M4), sulfation (M5) and glucuronidation (M6 and M7). The oxidative metabolites detected in human hepatocytes also can be found in hepatocytes of each animal species. CYP3A4 was the major CYP isoform responsible for 3D185 metabolism. In addition, CYP2C8, CYP2D6 and CYP3A5 also participated in the oxidative metabolism of 3D185.

3D185 did not appear to be an inhibitor of CYP1A2 and CYP3A4 (midazolam 1'-hydroxylation) (IC_{50} was 100 μM). 3D185 was a weak inhibitor of CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (testosterone, as substrate) (IC_{50} ranged from 29.8 to 61.4 μM) and a moderate inhibitor of CYP2C8 (IC_{50} was 6.50 μM). 3D185 did not show potential to cause drug -drug interactions due to induction of CYP1A2, CYP2B6, and CYP3A4. 3D185 has low permeability and may have efflux transporters involved in the transport of 3D185 on Caco-2 cells. Please refer to IB for the results of non-clinical pharmacokinetics and product metabolism studies of 3D185.

2.2.1.2. Pharmacodynamics and antitumor activity

3D185 exhibited potent inhibition of FGFR1, FGFR2 and FGFR3 in vitro, with IC_{50} values of 0.5 ±0.1 nM, 1.3 ±0.1 n M, and 3.6 ±0.5 nM, respectively, and exhibited much weaker activity against FGFR4 (IC_{50} = 51.4 ±8.5 nM). Meanwhile, 3D185 exhibited only a marginal inhibitory effect against the activity of recombinant KDR kinase, with an IC_{50} of 381.5 ±10.9 nM. Moreover, the selectivity for FGFR1 over KDR was greater than 700-fold, which is much better than the selectivity exhibited by AZD4547. Interestingly, 3D185 exhibited potent inhibition of the colony stimulating factor-1 receptor (CSF-1R) tyrosine kinase, an important target in tumor-associated macrophages, suggesting that 3D185 has the potential to exert antitumor activity by synergistically targeting the tumor microenvironment. Also, the enzyme kinetic study confirmed that the compound of 3D185 is an ATP-competitive FGFR small molecule inhibitor.

Non-small cell lung cancer, gastric cancer and bladder cancer cells with different FGFR family members and different activation mechanisms (FGFR1, FGFR2 amplification, and FGFR3 mutant) were further selected to assess the cellular targeting activity of 3D185 against FGFR kinase at the cellular level. The result indicated that 3D185 significantly inhibited FGFR phosphorylation in a dose-dependent manner in the individual cancer cell lines. The phosphorylation of ERK1/2, a downstream signaling core molecule of FGFR, was also inhibited.

Abnormal activation of FGFR significantly promotes tumor cell proliferation. Thirty (30) human tumor cell lines from different family members, different activation mechanisms, and different tumor sources were selected to test the cell proliferation inhibition of 3D185. The result showed that 3D185 strongly inhibited FGFR driven cancer cell proliferation, with IC_{50} values ranging from 0.9 to 49.8 nM, which was comparable or slightly better than AZD4547. In contrast, 3D185 was inactive against 20 additional tumor cell lines that exhibited low expression or activation of FGFR (IC_{50} > 1μM or 10μM), further demonstrating that 3D185 is a highly potent and selective inhibitor

of FGFR. In-depth studies showed that 3D185 achieves potent antiproliferative activity by targeting FGFR signaling to induce G1/S phase arrest in cells.

In addition, 3D185 significantly inhibited the activation of bFGF/FGFR signaling pathway in primary human umbilical vein endothelial cells and FGFR-mediated endothelial cell proliferation, suggesting that it has a role in targeting FGFR pathways to antagonize angiogenesis. However, the effect of VEGF-induced KDR-mediated endothelial cell proliferation was weaker, and the IC_{50} was nearly 200-fold different, which further showed that KDR achieved better selectivity.

Based on the good activity of 3D185 at the molecular and cellular levels, we further selected the subcutaneous xenograft model of human tumor cell lines derived from different tumor tissues driven by FGFR to investigate the in vivo antitumor effect of the drug candidate. We used a FGFR1 amplified human lung cancer NCI-H1581 model and two FGFR2 amplified models: a human gastric cancer SNU-16 model and a human colorectal cancer NCI-H716 subcutaneous xenograft model. The result indicated that 3D185 can dose-dependently inhibit the growth of subcutaneous xenografts in these three FGFR-dependent models, with NCI-H1581 being relatively more sensitive. In this model, the compounds were orally administered at 50, 25 and 12.5 mg/kg for 2 weeks, and their T/C percentages were 1.92-4.70%, 10.30-24.17% and 24.54-39.66%, respectively. It was equivalent to the same dose of the positive control compound AZD4547 (12.5 mg/kg). In FGFR2 amplified tumor models, 3D185 also showed good tumor inhibiting effect. In the human gastric cancer SNU-16 model, the percentage of T/C after 3 weeks of continuous administration in the 3D185 50 mg/kg group was 26.39-26.40%. This compound, at the dose of 25mg/kg, also significantly inhibited the growth of SNU-16 subcutaneous xenografts, with a T/C percentage of 43.83-55.41%. In the human colon cancer NCI-H716 model, after 3 weeks of continuous administration of 3D185, the T/C percentages of the 50 mg/kg and 25 mg/kg groups were 11.58-18.28% and 58.08-65.82%, respectively. Overall, 3D185 was slightly weaker in the FGFR2 amplified SNU-16 and NCI-H716 *in vivo* models compared to the same dose of AZD4547. Further immunohistochemical assays on Ki67 and platelet - endothelial cell adhesion molecule (CD31) in NCIH1581 and SNU16 models, indicated the *in vivo* antitumor activity of 3D185 involves inhibition of the downstream signaling of FGFR, with both antiproliferative and antiangiogenic consequences.

Finally, we selected FGFR-dependent human gastric cancer SNU-16 nude mouse subcutaneous xenograft model to further investigate the distribution of 3D185 in tumor tissues and plasma of tumor-bearing mice and its inhibition of FGFR signaling pathway in tumor tissues after single dose administration. The results showed that the T_{max} of 3D185 in plasma and tumor were 2-4 h and 4-8 h, respectively. Tumor exposure (AUC_{0-t}) was about 1.82- to 2.87-fold higher than plasma exposure. The elimination of 3D185 from tumor was slower than that from plasma. Dose proportional increases in plasma exposure and slightly greater than dose proportional increases in tumor exposure (AUC_{0-t}) were observed after single oral doses of 12.5 to 50 mg. The phosphorylation of ERK1/2, a key FGFR downstream signaling molecules was detected in tumor tissues, and was used to indicate inhibition of the FGFR pathway by 3D185. Significant ERK1/2

inhibition was observed in the three dose groups at 1 hour after single dose administration. After 6-8 hours, the inhibition on p-ERK was reduced in tumoral tissues with the decrease of the concentration of the compound in plasma and subcutaneous xenograft tissue. The phosphorylation levels of ERK almost fully recovered after 6 hours in low-dose group, and after 24 hours in the high-dose group. The result showed that 3D185 has a dose-dependent effect on the inhibition of FGFR pathway, and this activity also has a certain correspondence with the anti-tumor effect of 3D185 in SNU-16 model. This indicates that 3D185 significantly inhibits the growth of FGFR-dependent subcutaneous xenografts by targeted inhibition of FGFR.

3D185 selectively inhibit FGFR1-3 with selectivity over other kinases including KDR. This high selectivity may prove to be advantageous over the selective inhibitor, AZD4547 which is at a more advanced stage of clinical development. 3D185 has significant anti-tumor activity *in vitro* and *in vivo* and is highly effective in FGFR-dependent tumor models. Therefore, 3D185 has the potential to become a competitive, efficient and safe candidate new drug for tumors driven by abnormal activation of FGFRs.

2.2.1.3. Safety Pharmacology and Toxicology

- **Safety Pharmacology**

Respiratory system: Sprague Dawley rats were continuously monitored for 3 hours (12.5, 50, and 200 mg/kg) for at least 6 hours, and no significant drug-related changes were observed in the respiratory parameters. After a single oral gavage of Sprague Dawley rats, 3D185 12.5 mg/kg, 50 mg/kg and 200 mg/kg, no significant effect on the central nervous system was observed.

Cardiovascular system: conscious Beagle dogs were monitored for at least 24 consecutive hours after single-dose oral gavage of 3D185 (5, 20 and 60 mg/kg), and no significant drug-related change in electrocardiogram, blood pressure and body temperature were observed.

Central nervous system: Sprague Dawley rats were given 3D185 12.5 mg/kg, 50 mg/kg and 200 mg/kg in a single oral gavage, and no significant effect on the central nervous system was observed.

- **Reproductive and Developmental Toxicity**

After oral dose of 3D185 at 30, 10 and 3 mg/kg from GD6 to GD15 in pregnant Sprague Dawley rats, the no-observed-adverse-effect-level (NOAEL) in pregnant rats was 30 mg/kg/day. And the NOAEL for embryo-fetal development was 3 mg/kg. No significant toxicity changes were observed in the clinical symptoms, body weight and food consumption of pregnant rats in each dose group. There were no significant drug-related changes in embryonic development and fetal appearance, visceral and bone examinations in the 3 mg/kg group.

- **Single-Dose Toxicity**

Sprague Dawley rats were given 200, 1000 and 2000 mg/kg 3D185 by single oral gavage. Both male and female animals were well tolerated, and the MTD was greater than 2000 mg/kg.

Beagle dogs were given 50, 250 and 1000 mg/kg 3D185 by single oral gavage and were tolerated by both male and female animals. The main toxicity is mild gastrointestinal symptoms and elevated PHOS. The MTD is greater than 1000 mg/kg.

- **Repeat-Dose Toxicity**

Sprague Dawley rats were given 3D185 (10, 40 and 120 mg/kg) once a day for 28 days. Male animals in the 120 mg/kg group were intolerant and female animals in each dose group were tolerated. The MTDs of male and female animals were 120 and 40 mg/kg, respectively. The main toxicities are gastrointestinal reactions, bone (sternal and femur) dysplasia, elevated liver function, elevated PHOS, and associated multiple organ mineralization. After 28 days of withdrawal, the above changes were all seen to recover or have a recovery trend. No adverse NOAEL was 10 mg/kg (the plasma $AUC_{0\text{-}24h}$ of male and female animals was 2446.4 and 1134.7 ng*h/mL, respectively).

Beagle dogs were given 3D185 (1, 4, and 12/20 mg/kg by oral gavage once a day for 28 consecutive days, including 12 mg/kg for Day 1~20 and 20 mg/kg for Day 21~28 in high dose group). All groups of animals were tolerated. The MTD was > 12 mg/kg. The main toxicities were abnormal skeletal plate development, atrophy of the esophageal mucosa epithelium, and elevated PHOS in some animals. At this dose, the exposure of 3D185 in male and female animals ($AUC_{0\text{-}24h}$) was 9500 and 9260 ng*h/mL, respectively. After 28 days of withdrawal, these changes were seen to recover or have a recovery trend.

2.3. Benefit-risk assessment

3D185 is a highly potent and highly selective FGFR1-3 inhibitor. Since this novel drug is still in the initial stage of clinical development, the available safety and efficacy data mainly comes from preclinical data, and clinical research results of similar drugs. The clinical experience of 3D185 still needs further accumulation.

To date, most of the significant AEs associated with similar drugs that have been observed in the clinical studies are mild to moderate and reversible, such as hyperphosphatemia, nail and mucosal disorders, fatigue, reversible retinal pigment epithelial detachment (RPED), elevated transaminases, hypercalcemia, dyspnea, etc[10-17]. It was reported that the ORR of FGFR inhibitors in subjects with solid tumors (screened or unscreened) was at the range of 0% to 37.5%, and the DCR was at the range of 22.2% to 91.3%. (Table 1 and Table 2)

Table 1 Anti-Tumor Activity of Different FGFR Inhibitors

NCT	Phases	Drugs	Tumor Types	Results
NCT01212107	Phase 1	LY2874455	Gastric Cancer & NSCLC (no selected)	Gastric cancer (n=29), no ORR; NSCLC (n=24), no ORR.
NCT01703481	Phase 1	JNJ-42756493	Urothelial cancer and other cancers	23 evaluable cases, ORR: 21.7%; DCR: 91.3% (4 PR and 1 unconfirmed PR; 16 SD).
NCT01703481	Phase 1	JNJ-42756493	Cholangiocarcinoma	n=11; ORR: 27.3%; DCR: 54.5%.
NCT02365597	Phase 2	JNJ-42756493	Urothelial cancer	N=87; ORR=32.3%; DCR=78.2%
NCT02393248	Phase 1/2	INCB054828	Cholangiocarcinoma and other cancers	n=49 (part 1, n=22; part 2, n=27). Part 2 ORR: 11%; DCR :37%。
NCT01948297	Phase 1	Debio 1347	Solid tumors	n=57. PR: 6 (8.45%); SD: 16 (28.07%)
NCT01004224	Phase 1	BGJ398	Squamous Lung Cancer	n=36. PR: 11.1%; DCR: 50%
			Bladder/urothelial cancer	n=8. PR: 37.5%; DCR: 75%
			Breast cancer	n=32; SD: 31%
NCT02150967	Phase 2	BGJ398	Cholangiocarcinoma	N=61. ORR: 14.8%; DCR: 75.4%
NCT01976741	Phase 1	BAY 1163877	Bladder/urothelial cancer	n=8; PR: 37.5% (2 FGFR3 mutation or fusion, 1 wild type)
NCT01752920	Phase 1/2	ARQ 087	Cholangiocarcinoma	n=35. PR: 17%; SD: 63%
NCT00979134	Phase 1	AZD4547	Squamous cell carcinoma	n=13. PR: 7.7%; SD: 38.5%
NCT00979134	Phase 1	AZD4547	Gastric cancer	n=13. PR: 7.7%; SD: 30.8%
NCT01795768	Phase 2	AZD4547	Esophageal cancer	n=9 (FGFR2); PR: 33.3%; SD: 22.2%
			Breast cancer	n=8 (FGFR1); PR: 12.5%; SD: 25%
NCT02965378	Phase 2/3	AZD4547	Squamous cell carcinoma	n=27. PR: 8% (4% unconfirmed); SD 48%.

Table 2 Anti-Tumor Activity of Different FGFR Inhibitors in Subjects with Selective Solid Tumors

Indications	Types (Frequency)	Drugs	NCT	ORR	SD
NSCLC Squamous Lung Cancer	FGFR1 amplification (~10%); FGFR3 amplification (~1%); FGFR3 fusion (~0.5%); FGFR3mutation (~1%)	AZD4547	NCT00979134	7.7%	38.5%
			NCT02965378	8%	48%
		BGJ398	NCT01004224	11.1%	38.9%
Breast Cancer	FGFR1 amplification (~18%)	AZD4547	NCT01795768	12.5%	25%
		BGJ398	NCT01004224	0	31%
Metastatic Urothelial Cancer	FGFR3 mutation (~20%); FGFR3 amplification (~2%)	BGJ398	NCT01004224	37.5%	37.5%
		BAY 1163877	NCT01976741	37.5%	Undisclosed
		JNJ-42756493*	NCT01703481	21.7%	69.6%
		JNJ-42756493	NCT02365597	32.2%	46%
Gastric Cancer/Gastroesophageal Junction Cancer	FGFR2 amplification (10-20%)	AZD4547	NCT00979134	7.7%	30.8%
			NCT01795768	33.3%	22.2%
Cholangiocarcinoma	FGFR2 fusion (10-20%) FGFR2 mutation (<10%)	ARQ 087	NCT01752920	17%	63%
		BGJ398	NCT02150967	14.8%	60.6%
		INCB054828*	NCT02393248	11%	26%
		JNJ-42756493	NCT01703481	27.3%	27.3%
Multi-cancers	/	Debio 1347	NCT01948297	8.5%	28.1%

In conclusion, extensive clinical research with selective FGFR inhibitors have demonstrated promising clinical activity in FGFR driven solid tumors with a well characterized and manageable safety profile. Owing to its high selectivity for FGFR1-3, 3D185 has the potential advantage in avoiding the potential toxicity of multi-target inhibition, selecting subjects based on FGFR alterations, and, and enabling rational combination therapy. 3D185 has the potential to become a new and effective drug for cancer subjects.

3. STUDY OBJECTIVES

3.1. Primary Objectives

a. To assess the safety and tolerability of 3D185 monotherapy in subjects with advanced solid tumors;

b. To explore the MTD and the RPTD of 3D185 monotherapy in subjects with advanced solid tumors.

3.2. Secondary Objectives

c. To preliminarily characterize the PK and the PD profiles of single and multiple-dose of 3D185 monotherapy in subjects with advanced solid tumors;

d. To preliminarily evaluate the anti-tumor activity of 3D185 monotherapy in subjects with advanced solid tumors.

3.3. Exploratory Objective:

e. To explore the relationship between the anti-tumor activity of 3D185 monotherapy and the FGFR alterations in subjects with advanced solid tumors.

4. STUDY DESIGN AND PLAN

4.1. Overall Plan

This is an open-label, global multicenter, dose-escalation phase 1 study of 3D185 monotherapy in subjects with advanced solid tumors.

The starting dose in this dose-escalation study is 25 mg, and the preset 7 dose-escalation cohorts are 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg, respectively. This study adopts a combination of accelerated titration and i3+3[1] for dose escalation. All subjects in each cohort will receive a single oral dose of 3D185, followed by a 7-day washout period (i.e. single-dose PK study period). Then, subjects will receive consecutive daily doses (QD, 28 days/cycle) until disease progression, death, unacceptable toxicity, or withdraw of informed consent, whichever comes first. The DLT evaluation period includes the single-dose PK study period and the first treatment cycle (within 35 days after the first dose). The enrolled subjects will be sequentially assigned to the planned dose cohorts according to the protocol, and receive 3D185 treatment to observe the occurrence of DLT:

Accelerated titration dose-escalation phase: One subject is to be enrolled sequentially to 25 mg and 50 mg cohorts, respectively. If no Grade ≥ 2 drug-related AE occurs during DLT evaluation period, the study will escalate to the next dose level. Otherwise, 2 additional subjects will be enrolled, and the subsequent study will convert to i3+3 dose-escalation design from this dose cohort.

In the accelerated titration phase, a subject may be replaced if he/she 1) does not reach to 75% of the total planned dose; 2) discontinued investigational product due to non-DLT reasons during the DLT evaluation period.

i3+3 dose-escalation phase: Starting at 100 mg cohort, 3 subjects are to be enrolled initially at each subsequent dose cohorts in accordance to i3+3 dose-escalation design. Each dose cohort should recruit at least one subject from each country after sites in both countries are activated. If a cohort requires ≥ 6 subjects, it must enroll at least 1 subject from each country and efforts will be made to ensure number of subjects enrolled from each country is similar.

After 3 subjects in each cohort completed DLT evaluation, the safety monitoring committee (SMC) will review all available safety and PK/PD data from all treated subjects (DLT evaluable and non-DLT evaluable subjects), taking into consideration the dose-assignment recommendation based on i3+3 decision rule (Figure 1; Section 4.2), to make the recommendation on the conduct of the study including the dose level for subsequent subjects. In addition, the SMC will review and evaluate all available safety data if one of the following criteria is met:

- More than 30% of all subjects who received 3D185 experienced serious adverse events (exclude unrelated events assessed by investigator);
- Any investigational product toxicity related death is reported.

Enrollment will be paused while SMC is reviewing the data until a formal decision is made by SMC. The recommendations made by SMC include the following:

- Recommend to start enrollment to the next higher dose level per protocol;
- Recommend to enroll more subjects at a given dose level;
- Recommend whether a lower dose or a different schedule should be evaluated;
- Recommend whether the study should be terminated;
- Recommend to modify the study design

Details of the safety monitoring process will be specified in a dedicated SMC charter.

If a Grade ≥ 2 drug-related AE occurs during the accelerated titration dose-escalation phase, the i3+3 dose-escalation phase will be initiated earlier. If the i3+3 dose-escalation phase starts from 100 mg, the maximum sample size in this phase will be 30 subjects; and, if i3+3 design starts at the dose of 50 mg or 25 mg, the maximum sample size will be 36 or 42, respectively.

If a subject terminates treatment due to non-DLT reasons during the first treatment cycle, there is no need to replace the subject. When the study has increased to a dose level (d) that is beyond the MTD, and according to the i3+3 decision table (Figure 1), the dose-assignment recommendations in cohorts of d and d-1 are dose de-escalation (D) and escalation (E), respectively, a new cohort may be added between the d and d-1 dose cohort after SMC review and evaluation on the available clinical data of PK/PD, safety, and efficacy, the new cohort can be an intermediate dose cohort (25 mg increment/decrement) or an intermittent schedule (such as 3 weeks on, 1 week off; 5 days on, 2 days off, etc.). The sample size will be increased by 6 subjects accordingly.

At the end of the study, the MTD will be inferred based on the DLT data and all safety data observed at all dose levels. The specific MTD estimation method is shown in Section 4.2. The RPTD will be established by taking into consideration of the PK and/or PD profiles and safety data from the dose escalation phase.

The DLT evaluable subject is defined as the subject who received at least 75% of the planned doses of treatment and completed the safety assessment during DLT evaluation period.

During the DLT evaluation period, Subject can withhold 3D185 due to drug-related AEs. If the withholding time is more than 7 days, the AE will be considered as DLT. The subject's dose of 3D185 will not be reduced unless DLT occurs.

4.2. i3+3 Design

Similar to the 3+3 design[18], the i3+3 is rule-based design, and it is also an interval-based design similar to mTPI[19]. The specific algorithm of i3+3 design is shown in Appendix 7. Compared to the 3+3 design, the i3+3 design offers greater flexibility (e.g., flexible handling of subject, shedding), higher MTD selection probabilities, and better safety (see Appendix 8 for the comparison results of the simulation trials for 3+3 and i3+3). The target toxicity probability of the MTD in this study is set to pT = 25%, and the equivalence interval (EI) is (16%, 30%). This means

that the MTD should have a toxicity probability near 25% but not below 16% or above 30%. The decision table for the i3+3 design of this study is shown in Figure 1.

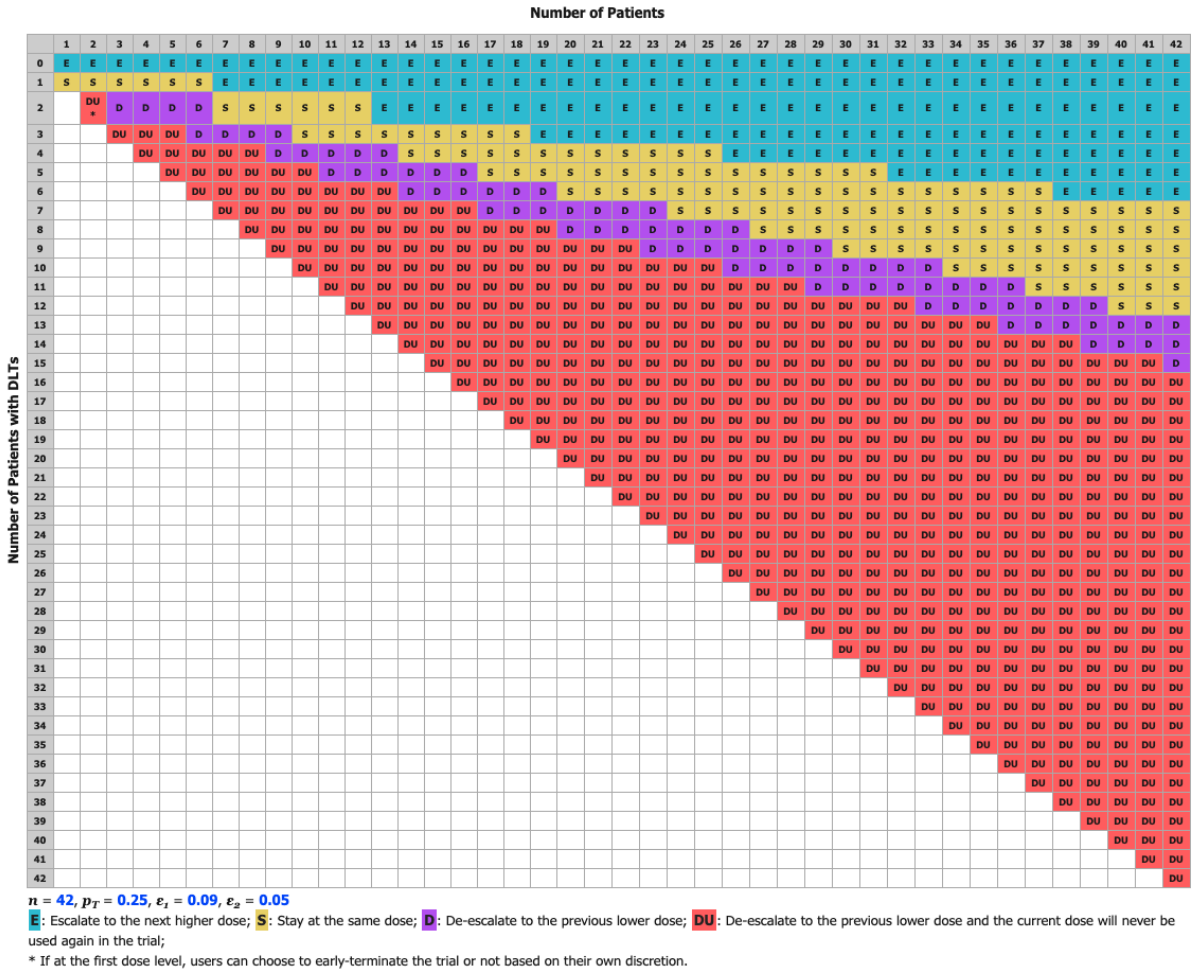


Figure 1 i3+3 Dose Escalation Decision Table

Note:

This is a decision table for the 3D185 dose-finding study. The target toxicity probability (pT) is 25% and the equivalence interval (EI) is (16%, 30%) for 42 subjects. Each column represents (n) number of DLT evaluable subjects treated at the current dose and each row represents (x) number of subjects with DLTs at the dose level. Each cell in the table provides the dose-assignment recommendation based on the readouts from the corresponding row (x) and column (n). The letters in the decision table represent different dose-assignment recommendations.

The i3+3 dose-escalation phase is expected to enroll 30-42 subjects (maximum sample size will be adjusted according to the first dose entering the i3+3 phase. For details, see Section 4.1). Every 3 subjects as a cohort will be sequentially enrolled.

The specific operation process of i3+3 design is as follows:

✧ Three subjects will be enrolled in a cohort to receive the planned dose of 3D185. When i3+3 dose-escalation phase starts, if there is no Grade ≥ 2 drug-related AE occurs during the accelerated titration phase, the subjects in the first cohort in this phase will receive 100 mg 3D185. Otherwise, one of the subjects from the accelerated titration dose-escalation cohort will be enrolled in the first cohort of the i3+3 phase. And 2 additional subjects will be enrolled in this first cohort.

✧ After the three subjects in each cohort complete the DLT evaluation, the dose-assignment recommendation for the next cohort will be determined according to the decision table (Figure 1) by using the safety data from the DLT evaluable subjects.

1) In Figure 1, "E" stands for escalating to the next higher dose; "S" stands for staying at the current dose; "D" stands for de-escalating to the previous lower dose.
2) "DU" indicates that the toxicity at the current dose level is too high. Thence, it stands for de-escalating to the previous lower dose and marking the current and the higher doses as unacceptable so that it will never be used again in the remainder of the trial to avoid other subjects receiving treatment at these doses to ensure their safety. If the current dose is the lowest dose and the dose-assignment recommendation is "DU", the study should be terminated to ensure the safety and no dose level will be selected as the MTD.
3) If the current dose is the lowest dose and the dose-assignment recommendation is "D", the study will continue to enroll new subjects at the current dose. Once the dose-assignment recommendation is "DU", the study should be terminated to ensure safety.
4) If the current dose is the highest dose and the dose-assignment recommendation is "E", the study will continue to enroll new subjects at the current dose.
5) Figure 1 is still applicable in the situation of subjects who have withdrawn due to some reason or more than 3 subjects enrolled in the current dose cohort. For example, if one of three enrolled subjects have withdrawn from the study due to some reasons, the i3+3 design will always appropriate to make a decision based on the data from the remaining 2 DLT evaluable subjects.

✧ Repeat the steps of 1) and 2) until the maximum sample size is reached.

After all of the subjects have enrolled and the observations have completed, isotonic regression will be used to select the MTD based on the observed DLT data and all safety data from all the dose levels[19]. That is, if the toxicity probability of a dose is close to the target toxicity probability

after isotonic estimation, the dose will be selected as the MTD. In the case where the estimates of the toxicity probability of the two doses are consistent, if the estimate is less than the target toxicity probability, the higher dose will be selected as the MTD; if the estimate is greater than or equal to the target toxicity probability, the lower dose will be selected as the MTD. The MTD selection process can be implemented in the U-Design (https://udesign.laiyaconsulting.com/decision).

4.3. Study Plan and Process

The study comprises a screening period (Day -28 to -1), a treatment period (28 days/cycle, including a single dose PK study period [Day 1-7]), and a safety follow-up period (28 days after the last dose).

4.3.1. Screening/Baseline Period (Day -28 to Day -1)

Informed consent must be obtained before all the specific study procedures in this clinical trial. Subject is eligible for participation in this clinical trial after reviewing the inclusion and exclusion criteria. Candidates could be re-screened once if they did not fulfill the entry eligibility (failed screening) at the first screening visit. Subjects need to re-sign the ICF and obtain a new screening number during re-screening.

4.3.2. Treatment Period

✧ **PK Sampling:**

During the single dose PK study period, venous blood (3 mL each) will be collected within 1 h before the first dose, and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 48 h, 72 h, and 96 h after the first dose.

During the first cycle treatment period, venous blood (3 mL each) will be collected within 1 h before dosing on C1D8, C1D15, and C1D28, and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h after dosing on C1D28.

✧ **Safety Evaluation:**

The safety evaluation includes physical examinations, vital signs, laboratory evaluations, ECG, ophthalmological examination, and AE collection. Please refer to flow chat for detail safety visit schedules.

✧ **Efficacy Evaluation:**

The anti-tumor activity will be evaluated according to the RECIST 1.1 criteria. Tumor imaging assessments will be performed every 8 weeks (±7 days) until disease progression, death, withdrawal of informed consent, or termination of treatment. Subjects who discontinue treatment for reasons other than disease progression or death should continue with imaging assessments per

protocol-defined schedule until disease progression, death, or withdrawal of informed consent, whichever occurs first.

If the imaging result shows a CR or PR for the first time, it is necessary to repeat the tumor imaging at least 4 weeks later to confirm the response. Imaging assessments will be performed according to the aforementioned schedule regardless of the efficacy confirmation scan.

If a subject terminates 3D185 treatment due to symptomatic deterioration/disease progression, the Investigator should continue to perform imaging scan until documented radiographic disease progression.

✧ **Tumor Tissue Specimen:**

For subjects with benefit from receiving 3D185 monotherapy (CR or PR or SD), it is recommended to obtain the disease-related archived tumor tissue or fresh tumor biopsy as much as possible with their consent to explore the relationship between the anti-tumor activity of 3D185 and FGFR alterations in tumor tissue.

✧ **Safety Follow-up:**

Safety follow-up will be performed on Day 28 (±7 days) after the last dose. Subjects in this visit will receive safety assessments, including evaluation of AEs, vital signs, physical examinations, ECG, ophthalmological examination, laboratory tests, etc.

The detailed flow chart of this study is shown in Table 3.

Table 3 Study Flow Chat

Date / Items	Screening		Treatment Period												Follow-up
			Single dose PK study period					1st Treatment cycle				2nd Treatment cycle		Additional cycles	28 Days after last dose (±7 days)[18]
	Days-28 to -1	Days-7 to -1	C0D1	C0D2	C0D3	C0D4	C0D5	C1D1	C1D8	C1D15	C1D28	C2D15	C2D28	CxD28	
Informed Consent[1]	X														
Inclusion/Exclusion Criteria		X													
Demographics/Medical History	X														
Tumor History/Treatment History[2]	X														
Physical Examination[3]		X						X	X	X	X	X	X	X	X
ECOG Performance Status		X									X		X	X	X
Vital Signs		X						X	X	X	X	X	X	X	X
CBC with Differential[4]		X						X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[5]		X						X	X	X	X	X	X	X	X

Date / Items	Screening		Treatment Period											Follow-up
			Single dose PK study period					1st Treatment cycle				2nd Treatment cycle		Additional cycles	28 Days after last dose (±7 days)[18]
	Days-28 to -1	Days-7 to -1	C0D1	C0D2	C0D3	C0D4	C0D5	C1D1	C1D8	C1D15	C1D28	C2D15	C2D28	CxD28	
Coagulation Parameters[6]		X									X			X (every 8 weeks ±7 days after C3D28)	X
Urinalysis[7]		X						X	X	X	X	X	X	X	X
12-Lead ECG[8]		X	X					X	X	X	X	X	X	X	X
Ophthalmological examination [9]		X									X			X (every 8 weeks ±7 days after C3D28)	X
Pregnancy Test - Serum β-HCG[10]		X													
Echocardiography [11]	X		X (clinically indicated)												X
Tumor assessment[12]	X												X	X (every 8 weeks ±7 days after C4D28)	
Concomitant medications[13]	X	X	X												X

Date / Items	Screening		Treatment Period											Follow-up
			Single dose PK study period					1st Treatment cycle				2nd Treatment cycle		Additional cycles	28 Days after last dose (±7 days)[18]
	Days-28 to -1	Days-7 to -1	C0D1	C0D2	C0D3	C0D4	C0D5	C1D1	C1D8	C1D15	C1D28	C2D15	C2D28	CxD28	
Review Adverse Events[14]			X												X
Pharmacokinetics[15]			X	X	X	X	X		X	X	X				
Virologic examination[16]	X														
Archival Tumor Tissues[17]			X												

Notes:

1. Informed consent must be obtained prior to all the specific study procedures in this clinical trial. And the date of signature can be prior to the 28-day screening window period. Subjects who failed screening may be screened again but need to re-sign the informed consent form and obtain a new screening number.
2. The latest anti-tumor treatment history must be recorded.
3. Physical examination includes examination of whole human body systems.
4. CBC with differential: whole blood count (absolute value) includes red blood cell count, white blood cell counts, and differential counts (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit. This test should be completed within 7 days prior to the first dose. It is unnecessary to repeat on C0D1 if the subject has no clinical signs and indications. This test should be completed before dosing within 3 days prior to days C1D1, C1D8, C1D15, C1D28, C2D15, C2D28, CxD28, and safety follow-up period. An unscheduled exam can be performed if there are clinical indications.
5. Blood biochemistry includes ALT, AST, total bilirubin, BUN (urea nitrogen) or urea, Cr (creatinine), blood glucose, potassium, sodium, chlorine, calcium, phosphate, magnesium, total protein, albumin, albumin/globulin ratio, LDH (lactate dehydrogenase), and ALP (alkaline phosphatase). This test should be completed within 7 days prior to the first dose. It isn't required to repeat on C0D1 if the subject has no clinical signs and indications. This test should be completed before dosing within 3 days prior to days C1D1, C1D8, C1D15, C1D28, C2D15, C2D28, CxD28 and safety follow-up period. Among them, phosphate levels will also be used for PD analysis.
6. Coagulation functions include prothrombin time (PT), APTT, and INR. This test should be completed within 7 days prior to the first dose. It isn't required on C0D1 if the subject has no clinical signs and indications. This test should be completed before dosing within 3 days prior to C1D28, every 8 weeks (±7 days) in additional cycles, and safety follow up visit.

7. Urinalysis includes specific gravity, pH, white blood cells, red blood cells, proteins, glucose, ketones, and casts. This exam should be completed within 7 days prior to the first dose. If urine protein ++, it is recommended to test 24-hour urine protein quantitation as soon as possible (if within 72 hours). It isn't required on C0D1 if the subject has no clinical signs and indications. This test should be completed before dosing within 3 days prior to days C1D1, C1D8, C1D15, C1D28, C2D15, C2D28, CxD28, and safety follow-up period.
8. The 12-lead ECG should be completed within 7 days of the first dose. This test should be performed at 2 hours (±5 min) after dosing on C0D1 and C1D28. It also should be completed before dosing within 3 days prior to days C1D1, C1D8, C1D15, C2D15, C2D28, CxD28, and safety follow up visit.
9. Ophthalmological examination includes non-contact intraocular pressure, slit lamps, fundus examinations, and optical coherence tomography. The examination should be completed within 7 days prior to the first dose. It isn't required on C0D1. This test should be completed before dosing within 3 days prior to C1D28, every 8 weeks (±7 days) in additional cycles, and the safety follow-up period.
10. A serum pregnancy test should be completed at the screening period. Female subjects at childbearing age should complete the examination within 7 days prior to the first dose.
11. Echocardiography should be performed during the screening period, the treatment period (if clinically indicated), and the safety follow-up period.
12. Baseline tumor assessment should be completed within 28 days prior to the first dose. It is recommended to perform CT or MRI of the chest, abdomen, and pelvic at baseline. Subjects with known or suspected brain metastases should have a CT or MRI of the brain at baseline. If there are clinical indications or suspicious lesions in other areas, tumor imaging evaluation must also be performed. Baseline assessment and post-treatment efficacy assessment will be performed using the same method and as much as possible by the same Investigator (RECIST 1.1 criteria). Tumor imaging assessment (CT or MRI) should be performed every 8 weeks (±7 days) from C1D1 until disease progression, death, withdrawal of informed consent, or termination of treatment. Subjects who discontinue treatment for reasons other than disease progression or death should continue with imaging assessments per protocol-defined schedule until disease progression, death, or withdrawal of informed consent, whichever occurs first. If the imaging result shows a CR or PR for the first time, it is necessary to repeat the tumor imaging at least 4 weeks later to confirm the response. If clinically indicated, the Investigator can perform an unscheduled tumor assessment.
13. Concomitant medications include any prescription and OTC medications. During the baseline screening, all medications that used by the subjects should be recorded from 28 days prior to the first dose to safety follow-up 28 days after the last dose. And after safety follow-up, record other anti-tumor drugs only.
14. AEs will be collected from C0D1 to 28 days after the last dose. After signing the informed consent form, any SAE associated with the protocol required operation that occurs before the start of dosing should also be reported. Investigational product related AEs and investigational product unrelated SAEs or life-threatening AEs will be followed up until recovery to Grade 0-1 or baseline status, or the Investigator has assessed that it is in a stable status, or confirmed not investigational product related AE, or subject has begun a new anti-tumor treatment, lost follow-up, or withdraw informed consent. Investigational product related SAEs occurred after safety follow-up visit should also be recorded, reported and follow up.
15. PK blood sample during single dose treatment period will be collected within 1 h before dosing and 0.5 (±5 min), 1 (±5 min), 2 (±5 min), 3 (±5 min), 4 (±5 min), 6 (±5 min), 8 (±5 min), 12 (±5 min), 24 (±10 min), 48 (±10 min), 72 (±10 min), and 96 (±10 min) hours after dosing. PK sampling during multiple dose treatment period will be performed within 1 h before dosing on C1D8, C1D15 and C1D28, and at 0.5 (±5 min), 1 (±5 min), 2 (±5 min), 3 (±5 min), 4 (±5 min), 6 (±5 min), 8 (±5 min), 12 (±5 min), and 24 (±10 min) after dosing on C1D28. Each time will collect venous blood 3 mL. PK will be tested by a central laboratory. Details see Laboratory Manual.
16. Virological examinations (including HBV DNA quantification and HCV antibody testing) should be tested during screening period. To avoid repeat exam, the results before informed consent are acceptable if within 28 days prior to the first dose.
17. For subjects with benefit from receiving 3D185 monotherapy (CR or PR or SD), it is recommended to obtain the disease-related archived tumor tissue or fresh tumor biopsy as much as possible with their consent to explore the relationship between anti-tumor activity of 3D185 and FGFR alterations in tumor tissue.
18. Subjects who completed or prematurely discontinued investigational product therapy should return to the study center for safety assessment on 28 (±7) days after the last dose or before starting other anti-tumor treatments, whichever occurs first. For subjects who have completed investigational product therapy but have not assessed disease progression, it is recommended to continue the tumor imaging assessment during this follow-up.

4.4. Rationale for Selection of the Starting Dose

Per FDA/CFDA guidelines, the clinical starting dose for molecular targeted drugs should be selected by the approach of converting preclinical NOAEL dose to a human equivalent dose based on body surface area. The safety factor should then be considered. Based on the result of preclinical repeat-dose toxicity study of 3D185, the NOAEL in rats was 10 mg/kg. The human starting dose was estimated by 1/3 NOAEL dose of the rat, which was approximately 1/3 × 10 mg/kg × 0.162 × 60 kg = 32.4 mg.

Per ICH guideline S9, it is typically used body surface area for interspecies dose conversion to select the starting dose for most systemically administered small molecule drugs. A common practice is to use 1/10 STD_{10} (Severely Toxic Dose in 10% animal) in rodents as the starting dose. If non-rodent is the closely related species, then 1/6 HNSTD (Highest Non-Severely Toxic Dose) can be selected as the starting dose. Based on the preclinical repeat-dose toxicity study of 3D185, the HNSTD in dogs was 12 mg/kg. The human initial dose was estimated by 1/6 NOAEL dose of the dogs, which was approximately 1/6×12 mg/kg×0.541×60 kg = 64.92 mg.

In comparison, a relatively safer dose will be selected. Considering the strength of the drug, the starting dose of 3D185 for the clinical trial will be 25 mg orally once a day.

Based on the existing preclinical data, 3D185 will start at the dose of 25 mg by using the combination of accelerated titration and i3+3 for dose-escalation[1]. The seven dose-escalation cohorts are 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg, respectively. The pre-set dose cohorts may be adjusted during this study. The decision of the actual dose will be made by the Investigators and the Sponsor.

4.5. Dose Limiting Toxicity (DLT) Definition

A DLT is defined as the occurrence of any of the following toxic reactions that are considered to be causally related to 3D185 by the PI within the first 35 days after the first dose.

1. Hematological toxicity:
    1. Grade 4 hematologic toxicity;
    2. Grade 3 febrile neutropenia (defined as ANC < 1,000/mm^3, a single temperature of > 38.3 ℃ or a sustained temperature of ≥ 38 °C for more than 1 hour) or Grade 3 neutropenia lasts for more than 7 days with or without drug intervention;
    3. Grade 3 thrombocytopenia with bleeding or require to platelet transfusion;

2. Non-hematologic toxicity:

    4. Any Grade ≥ 3 non-hematologic toxicity (except the following conditions that can be controlled by symptomatic treatment within 48 hours: nausea, diarrhea, vomiting, and electrolyte imbalance [except serum phosphorus]; Grade 3 fatigue with duration ≤ 7 days; Grade 3 hypertension that can be self-resolved or controlled by drugs to below 140/90 mmHg or baseline level within 72 hours);
    5. Serum phosphorus ≥7 mg/dL that is unable to recover to < 7 mg/dL within 14 days after phosphorus removal;
    6. With liver metastasis or baseline transaminase abnormalities: ALT/AST > 8 × ULN; without liver metastasis or baseline transaminase abnormalities: ALT/AST > 5 ×ULN ;
    7. 3D185-related AEs that resulted in dose interruption of 3D185 for ≥ 7 days in the first treatment cycle.

If the DLT is clinically recovered to Grade 0-1 within 28 days, the subject can resume the treatment of 3D185. If the subject can resume treatment, the Investigator may refer to the provisions of Section 6.3 (Precautions and Dose Modifications) for dose modifications to the same dose or reduce by one dose level.

4.6. Screening and Enrollment

Informed consent must be obtained before all the specific study procedures in this clinical trial. Subject is eligible for participation in this clinical trial after reviewing the inclusion and exclusion criteria. Candidates could be re-screened once if they did not fulfill the entry eligibility (failed screening) at the first screening visit. Subjects need to re-sign the ICF and obtain a new screening number during re-screening. Each eligible subject will be assigned a subject number to receive 3D185 treatment. The screening number and subject number will be assigned starting from the lowest number in chronological order.

5. STUDY POPULATION

5.1. Target Population

Subjects with advanced solid tumors who have no available standard therapy or who have failed standard therapies.

5.2. Inclusion Criteria

Subjects must meet all of the following criteria before they can be enrolled:

1. Age ≥ 18 years.
2. Subjects must have a histological diagnosis of locally advanced or metastatic malignant solid tumors. Subjects must have failed the established standard treatment, or the standard treatment does not exist; or subjects are intolerant of or have refused to receive standard treatment. All subjects must have received at least one previous line of systemic treatment. Subjects with known genomic alterations for which there are approved therapies (e.g., ALK mutated NSCLC, microsatellite instability high/mismatch repair deficient solid tumors, EGFR NSCLC, etc.,) will have received such therapies prior to the enrolling in this study.
3. Subjects must have measurable or evaluable disease (according to RECIST 1.1, see Appendix 1);
4. ECOG Performance Status ≤ 2.
5. Life expectancy ≥ 12 weeks.
6. Subjects must have normal levels of total serum calcium and total phosphate.
7. Subjects must have adequate organ and bone marrow function (subjects must not have received any hematopoietic growth factors, transfusion, or platelet within 1 week before the first dose).
    - CBC: neutrophils ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, hemoglobin ≥ 9.0 g/dL.
    - Liver function: total bilirubin ≤ 1.5 × ULN, unless known to have Gilbert's disease; ALT/AST ≤ 2.5 × ULN without liver metastasis; ALT/AST ≤ 5 × ULN with liver metastasis;
    - Coagulation: INR ≤ 1.5 × ULN and APTT ≤ 1.5 × ULN (for subjects undergoing anticoagulant therapy, the Investigator should ensure that both INR and APTT are within the safe and effective treatment range).
    - Renal function: serum creatinine ≤ 1.5 × ULN, or creatinine clearance ≥ 60 mL/min/1.73 m^2 in the condition of creatinine level > ULN; urine protein

analysis ≤ 1 + (if ≥ 2+, 24 hours of urine protein test is required, if 24 hours urine protein <1 g, then allowed to enroll);

- Adequate cardiac function: LVEF > 50% in two-dimensional echocardiography;

8. Subjects must have fully understood and voluntarily signed ICF for this study.

5.3. Exclusion Criteria

Subjects who meet any of the following criteria should be excluded from the study:

1. Subjects who received other investigational products or devices in other clinical trials within 4 weeks before the first dose.
2. Subjects who received anti-tumor therapy (except for mitomycin, nitrosourea, and fluorouracil oral drugs) within 4 weeks before the first dose, including but not limited to chemotherapy, radiotherapy (palliative radiotherapy is completed at least 2 weeks before the first dose can enroll), targeted therapy or immunotherapy.

Note: The last dose of mitomycin and nitrosourea should be at least 6 weeks before investigational product initiation; the last dose of oral fluorouracil such as tegafur and capecitabine should be at least 2 weeks before investigational product initiation.

3. Subjects who previously received selective FGFR1-3 inhibitor therapy.
4. Subjects who require the use of concomitant medications that prolong the QT/QTc interval.
5. Subjects who have previous toxicity of anti-tumor therapy that has not recovered to Grade 0 or 1. (alopecia, chemotherapy-induced peripheral neurotoxicity, and ototoxicity ≤ Grade 2 can enroll).
6. Subjects who received CYP3A4 and/or CYP2C8 strong inhibitors or CYP3A4 strong inducers (see Appendix 6) within 14 days prior to the first dose and the subjects who need to continue using these drugs.
7. Subjects who have any of the following eye diseases/conditions: 1) History of RPED; 2) History of laser treatment or intraocular injection for macular degeneration; 3) History of dry or wet age-related macular degeneration; 4) History of RVO; 5) History of retinal degenerative diseases; 6) History of chorioretinal lesions.
8. Subjects who received clinical intervention for biliary obstruction 14 days prior to the first dose or the Investigator judges that the symptoms have not resolved or require anti-infective treatment.
9. Subjects who have gastrointestinal disorders that will affect oral administration or the Investigator judges that the absorption of 3D185 will be interfered.

10. Subjects underwent major surgery (except biopsy) within 4 weeks, or the surgical incision has not completely healed prior to the first dose.
11. Subjects who had clinically uncontrollable pleural effusion, ascites, or pericardial effusion within 2 weeks prior to the first dose.
12. Subjects who have symptomatic brain metastases or spinal cord compression. For the subjects, who have previously treated for brain metastases, if the clinical condition is stable and imaging evidence does not show disease progression within 4 weeks prior to the first dose, and do not need corticosteroid treatment within 2 weeks prior to the first dose, can enroll.
13. Subjects who have active bacterial or fungal infections (CTCAE Grade ≥ 2) that required systemic treatment within 14 days prior to the first dose.
14. Subjects who have active HBV infection (HBV DNA ≥ 1000 copies/mL) and/or HCV antibody testing positive;
15. Subjects who have clinically significant cardiovascular diseases that occurred 6 months prior to first dose. Cardiovascular diseases include, but not limited to follows: acute myocardial infarction; severe/unstable angina; cerebrovascular accident or transient ischemic attack; congestive heart failure (NYHA > Class II, see Appendix 3); arrhythmias that require antiarrhythmic treatment except for beta blockers or digoxin; repeated ECG with QTc interval > 450 ms; high blood pressure that cannot be controlled by antihypertensive drugs (systolic blood pressure > 150 mm Hg, diastolic blood pressure > 100 mmHg).
16. Subjects who have clinically significant abnormal serum electrolyte levels.
17. Subjects who are receiving warfarin (low-dose warfarin up to 2 mg/day is allowed); or receiving antiplatelet anticoagulant therapy (aspirin at dose ≥ 300 mg/day, clopidogrel at dose ≥75 mg/day).
18. Female subjects in pregnancy or lactation. Male subjects or female subjects at reproductive ages who are unwilling to receive effective contraceptive measures.
19. Subjects who are judged by the Investigator to be unsuitable for this study.

5.4. Subject Study Completion and Withdrawal Criteria

5.4.1. Subject Study Completion

A subject will be considered to complete study if he/she has a valid PK profile and has not withdrawn from the study prior to the DLT evaluation period (first treatment cycle). A subject also will be considered to complete study if he/she discontinued study treatment due to a DLT with or without a valid PK profile.

5.4.2. Subject Withdrawal/Discontinuation

If a subject has any medical condition and the Investigator believes that his or her continued participation in the study may jeopardize the safety, the Investigator has the right to decide that the subject will discontinue the study treatment early. All subjects, who signed the ICF and screened eligible into the trial, have the right at any time to withdraw or discontinue from the treatment of investigational product. In addition, a subject may be withdrawn by the Investigator if he/she violates the study plan or management and/or other safety reasons.

When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the safety follow-up visit should be performed. Any drug-related AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements.

During the treatment period, subjects can receive 3D185 treatment until one of the following events occurs:

- Subject withdrew consent;
- Progressive disease;
- Death;
- Unacceptable treatment toxicity;
- Start other anti-cancer therapy;
- The Investigator determines it is in the best benefit of the subject to discontinue the investigational product treatment;
- Poor compliance or severe protocol violations, and have an impact on drug tolerance, safety, or PK evaluation;
- Pregnancy during the treatment period;
- Lost to follow-up;
- Others.

Subjects who stop treatment prior to the documentation of disease progression will undergo repeated imaging for tumor response assessments at the frequency according to protocol until unequivocal disease progression is documented or the subject starts new anticancer therapies or subject withdraws consent from the trial, whichever occurs first. Subjects who withdraw from the study for clinical or symptomatic deterioration before objective documentation of disease progression will be requested to undergo appropriate imaging to confirm disease progression. Every effort will be made to confirm a clinical diagnosis of disease progression by imaging.

5.5. Study Termination Criteria

The Sponsor may terminate the study for reasons of clinical significance, including but not limited to:

1. The study objectives have been achieved;

2. The incidence and severity of AEs in this study suggest that it is not appropriate to continue this clinical trial.

During the termination of the study, the Sponsor will ensure that the rights of the subjects are fully protected.

6. TREATMENTS ADMINISTRATED

6.1. Investigational Product

6.1.1. Acquisition

The investigational product 3D185 is provided by 3D Medicine (Beijing) Co., Ltd, for clinical studies.

6.1.2. Specification

3D185 are white to off-white, round, scored tablets. The dosage strength for clinical trials is 50 mg/tablets and 30 tablets/bottle.

6.1.3. Drug Labeling

The packaging and the sample labeling of the investigational product will be prepared in accordance with the Good Manufacturing Practice (GMP) and GCP regulatory requirements.

6.1.4. Product Storage

3D185 should be stored at room temperature (15-25℃) , sealed and protected from light. Based on the currently stability data, the storage period of 3D185 is 2 years. The storage period can be extended according to further stability data. The investigational product should be stored as specified, and the storage temperature should be recorded and saved in the corresponding documents. All investigational products will be used in this study only and the protocol required operations.

6.1.5. Drug Accountability

A designated person is required to manage the reconciliation and recording of investigational products. The study center should ensure that there is a designee responsible for receiving the investigational product, that the drug treatment has an accurate record, and that the study drug is properly used and stored. Unused investigational products should be stored according to the requirements for drug storage. The fixed personnel will periodically check whether the storage meets the requirements. After completion of the study, all remaining drugs must be reconciled and recorded, then returned to the Sponsor to destroy.

6.2. Dosing Regimens and Methods

6.2.1. Dosing Regimens and Cycle

The starting dose in this study is 25 mg (half tablet). The preset seven dose-escalation cohorts are 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg of 3D185 orally once a day, every 28 days in a treatment cycle. Eligible subjects in each cohort will receive a single oral dose of 3D185, followed by a 7-day washout period. Then, continue to receive the same dose of 3D185

until disease progression, death, toxicity intolerance, or withdraw informed consent, whichever comes first. At the end of each dose-escalation cohort, the PI and the Sponsor may work together to adjust the dose of the subsequent dose levels based on the safety data obtained from the previously completed cohorts.

Route of administration: (fasting) oral administration.

Treatment cycle: every 28 days in a treatment cycle.

6.2.2. Method of Administration

3D185 should be administered in accordance with the following principles:

- Subjects should be instructed to take 3D185 every morning with the same daily medication time;
- Subjects are advised to take 3D185 in a fasted state. No food should be consumed two hours before and two hours after the 3D185 dose;
- 3D185 should be swallowed with warm water;
- If vomiting occurs after taking 3D185, it is not required to make up for the dose, the subsequent dose should be taken in the next day. The occurrence and severity of vomiting during the treatment period must be recorded.

6.2.3. Delayed or Missed Dosing

If a dose of 3D185 is missed within 12 hours of the scheduled medication time, it can be taken as soon as possible on the same day. If a dose is missed more than 12 hours of scheduled medication time, it is not allowed to make up for the missed dose. Subject can resume the regular daily dose schedule in the next day. The medication interval must be more than 12 hours.

All cases of delayed or missed dosing must be recorded in the subject log and reported in the eCRF. The remaining tablets must be returned to the Investigator at the end of each cycle.

6.2.4. Overdose

Study treatment overdose is the accidental or intentional use of 3D185 in an amount higher than the protocol required dose.

When an overdose occurs, the Investigator should discuss with the sponsor's medical monitor and provide appropriate supportive care for drug overdose induced adverse reactions. The Investigator also should promptly report the adverse reactions to the Sponsor.

6.3. Precautions and Dose Modifications

6.3.1. Precautions

According to preclinical study results of 3D185, the possible toxicity of 3D185 included hyperphosphatemia, liver function abnormalities, gastrointestinal abnormalities, and skeletal system disorders. Based on clinical study results of the similar selective FGFR inhibitors, the common toxicities include hyperphosphatemia, nail and mucosal abnormalities, gastrointestinal abnormalities, ocular abnormalities (including reversible RPED), fatigue, cough, elevated lipase, etc.

Therefore, it must be important to monitor the liver and kidney function, serum phosphate, and skeletal system in this study. The clinical symptoms and signs also should be observed strictly. Once any above abnormalities occur, the Investigator should provide timely and effective medical treatment based on the subject's specific condition.

✧ **Hyperphosphatemia & Hypercalcemia Management Guideline**

During the study treatment period (including the DLT assessment period), all subjects should restrict phosphate intake to 600-800 mg/day (see Appendix 5 for phosphorus-rich foods). Guidelines for the clinical management of elevated serum phosphate levels are presented in Table 4.

Hypercalcemia is also a known adverse event in patients who received selective FGFR inhibitor treatment. A hypercalcemia should be considered when serum calcium corrected for albumin level is above Upper Limit of Normal (ULN).

In case of grade 2 hypercalcemia concurrent with hyperphosphatemia or grade 3 hypercalcemia in absence of hyperphosphatemia, 3D185 should be discontinued permanently.

Table 4 Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Dose Modification	Medical Management
5.6-6.9 mg/dL (1.8-2.2 mmol/L)	Continue 3D185 at current dose level.	Restriction of phosphate intake to 600 – 800 mg/day. May consider sevelamer 800 mg to 1,600 mg 3 times a day (with food)
7.0-9.0 mg/dL (2.3-2.9 mmol/L)	Withhold[a] 3D185 treatment until the serum phosphate level returns to < 5.5 mg/dL. Resume at the same dose level. A dose reduction may be implemented for persistent[b] hyperphosphatemia (≥ 7 mg/dL) if	Restriction of phosphate intake to 600 - 800 mg/day. Sevelamer 800 to 1,600 mg 3 times a day with food until phosphate level is < 5.5 mg/dL.

Serum Phosphate Level	Dose Modification	Medical Management
	clinically necessary.	
> 9.0 mg/dL (> 2.9 mmol/L)	Withhold[a] 3D185 treatment until the serum phosphate level returns to < 5.5 mg/dL. Resume at the next lower dose level in case of serum phosphate level returns to below 5.5 mg/dL within 7 days. Reduce by two dose levels if it takes 7~28 days to return to below 5.5 mg/dL despite adequate medical management. A second dose reduction may be implemented if needed or clinically indicated for persistent[b] hyperphosphatemia (≥ 7 mg/dL) at every cycle.	Restriction of phosphate intake to 600 – 800 mg/day. Sevelamer up to 1,600 mg 3 times a day with food AND Acetazolamide 250 mg 2 or 3 times a day only until serum phosphate level returns to < 5.5 mg/dL.
> 10.0 mg/dL (> 3.2 mmol/L) or significant alteration in baseline renal function OR Grade 2 hypercalcemia concurrent with hyperphosphatemia	3D185 should be discontinued permanently. (In situations where the subject is having clinical benefit and the investigator and the sponsor's medical monitor agree that re-starting drug is in the best interest of the subject, the drug may be re-introduced at two dose levels lower if appropriate[c]. Follow other recommendations described above.)	Medical management as clinically appropriate.

Note: These are general guidelines that are based on emerging data of other selective FGFR inhibitors and and/or the experts in the field. The treating physicians must use clinical judgment and local standard of care to decide the best way to manage phosphate elevation. If Sevelamer hydrochloride (renagel) is not available, use of other phosphate binders (non-calcium containing) based on the local standard is recommended, including Sevelamer carbonate (Renvela) or lanthanum carbonate (Fosrenol).
a. Drug interruptions for hyperphosphatemia suggested to be 7 days duration
b. Persistent hyperphosphatemia is considered to be more than 1 sequential phosphate value of ≥ 7 mg/dL
c. If a subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in

Serum Phosphate Level	Dose Modification	Medical Management
agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator. The investigator should also have the subject re-consent, explaining that re-introduction of investigational product could lead to increased risk of recurrent toxicities.		

✧ Ocular Toxicity Management Guideline

FGFR target therapy can cause ocular toxicities, including dry eye, central serous retinopathy (CSR)/retinal pigment epithelial detachments (RPED), blurred vision, visual impairment, etc.

Ophthalmological examinations, including non-contact intraocular pressure, slit lamps, fundus examinations, and optical coherence tomography, should be performed regularly during screening period, treatment period, and safety follow-up period.

If the subject has any ocular toxicity, (such as dry eye, blurred vision, visual impairment, etc.), it is recommended to consult an ophthalmologist in time. If the subject has any significant eye discomfort at the unscheduled visit time during treatment period and safety follow-up visit, the subject should contact the Investigator as soon as possible and visit the ophthalmology clinic if necessary.

Guidelines for Management of Eye Toxicity are presented to Table 5.

Table 5 Guidelines for Management of Eye Toxicity

Grade and Definition	Dose Modification	Medical Management
Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only	Refer for an ophthalmologic examination. If an ophthalmologic exam cannot be performed within 7 days, withhold treatment of 3D185 until an examination can be performed. If there is no evidence of eye toxicity on ophthalmologic examination, continue 3D185 therapy at the same dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as CSR/RPED, withhold 3D185 until signs and symptoms have resolved to baseline or stabilized. After consultation with the medical monitor, resume 3D185 therapy at the next lower dose level when toxicity is completely resolved to baseline, or stabilized and asymptomatic in 4 weeks according to ophthalmologic examination. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter.	Refer the subject for an Ophthalmologic examination. For retinal pathology perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)	Immediately withhold 3D185 therapy. If there is no evidence of drug-related corneal or retinal pathology on ophthalmologic examination, withhold 3D185 until signs and symptoms have resolved to baseline. Resume 3D185 therapy at the next lower dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as CSR/RPED, withhold 3D185 until signs and symptoms have resolved to baseline, stabilized, or subject is lost to	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation.

	follow-up or withdraws consent (which ever happens first). If toxicity is Grade 2 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks according to ophthalmologic examination, resume 3D185 therapy at the next lower dose level after consultation with the medical monitor. In the case of Grade 2 CSR/RPED lasting more than 4 weeks, permanently discontinuing 3D185[a].	Follow specific treatment per the ophthalmologist's recommendation.
Grade 3: Severe or medically significant but not immediate sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	If the toxicity is Grade 3, report as a serious adverse event and permanently discontinue 3D185. If however the toxicity is Grade 3 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks and the subject is having clinical benefit, and the investigator and the sponsor's medical monitor agree that restarting drug is in the best interest of the subject, then 3D185 therapy may be resumed at two dose levels lower if appropriate.[a] Monitor for recurrence using appropriate investigations every 1 to 2 weeks for a month and as clinically appropriate thereafter. For cases of recurrence or grade 3 CSR/RPED lasting more than 4 weeks, consider permanent discontinuation[a].	
Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	Permanently discontinue treatment with 3D185. Report as a serious adverse event and monitor resolution of the event until complete resolution, stabilization or the subject is lost to follow-up or withdraws consent (which ever happens first).	Promptly refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. Follow specific treatment per the ophthalmologist's recommendation.
a. If a subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease,		

the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator. The investigator should also have the subject re-consent, explaining that re-introduction of investigational product could lead to increased risk of recurrent toxicities.

Guidelines for the Management of Dry Eye as follows:

General considerations: Avoid unnecessary exposure to sunlight, use sunglasses in bright light.

Prophylactic management: Frequent use of artificial tear substitutes is strongly recommended.

Reactive management:

20. Withhold 3D185 for grade 3 toxicity, until resolves to Grade 1 or baseline, then may resume dose level lower. Permanently discontinue 3D185 for grade 4 toxicity
21. Artificial tear substitutes if not started, every 4 to 6 hours
22. Hydrating /lubricating eye gels and ointments
23. Severe treatment-related dry eye should be evaluated by an ophthalmologist

✧ **Hepatotoxicity Management Guideline**

In case of Grade 2 AST/ALT elevation in patients without liver metastasis or AST/ALT elevation ≥ 3.0-5.0 folds over baseline value in patients with liver metastasis, withhold 3D185 until the level returns to grade ≤ 1 or baseline, and the liver test should be evaluated at least twice a week. Restart treatment with 3D185 at the same dose level.

In case of total bilirubin ≥ 2 folds over ULN, withhold 3D185 until the level returns to CTCAE Grade ≤ 1 or baseline, and the liver test should be evaluated at least twice a week. Restart treatment with 3D185 at same dose level.

In case of Grade 3 AST/ALT elevation, subjects should withhold 3D185 until the AST/ALT level returns to CTCAE Grade ≤ 1 or baseline. If the AE resolves within 7 days, dosing may resume at the same dose level. If the AE resolves within 7-14 days, dosing may resume at the previous lower dose level or may be modified according to the Investigator's judgment. If the AE cannot resolve within 28 days, the treatment of 3D185 will be permanently discontinued. Liver enzymes should be monitored once a week when the subject receives 3D185 treatment again.

When a hepatic injury is suspected due to abnormal liver function test (such as Grade ≥ 3 AST/ALT elevation), it is recommended to perform a comprehensive assessment (liver imaging, liver function tests and pathogen tests, etc.) as soon as possible.

Abnormal values in AST and/or ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered

potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events, 3D185 must be discontinued immediately. The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities (potential drug-induced liver injury) should be evaluated further to determine the etiology of the abnormal laboratory values definitively:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥ 3 folds over ULN concurrent with a total bilirubin value ≥ 2 folds over ULN with no evidence of hemolysis and an alkaline phosphatase value ≤ 2 folds over ULN.
- For subjects with preexisting ALT or AST or total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
  - ✧ For subjects with preexisting AST or ALT baseline values > ULN, AST or ALT value ≥ 2 folds over the baseline values and ≥ 3 folds over ULN, or ≥ 8 folds over ULN (whichever is smaller).

  Concurrent with:

  - ✧ For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least 1-fold over ULN or if the value reaches ≥ 3 folds over ULN (whichever is smaller). Exception to the bilirubin elevation is made if the subject has Gilbert's disease and the elevated bilirubin is predominantly unconjugated.

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. It is highly recommended to consult a hepatologist. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for Liver Function Test (LFT) abnormalities identified at the time should be considered potential drug-induced liver injury event. Such potential drug-induced liver injury should be reported as SAEs. When there is no other reason to explain the elevation of liver enzymes (Hy's law confirmed), 3D185 must be permanently discontinued.

- ✧ **Nephrotoxicity (Proteinuria) Management Guideline**

During the study, once the urinary protein test ≥ 2+ (Grade ≥ 2 proteinuria), the subject should withhold 3D185 with 24-hour urine protein quantitative test and urine sediment test to detect microscopic hematuria. Dosing may continue while waiting for test results. If urine protein <

2 g/24 h, dosing may resume at the same dose level and it is recommended to continuously monitor urine protein. If urine protein ≥ 2 g/24 h, withhold until urine protein is < 2 g/24 h, restart at the same dose level or previous lower dose level per Investigator judgment. If Grade ≥ 2 proteinuria persists more than 28 days, the treatment of 3D185 should be permanently discontinued.

If the urinary protein test ≥ 2+ (Grade ≥ 2 proteinuria) experience second recurrence or nephrotic syndrome occurs, 3D185 should be permanently discontinued.

A nephrologist is recommended to consult, when any Grade 3 proteinuria or other risk factors (e.g., microscopic hematuria, high blood pressure, etc.) occur.

6.3.2. Dose Delay/Dose Modification

During the DLT evaluation period of the dose escalation phase, subject can withhold 3D185 due to drug-related AEs. If the withholding time is more than 7 days, the AE will be considered as DLT. Unless DLT occurs, subject's dose of 3D185 will not be reduced during this period.

Treatment can be modified or terminated based on toxicity as described in Table 6. For phosphate, liver, eye, kidney toxicity, specific recommendations in the management guidelines are provided in Section 6.3.1.

Table 6 Dose Modification Guidelines

Toxicity Grade	Action	Dose Modification After Resolution of Adverse Event
1	None	Continue same dose
2	None or consider withheld or discontinue	If withheld, restart at same dose or 1 dose lower, if necessary.
3	Withheld	Restart at 1 or 2 doses lower if recovery (to ≤ Grade 1 or back to baseline for non-hematologic toxicity) is within 28 days. Discontinue drug if unresolved for >28 days.
4	Withheld or discontinue	Discontinue*

For general toxicity management:

- Subjects with any grade of toxicity (Grade 1 to 4) should be provided symptomatic treatment when applicable.
- Subjects may have more than 1 dose reduction.

- If 3D185 must be withheld for more than 28 days for a drug-related adverse event that fails to resolve to acceptable level (e.g., ≤ Grade 1 non-hematologic toxicity or back to baseline), treatment with 3D185 should be discontinued with the exception noted below.*
- In all cases of clinically significant impaired wound healing or imminent surgery or potential bleeding complications, it is recommended that dose administration be interrupted, appropriate clinical laboratory data be carefully monitored, and supportive therapy administered, where applicable. Dose administration may be restarted when it is considered safe and at an appropriate dose, according to the investigator's assessment.

*Exception: if a subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator.

The interval of withhold treatment should be no more than 28 days. If the interval is more than 28 days due to 3D185 probably unrelated or unrelated AEs or other reasons, it is necessary to discuss with the Sponsor whether it is possible to continue treatment with 3D185.

6.3.3. Discontinuation criteria for study treatment

When the following 3D185 related severe or life-threatening AEs occur, the investigational product must be permanently discontinued.

- Drug-related Grade 3 AEs or Grade 2 CSR/RPED that cannot recover to Grade ≤ 1 or baseline levels by symptomatic treatment within 28 days;
- Any grade 4 toxicities;
- Recurrent ≥ 2 Grade proteinuria;
- Recurrent Grade 3 eye toxicity associated with vision changes;
- Hy's law confirmed drug-induced liver injury;
- Grade 2 hypercalcemia concurrent with hyperphosphatemia or ≥ Grade 3 hypercalcemia in absence of hyperphosphatemia;
- Other AEs that the Investigator judged to be inappropriate to continue dosing.

If a subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated

with a 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator.

6.4. Concomitant Medications and Prohibit Medications

6.4.1. Concomitant Medications

Concomitant medications include any prescription or over-the-counter (OTC) medications used from the screening period (within 28 days prior to the first dose) to the safe follow-up period. All concomitant medications will be recorded in detail. The following drugs are allowed during the study:

- Subjects with other diseases may continue to receive the relevant medications as required or at any time during the study period;
- Symptomatic treatment for AEs;
- Best supportive care. Subjects with bone metastases can receive bisphosphonate treatment. Subjects can also undergo palliative radiotherapy for bone metastasis cancerous pain.

6.4.2. Prohibit Medications

Prohibit concomitant use with Chinese herbal medicine during the single-dose PK study period and the first treatment cycle to avoid interfering with the 3D185 PK study.

Prohibit concomitant use with gastric acid reducing agents throughout the treatment period.

Prohibit concomitant use with other specific anti-tumor drugs, including chemotherapy, targeted therapy, immunotherapy, and Chinese herbal medicine with anti-tumor indication throughout the study.

Prohibit concomitant use with P-glycoprotein (P-gp) inhibitors throughout the treatment period.

Prohibit concomitant use with CYP3A4 strong inducers or CYP3A4/CYP2C8 strong inhibitors and strong dual inhibitors. (see Appendix 6 for details).

CYP3A4 moderate inhibitors (amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir, ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, and verapamil) and CYP3A4/2C8 moderate dual inhibitors (trimethoprim, ticagrelor, nifedipine) are not recommended throughout the treatment period.

Prohibit long-term use of high-dose anticoagulant or antiplatelet agents throughout the treatment period (e.g., warfarin >2 mg/day, aspirin ≥ 300 mg/day, clopidogrel ≥ 75 mg/day).

If the subject needs palliative radiotherapy (e.g., local radiation therapy to relieve cancerous pain for subjects with bone metastases) for symptom relief during treatment period, the investigational

product should be discontinued during radiation therapy. Subjects can resume the investigational product 7 days after the completion of radiation therapy and must meet the following conditions:

- Radiation-related toxicity has recovered to Grade ≤ 2;
- No disease progression occurs.

6.4.3. Drug-Drug Interactions

Preclinical data showed that 3D185 is primarily catalyzed by CYP3A4. Besides, CYP2C8, CYP2D6, and CYP3A5 also participated a little bit. Therefore, the concomitant use of CYP3A4 inducers and inhibitors should be prohibited in clinical trials. If the Investigator considers it is necessary to concomitant use, it needs to closely monitor the possible reduced efficacy or increased toxicity due to the concomitant use.

6.5. Treatment compliance

The Investigator should accurately record the date and amount of each subject's actual study medication. Subjects will be required to return all kits, bottles, unused tablets, etc. at every visit. The treatment compliance should be estimated during the study and be recorded in the appropriate sections of the eCRF. The Investigator should calculate the actual dose by counting the number of unused tablets returned per cycle, and the Investigator will also need to collect data from the subject diary. In the diary, subjects should record the number of all tablets taken and the corresponding number of times.

Any non-compliance for any reason should be recorded. Subjects who postpone treatment for more than 14 days for reasons other than medical care will be defined as poor compliance. If there is a poor compliance, the Investigator will decide whether to discontinue the study treatment based on the subject's condition.

7. EVALUATION INDICATORS AND EVALUATION CRITERIA

7.1. Screening Period

All subjects must sign ICF prior to the start of the study-related examination or operation. The study center should maintain the ICFs signed by the subjects, including those not enrolled.

During the screening period, complete prior medical history, demographic information, tumor history and prior tumor treatment history, vital signs, physical examination, and ECOG performance status should be recorded. The screening exams and evaluations should be performed within 28 days prior to the first dose. To avoid repeat exam, the results of clinical routine examination (such as echocardiography, virologic examination, tumor imaging evaluation) before informed consent are acceptable if within 28 days prior to the first dose. CBC with differential, serum chemistry, coagulation parameters, urinalysis, serum β-hCG test, 12-lead ECG, and ophthalmological examination should be performed within 7 days prior to the start of study treatment. The detailed screening examinations and evaluations can refer to Table 4 study flow chat.

Any prior medications taken within 28 days before the first dose must be recorded in the eCRF. The information includes generic name, administration and dosage, the reason for the treatment, dates of start and stop, whether to continue taking the medication during this trial, etc.

After the signing of the ICF and before starting dose, any SAEs associated with the protocol required procedures should be reported.

Baseline tumor assessment should be completed by imaging (CT, MRI) according to RECIST 1.1 within 28 days prior to enrollment.

The following screening procedures will be performed within 28 days (-28 to -1 days) before the first dose:

- Informed consent;
- Demographic information (including body weight and height)
- Medical history information,
- Tumor history and prior tumor treatment history;
- Inclusion/Exclusion criteria;
- Complete physical examination (perform within 7 days before the first dose);
- ECOG performance status (perform within 7 days before the first dose);

- Vital signs (perform within 7 days before the first dose);
- CBC with differential (perform within 7 days before the first dose);
- Serum chemistry (perform within 7 days before the first dose);
- Coagulation parameters (perform within 7 days before the first dose);
- Urinalysis (perform within 7 days before the first dose);
- 12-lead ECG (perform within 7 days before the first dose);
- Ophthalmological examination (perform within 7 days before the first dose);
- Pregnancy test: serum β-hCG (female subjects at childbearing age should perform within 7 days before the first dose);
- Echocardiography (perform within 28 days before the first dose);
- Virologic examination (perform within 28 days before the first dose);
- Tumor assessment (CT or MRI, perform within 28 days before the first dose), the imaging method can be decided by the Investigator, but should be consistent before and after treatment;
- Concomitant medication;
- AE collection.

7.2. Eligible Subject Enrollment

Informed consent must be obtained before all the specific study procedures in this clinical trial. The eligibility will be determined after reviewing the inclusion/exclusion criteria. Candidates could be re-screened once if they did not fulfill the entry eligibility (failed screening) at the first screening visit. Subjects need to re-sign the ICF and obtain a new screening number during re-screening.

If an enrolled subject is found to unsatisfied the eligibility criteria, the Investigator will discuss with the Sponsor to determine whether the subject continues to participate in the study to treat with the investigational product.

7.3. Treatment Period Evaluation Indicators

7.3.1. Single Dose PK Study Period

Day 1 (C0D1)

- PK blood sample collection: within 1 h before dosing and 0.5 h (± 5 min), 1 h (± 5 min), 2 h (±5 min), 3 h (±5 min), 4 h (±5 min), 6 h (±5 min), 8 h (±5 min), and 12 h (± 5 min) after dosing;
- Record the concomitant medications;
- AE collection;
- 12-lead ECG (2 h [±5 min] after dosing) .

Day 2 (C0D2)

- PK blood sample collection: 24 h (±5 min) after dosing;
- Record the concomitant medications;
- AE collection.

Day 3 (C0D3)

- PK blood sample collection: 48 h (±10 min) after dosing;
- Record the concomitant medications;
- Adverse event collection.

Day 4 (C0D4)

- PK blood sample collection: 72 h (±10 min) after dosing;
- Record the concomitant medications;
- AE collection.

Day 5 (C0D5)

- PK blood sample collection: 96 h (±10 min) after dosing;
- Record the concomitant medications;
- AE collection.

7.3.2. Cycle 1 Treatment Period

C1D1 (-3/+0 days)

- Physical examination;
- Vital signs;

- CBC with differential;
- Serum chemistry;
- Urinalysis;
- 12-lead ECG;
- Concomitant medications;
- AE collection.

C1D8 (-3/+0 days)

- Physical examination;
- Vital signs;
- CBC with differential;
- Serum chemistry;
- Urinalysis;
- 12-lead ECG;
- PK blood sample collection: within 1 h before dosing;
- Concomitant medications;
- AE collection.

C1D15 (-3/+0 days)

- Physical examination;
- Vital signs;
- CBC with differential
- Serum chemistry;
- Urinalysis;
- 12-lead ECG;
- PK blood sample collection: within 1 h before dosing;
- Concomitant medications;
- AE collection.

C1D28 (-3/+0 days)

- Physical examination;
- ECOG Performance Status;
- Vital signs;
- CBC with differential;
- Serum chemistry;
- Coagulation parameters;
- Urinalysis;
- 12-lead ECG (2 h [±5 min] after dosing) ;
- Ophthalmological examination;
- PK blood sample collection: within 1 h before dosing and 0.5 h (± 5 min), 1 h (± 5 min), 2 h (±5 min), 3 h (±5 min), 4 h (±5 min), 6 h (±5 min), 8 h (±5 min), 12 h (±5 min), and 24 (±10 min) after dosing;
- Concomitant medications;
- AE collection.

7.3.3. Cycle 2 Treatment Period

C2D15 (-3/+0 days)

- Physical examination;
- Vital signs;
- CBC with differential;
- Serum chemistry;
- Urinalysis;
- 12-lead ECG;
- Concomitant medications;
- AE collection.

C2D28 (-3/+0 days)

- Physical examination;

- ECOG Performance Status;
- Vital signs;
- CBC with differential;
- Serum chemistry;
- Urinalysis;
- 12-lead ECG;
- Tumor imaging assessment;
- Tumor tissues collection (For subjects with imaging assessments of CR, PR, or SD, it is recommended to obtain the disease-related archived tumor tissue or fresh tumor biopsy as much as possible with their consent)
- Concomitant medications;
- AE collection.

7.3.4. Cycle 3 And Additional Cycles Treatment Period

CxD28 (-3/+0 days)

- Physical examination;
- ECOG Performance Status;
- Vital signs;
- CBC with differential;
- Serum chemistry;
- Coagulation parameters (C3D28, every 8 weeks ±7 days thereafter) ;
- Urinalysis;
- 12-lead ECG;
- Ophthalmological examination (C3D28, every 8 weeks ±7 days thereafter) ;
- Echocardiography (clinically indicated);
- Tumor imaging assessment (C4D28, every 8 weeks ±7 days thereafter) ;

- Tumor tissues collection (For subjects with imaging assessments of CR, PR, or SD, it is recommended to obtain the disease-related archived tumor tissue or fresh tumor biopsy as much as possible with their consent.);
- Concomitant medications;
- AE collection.

7.3.5. Safety Follow-up After the Last Dose

The safety follow-up visit will be performed 28 days (±7 days) after the last dose. Subjects who completed or prematurely discontinued investigational product therapy should return to the study center for safety assessment on 28 (±7) days after the last dose or before starting other anti-tumor treatments, whichever occurs first. This follow-up includes assessment of AEs, laboratory tests, physical examination, ECOG scores, 12-lead ECG, ophthalmological examination, etc. Subjects who discontinued treatment for reasons other than disease progression are recommended to continue with imaging assessments at this visit.

Safety follow-up clinical evaluation indicators:

- Physical examination;
- ECOG Performance Status;
- Vital signs;
- CBC with differential;
- Serum chemistry;
- Coagulation functions;
- Urinalysis;
- 12-lead ECG;
- Ophthalmological examination;
- Echocardiography;
- Concomitant medications;
- AE collection.

7.4. Clinical Evaluation

7.4.1. Safety Evaluation

7.4.1.1. Safety Endpoint

The safety and tolerability of 3D185 will be evaluated based on the frequency and severity of AEs according to NCI CTCAE v4.03.

7.4.1.2. Safety Assessments

Safety assessments include AEs, physical examination, laboratory evaluations (CBC with differential, serum chemistry, coagulation, urinalysis, and pregnancy test), vital signs (blood pressure, heart rate, respiratory rate, body temperature), 12-lead ECG, echocardiography, and ophthalmologic examination (non-contact intraocular pressure, slit lamps, fundus examinations, and optical coherence tomography). An unscheduled exam can be performed if there are clinical indications. For detailed visit arrangement, please refer to Table 3 study flow chart.

Safety laboratory evaluations, including CBC with differential, serum chemistry, urinalysis, etc. will be performed by the site's local laboratory.

7.4.1.3. Safety Monitoring Committee (SMC)

The SMC consists of the lead principal investigator, principal investigators from each site participating in Study 3D185-CN-001, and the sponsor's medical monitor. Optional members may include but are not restricted to sponsor's biostatistician, pharmacologist, and safety physician from pharmacovigilance group.

Before moving to the next dose level, the SMC will review all available data to determine whether recruitment to the next cohort should be initiated. In addition, the SMC will review and evaluate all available safety data if one of the following criteria is met:

- More than 30% of all subjects who received 3D185 experienced serious adverse events (exclude unrelated events assessed by investigator);
- Any investigational product toxicity related death is reported.

Enrollment will be paused while SMC is reviewing the data until a formal decision is made by SMC. The recommendations made by SMC include the following:

- Recommend to start enrollment to the next higher dose level per the protocol;
- Recommend to enroll more subjects at a given dose level;
- Recommend whether a lower dose or a different schedule should be evaluated;
- Recommend whether the study should be terminated;
- Recommend to modify the study design;

Details of the safety monitoring process will be specified in a dedicated SMC charter.

CBC with differential

Complete blood count (absolute) comprises red blood cell (RBC) count, white blood cell (WBC) count and differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and platelet count; hemoglobin, and hematocrit.

Serum chemistry

ALT, AST, total bilirubin, urea nitrogen (BUN) or urea, creatinine (Cr), amylase, lipase, glucose, potassium, sodium, chlorine, calcium, phosphorus, magnesium, total protein, albumin, A/G, lactate dehydrogenase (LDH), alkaline phosphatase (ALP).

Coagulation

PT, APTT, and INR.

Urinalysis

Urine specific gravity, pH, WBC, RBC, protein, glucose, ketones and casts. Once the urinary protein ≥ 2+ in routine urinalysis, it is recommended to perform 24-hour urine protein test as soon as possible (e.g. within 72 hours).

Pregnancy Test

Serum hCG.

7.4.2. Efficacy Assessments

Baseline tumor assessment should be completed within 28 days prior to the first dose. It is recommended to perform CT or MRI of the chest, abdomen and pelvic cavity at baseline. If there are clinical indications or suspicious lesions in other areas, tumor imaging evaluation must also be performed. Baseline assessment and post-treatment efficacy assessment will be performed using the same method and as much as possible by the same Investigator (RECIST

1.1 criteria, Appendix 1). Tumor imaging assessment (CT or MRI) should be performed every 8 weeks (±7 days) from C1D1 regardless of study treatment status until disease progression, withdrawal of consent, or death, whichever comes first. Subjects who discontinue treatment for reasons other than disease progression or death should continue with imaging assessments per protocol-defined schedule until disease progression, death, or withdrawal of informed consent, whichever occurs first. If the imaging result shows a CR or PR for the first time, it is necessary to repeat the tumor imaging at least 4 weeks later to confirm the response.

Efficacy assessments include ORR (RECIST V1.1 standard) and DCR (RECIST V1.1 standard).

7.4.3. Pharmacokinetics Assessments

During single dose PK study period, venous blood (3 mL each) will be collected within 1 h before the first dose, and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 48 h, 72 h, and 96 h after the first dose. During the first cycle in treatment period, venous blood (3 mL each) will be collected within 1 h before dosing on C1D8, C1D15, and C1D28, and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h after dosing on C1D28. The actual drug administration time and PK sampling time should be accurately recorded.

The test of PK samples will be performed by central laboratory. The PK sample collection, labeling, storage, and shipping will be carried out in accordance with the instructions in the Central Lab Manual.

PK parameters including, but not limited to, C_{max}, T_{max}, $AUC_{0\text{-}24\ h}$, $AUC_{0\text{-}96\ h}$, $AUC_{0\ \infty}$, $t_{1/2}$, CL, and Vd.

7.4.4. Pharmacodynamic Assessment

Pharmacodynamic effect may be assessed by analyzing the change in serum phosphate levels relative to baseline level over time (Serum biochemistry test).

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENT

During the study, the Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. When there is a safety evaluation, the Investigator or study center personnel will be responsible for detecting and recording AEs and SAEs, as detailed in this section of the protocol.

8.1. Adverse Events

An AE is defined as any untoward medical event that occurs after receiving a drug or treatment or any deterioration of a disease or symptom that existed before receiving the investigational product or treatment (excluding the disease studied in this trial), in a subject or a clinical investigation subject, whether or not considered related to the investigational product or treatment. Therefore, an AE can be a discomfort sign (including an abnormal laboratory finding), symptom or transient disease beyond any indication, whether or not related to the investigational product or treatment.

8.2. Serious Adverse Event

An SAE is defined as an AE that meets any of the following conditions.:

Table 7 Definition of a Serious Adverse Event

Death	AEs result in death.
Life-threatening	The Investigator believes that if medical measures are not taken, AEs may lead to immediate death, rather than hypothetically that AEs deterioration might have caused death.
Hospitalization	AEs result in hospitalization. In general, “hospitalization” means that the subject is not suitable for observation or treatment in an outpatient or emergency department, but requires formal admission or emergency visits (usually at least overnight).
Prolongation of existing hospitalization	AEs occurred during the subject's hospitalization and prolonged hospitalization.
Congenital anomaly	Malformations are found at birth or after birth, or any malformation that caused miscarriage.
Permanent or significant disability/ Loss of function	The conditions caused by the event will greatly affect subject’s daily life. Loss of function does not include events of lesser importance, such as headache, nausea, vomiting, diarrhea,

	influenza, and accidental trauma (such as an ankle sprain).
Important medical events requiring medical intervention	Important medical events may not immediately cause life-threatening, death or hospitalization, but may harm the subject and may require medication or surgery to prevent any of the above results (death, life-threatening, hospitalization, prolongation of existing hospitalization, congenital anomaly).

8.3. Time Period and Method of Adverse Events/Serious Adverse Events Collection

8.3.1. Time Period of Adverse Events/Serious Adverse Events Collection

The collection of AEs will be performed from the time the subject signs informed consent until the end of the safety follow-up visit.

Any adverse medical events that occur after the signing of the ICF and before the start of the study treatment will be recorded as a history/concomitant disease and will not be recorded as an AE unless under one of the following conditions:

- Injuries/damages that are caused by any protocol required procedures or tests;
- AEs that are caused by protocol required withdrawal of concomitant treatment;
- AEs that are caused by a drug other than investigational product, and the drug is part of the treatment plan.

8.3.2. Method of Adverse Events and Serious Adverse Events Collection

Subjects will be assessed for AEs and SAEs beginning immediately after signing the informed consent form and continuing through to safety follow up. The Investigator or designee will collect AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

All AEs and SAEs will be recorded in source document and the eCRF.

8.4. Adverse Events and Serious Adverse Events Record

When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory findings, and diagnostics reports) relative to the event. The Investigator will then record all relevant information regarding an AE or SAE. For some SAEs, the Sponsor may need to verify the medical record to fully understand the information when reviewing the SAE report. When this happens, the Investigator must black out all the subject's identity information before submitting a copy to the sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE or SAE rather than the individual signs/symptoms.

The Investigator should use medical terminology/concept to record AE or SAE. Spoken and abbreviations should be avoided. All AEs (including SAEs) should be recorded in the eCRF AE form. The SAEs also should be recorded on the Serious Adverse Event Report Form. If the SAE occurs in China, it needs to be reported to the drug regulatory authority, the health administration, the Sponsor, and the ethics committee within 24 hours of being informed.

8.4.1. Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, elevated transaminases, and flapping tremor). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded. If a diagnosis is subsequently established later, the record should be updated to replace the previous symptoms/signs with the diagnosis.

8.4.2. Abnormal Laboratory Values

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the subject’s condition, will not be reported as AEs or SAEs. Abnormal laboratory findings or other abnormalities that are present or detected at baseline and do not worsen, will not be reported as AEs or SAEs.

It is the Investigator’s responsibility to review all laboratory findings and vital signs. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality or vital sign abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 ×ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded. If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 5.5 mmol/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AE or SAE, unless the severity or etiology changes.

8.4.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. The initial severity of the event should be recorded, and the severity should be updated when the grade of the events changes.

A recurrent AE is one that resolves between subject evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately.

8.4.4. Deaths

The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept and be expedited reported as an SAE term. If the cause of death at the time of reporting is unknown, it should be recorded as “death of unknown cause” which should be expedited for reportingas an SAE term, and then further investigate the exact cause of death.

8.4.5. Pre-existing Medical Conditions

A preexisting medical condition should be recorded as an AE only if the severity, frequency, or attribute of the condition worsens during the study (Except for the deterioration of the disease being studied). When recording such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

8.4.6. Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, except as outlined below:

- Planned hospitalization or prolonged hospitalization required by the protocol (e.g., for investigational product administration or efficacy assessment)

- Hospitalization due to existed medical conditions prior to the study and does not change. For example, elective surgery/treatment is scheduled before participating in the study.
- Hospitalization due to changes in living environment or social reasons rather than physical health (no medication or surgical intervention required), such as homeless, short of money, unattended, family environment, etc.

8.4.7. Pregnancy

In pregnant female subjects, study treatment must be discontinued immediately and notice the Investigator. The Investigator must report the pregnancies of a female subject or partner of a male subject occurring while the subject is on study treatment to the Sponsor within 24 hours. The Investigator should discuss with the subject the risk of continuing pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the end of pregnancy. Pregnancy occurring within 28 days (±7 days) of the last investigational product administration should be reported to the Investigator.

Any manual and spontaneous abortion should be classified as an SAE. Any congenital anomaly/birth defect in a child born to a female subject or female partner of a male subject exposed to investigational product should be classified as an SAE and reported.

8.4.8. Overdose

Study treatment overdose is the accidental or intentional use of 3D185 in an amount higher than the protocol required dose.

When an overdose occurs, the Investigator must clarify whether there are any symptoms in the report. If drug overdose induced adverse reaction occurs, it should be reported as AE. If the adverse reaction meets the SAE requirement, it should be reported in accordance with the process and time limit of the SAE report. If it is only a drug overdose without any relevant clinical symptoms or laboratory abnormalities, the Investigator should report to the Sponsor within 24 hours after learning of the event, using the term “accident or intentional drug overdose without AEs” (Drug overdose itself should not be reported as AE or SAE).

8.4.9. Disease Progression

Disease progression will be considered, if a new lesion or existing lesion progress in the disease to be treated with the investigational product. Clinical symptoms and signs of confirmed progression will not be reported as AEs unless it is more severe than expected, or the Investigator believes that tumor progression is related to study administration or study procedures.

8.4.10. New Disease

If a new primary malignancy is present, it will be considered as SAE. If a disease is detected after treatment with the investigational product and is not the indication of the study, it will be defined as a new tumor.

8.5. Assessment of Adverse Events

8.5.1. Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study according to the NCI CTCAE Version 4.03.

In addition, the severity of each AE and SAE should also be assigned to one of the following categories:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of Daily Living (refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3: Severe; severe medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of Daily Living (refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.).
- Grade 4: Severe; Life-threatening consequences; urgent intervention indicated.
- Grade 5: Severe; Death related to AE.

The severity and seriousness of AEs should be distinguished. The severity is used to describe intensity which may not an SAE. For example, a headache may be severe in intensity, but not an SAE unless it meets the criteria for SAE.

The NCI CTCAE version 4.03 doesn't include the classification of hyperphosphatemia. The grade of hyperphosphatemia in this study is defined as: Grade 1: > ULN ~ 7 mg/dL; Grade 2: > 7 mg/dL ~ 9 mg/dL; Grade 3: > 9 mg/dL).

8.5.2. Assessment of Causality

The Investigator is obligated to assess the relationship between the investigational product and the occurrence of each AE or SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as the natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The Investigator will also consult the Investigator's brochure (IB) in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always makes an assessment of causality for every event prior to transmission of the SAE. The Investigator may change his/her opinion of causality in light of follow up information, updating the SAE report accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The Investigator will determine the relationship between an AE and the investigational product based on the following criteria:

1） Definitely: An event that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the investigational product; that is improved by stopping or reducing the dosage of the investigational product; that is recurred by resuming the dosage of the investigational product.

2） Probably: An event that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the investigational product; that may be caused by the subject's clinical state or by other interventions.

3） Probably unrelated: An event that doesn't follow a reasonable temporal sequence from administration of the investigational product; that doesn't follow a known or expected response pattern to the investigational product; that may be caused by the subject's clinical state or by other interventions.

4） Unrelated: An event that doesn't follow a reasonable temporal sequence from administration of the investigational product; that follow a known or expected response pattern to the non-investigational product; that may be caused by the subject's clinical

state or by other interventions; that is improved or disappeared by stopping the dosage of the other treatment option; that is recurred by resuming the dosage of the other treatment option.

5） Uncertainty: An event that doesn't follow a reasonable temporal sequence from administration of the investigational product; that is similar to a known or expected response pattern to the investigational product; that may be caused by combining with other drugs.

When judging "Uncertainty", the Investigator should follow up, and make a clear causality in the follow-up report.

The "definitely", "Probably" and "Uncertainty" AEs will be considered as investigational drug related AEs.

8.6. Adverse Events Follow-up

After the initial AE or SAE report, the Investigator is required to proactively follow each subject and provide further information to the Sponsor on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow up. Once resolved, the appropriate AE or SAE will be updated.

The Investigator will ensure that follow up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE.

New or updated information will be recorded on the originally SAE report, with all changes signed and dated by the Investigator. The updated SAE report should be resent to the Sponsor as soon as possible.

After the safety follow-up visit, the Investigator needs to continue follow-up the AEs based on the criteria as below.

Investigational drug-related AEs will be followed up to meet one of the following criteria:

• Return to baseline;

• The severity reduced to level 2;

• Death;

• Start new anti-tumor treatments;

• The Investigator judges the AE is stable and will not improve further;

• No clinical or safety data is collected, or the final database is locked.

Investigational drug-unrelated serious or life-threatening AEs will be followed up to meet one of the following criteria:

• Return to baseline;

• Correlation is reassessed as unrelated;

• Death;

• Start new anti-tumor treatments;

• The Investigator judges the AE is stable and will not improve further;

• No clinical or safety data is collected, or the final database is locked.

Investigational drug-unrelated Grade 1-2 AEs will be followed up to 28 days after the last dose, which is the safety follow-up visit.

Investigational drug-related SAEs that occur after safety follow-up are also required to be reported, documented, and followed up.

The final outcome of each AE must be recorded to the eCRF.

8.7. Reporting Serious Adverse Events

8.7.1. Timeframes for Submitting Serious Adverse Events

The Investigator should report the initial SAE to the Sponsor with 24 hours of discovery. The frequency of follow-up visits will be determined based on the Investigator's opinion. The processing time for the follow-up SAE report should be the same as initial SAE report.

8.7.2. Completion and Transmission of the Serious Adverse Event Report

Once an Investigator becomes aware that an SAE has occurred in a subject, he/she must report the information to the Sponsor. If the Investigator does not have all information

regarding an SAE, he/she will not wait to receive additional information before notifying the Sponsor of the event and completing the form. The form will be updated when additional information is received. The Investigator will always provide an assessment of causality at each time of the SAE report. The SAE report will always be completed as thoroughly as possible with all available details of the event, signed by the Investigator or designee.

A copy of the SAE report will be sent to a project contact who is responsible for receiving the SAE report by priority email. In rare cases, sending a fax is also acceptable.

A copy of the SAE form must be emailed within 24 hours to the attention of 3DMedDrug Safety and Pharmacovigilance at:

Sponsor fax and email: +86-010-56315182, PV@3dmedcare.com

In addition to reporting all SAEs to the Sponsor, the Investigator must report the safety report to the local regulatory authority and other regulatory agencies. The Sponsor should also submit the safety report that occurred in this study to the regulatory authority in accordance with the requirements of the regulations.

The SUSAR report needs to be cross-submitted to NMPA and FDA, and the time limit should be in accordance with local regulations.

8.8. Post-study Adverse Events and Serious Adverse Events

A post-study AE/SAE is defined as any AE/SAE that occurs outside of the safety follow-up visit. Investigator is not obligated to actively seek AEs or SAEs in former subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the Investigator will promptly notify the Sponsor.

8.9. Precautions

To determine the reporting requirements for individual SAE, the Sponsor will evaluate the expectation of these events via the IB.

9. DATA ANALYSIS AND STATISTICAL

9.1. Sample Size Determination

The final sample size for the dose escalation study will depend on the number of dose levels evaluated and the occurrence of DLT for each dose cohort. The maximum sample size is expected to be 42 subjects.

9.2. General Considerations for Data Analysis

Data will be listed and summarized using SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina) according to Sponsor agreed reporting standards, where applicable. Complete details will be documented in the SAP.

The following statistical analysis is performed based on the nature of the parameters:

- ✧ Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum.
- ✧ Categorical variables: frequencies and percentages.
- ✧ Time-to-event variables: number of non-missing observations (N), median, minimum, and maximum. Kaplan-Meier event rates may also be provided if applicable for specific time-to-event variables.

Further description of the statistical methods and analyses will be provided in the SAP.

9.2.1. Analysis Population

Full Analysis Set (FAS)

The FAS will include all subjects who received 3D185 treatment in this study. The FAS will be the primary population for evaluating all efficacy, safety and subject characteristics.

DLT Analysis Set (DLT set)

The DLT set will include all subjects who received at least ≥ 75% of the planned doses of treatment and completed the safety assessment during DLT evaluation period. The frequency and severity of DLT will be analyzed.

PK Analysis Set (PKS)

The PK set will include subjects who have received at least one dose and have at least once evaluable PK sample collection after administration.

PD Analysis Set (PD set)

The PD set will include subjects who have received at least one dose and have at least once serum phosphate level measurement (serum biochemistry) after administration.

9.3. Efficacy Analyses

The Investigator will perform the tumor assessment according to RECIST Version 1.1 at screening and every 8 weeks after the first dose in Cycle 1. The best overall response will be classified into progressive disease, SD, CR and PR. A summary by category and a listing will be provided.

ORR is defined as the proportion of subjects who achieve a BOR of CR or PR in the full analysis set. Estimate of ORR and its 95% exact confidence interval (CI) (Clopper-Pearson) will be provided.

The DCR is defined as the proportion of subjects whose BOR achieve a disease control (CR, PR, or SD) in the full analysis set. Estimate of DCR and its 95% exact CI (Clopper-Pearson) will also be provided.

9.4. Safety Analysis

Safety data include AEs, physical examinations, vital signs, laboratory evaluations, ECG, ophthalmological examination, etc. All AEs will be coded using the latest version of MedDRA. The severity of AE will be graded according to NCI CTC AE V4.03 (Grade 1 to 5). All treatment emergent AEs frequency will be summarized by system organ class (SOC) and preferred term (PT), and also be further summarized based on the worst grade per NCI CTCAE v4.03 and relationship to investigational product. The number and the percentage of subjects reporting DLT events in each dose cohort during the dose escalation phase will be summarized. The relationship between exposure level and safety of 3D185 in all subjects (E-R model) will be analyzed.

9.5. Pharmacokinetics Analysis

For the PK parameters, in addition to the above general analysis, the coefficient of variation, geometric mean, and geometric coefficient of variation will be used for statistical description.

The concentration-time curve and the average concentration-time curve of each subject will be plotted based on the plasma concentration-time data measured in the trial. The PK parameters will be calculated using standard non-compartment models and WinNonlin® Professional 6.4 or higher version (Certara, Princeton, NJ, USA) or SAS® 9.3 or higher version (SAS Institute, Inc., Cary, North Carolina) to fully reflect the drug absorption, distribution and elimination characteristics in the human body. The interim PK parameters will be calculated using the planned blood collection time, and the final PK parameters will be calculated using the actual blood collection time.

- Power Model will be used to assess the dose proportionality. $\log(y) = \beta0 + \beta1*\log(dose)$, where y is the PK parameter ($AUC_{0\text{-}tau}$, C_{max}), β0 is the intercept, and β1 is the slope. The 90% CI for slope β1 will be estimated using a mixed-effects model, with the treatment group as a fixed effect, and then using CIs for linear pharmacokinetic evaluation.
- The potential relationship between dose level, PK variables, clinical safety and the preliminary clinical efficacy will be explored.
- The detailed analysis of the specific content in SAP.

10. ETHICS

10.1. National Regulations and the Helsinki Declaration

This study will be conducted in full conformance with the GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the subject.

10.2. Informed Consent

The Investigator or his or her authorized representative will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks, and benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. After the study has been fully explained, the signed informed consent will be obtained from either the subject or his/her guardian or legal representative prior to study participation. For those who are incapable of expressing consent, the above description and instructions should be provided to their legal representative. If the safety result leads to a major change in the risk/benefit assessment, the ICF should be reviewed and changed as necessary. All subjects, including those who have received treatment, must be informed of the updated information and signed a new informed consent form to continue the study.

10.3. Ethics Committee / Review Board (EC/RB)

This protocol and its amendments, the ICFs, any information to be given to the subject (e.g., advertisements for recruiting subjects), and relevant supporting information must be reviewed by the appropriate EC/RB.

The EC/RB must approve this study before the start of the study.

All SAEs will be reported to the relevant ethics committees and regulatory agencies in accordance with relevant regulatory requirements.

11.PROTOCOL AMENDMENT

The protocol amendment should be approved by the EC/RB before implementation. Before obtaining approval from the EC/RB, the Investigator will still follow the original protocol, unless the content of the revision can immediately eliminate the potential injury of the subject, or the revision only involves changes in study management (such as changes in phone numbers, etc.).

12.STUDY DOCUMENTATION

12.1. Storage of Study Documents

The Investigator must document the study process fully and accurately so that the investigational data can be verified. These documents can be divided into two categories, one is the investigator site file, and the other is the subject's source data.

The investigator site file includes protocol with all amendments, CRF and data questionnaire table, certification and correspondence with ethics committees and regulatory authorities, informed consent sample, drug records, Investigator's resumes and authorization forms, and other necessary documents and applicable correspondence.

Subject's source document (previously defined key efficacy/safety data to be recorded) includes inpatient/outpatient records, doctor's and nurse's orders, scheduled visit dates, original laboratory findings, ECG, X-ray, pathology reports and special assessment reports, signed informed consent, consultation records, subject's screening and enrollment tables, etc.

The Investigator must retain these records for at least five years after the completion of the clinical trial. After the retention period expires, further investigational material retention will discuss with the Sponsor. The Sponsor will retain clinical trial data until five years after the date a marketing application is approved for the drug.

Prior to transfer these records to other parties or locations, the Investigator must notice the Sponsor.

If the Investigator cannot ensure that these records are well retained in the study center, the Investigator and Sponsor can work together to keep the documents in other locations. These records must be kept in a custody, so that the Investigators can retrieve them when they are inspected by the regulatory authorities. If these records are still to be used, the Investigator can keep the copies in the sites.

12.2. Source Documents and Data

When the eCRF is unclear, or an error occurs during the data transfer, the Investigator is required to provide the source data or the medical records in the investigator site file to the Sponsor. If there are special questions, regulatory challenges, and/or inspection requirements, a complete study record should be provided if the subject's privacy is protected.

12.3. Audit and Inspection

The Investigator must understand that if an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant source documents. The eCRF data should be directly derived from the source data.

12.4. Electronic Case Report Form

The Investigator must complete the CRF for each study subjects, including subjects who did not complete the study, and those failed to screen.

It is the Investigator’s responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject’s CRF and related forms.

13.MONITORING

The sponsor-designated monitor will contact and visit the Investigator regularly. If the subject's privacy is protected as required by the regulations, the monitor will check the various records in the trial (eCRF and other subjects' data as needed). During the daily visit, the monitor will verify that the eCRF is filled following the protocol requirements and the integrity, consistency, and accuracy of the data. The monitor will also obtain laboratory records and other records from the subject to verify the accuracy of eCRF filling. The Investigator (or his assistant) should assist the monitor in resolving problems found during the monitoring.

14. USE OF INFORMATION AND PUBLICATION OF STUDY FINDINGS

14.1. Use of Information

All research materials on 3D185 such as patent applications, dosage forms, production processes, basic research, etc., are considered confidential as long as they have not been published.

The investigational data obtained in this study will also be considered confidential. 3D Medicines (Beijing) Co., Ltd. will disclose the data to other clinical investigators and the

FDA or other government agencies as appropriate. To ensure the integrity of this clinical investigational data analysis, the Investigators have an obligation to provide complete study results and data to the Sponsor.

The Investigator must ensure that the subject's privacy is not disclosed to unauthorized third parties. The eCRF and other documents submitted to the Sponsor do not include the subject's name. Subjects will be identified by their identification code only. The Investigator can retain the enrollment form that consists of the subject's signature code, name, and address. Informed consent documents and other documents should be kept strictly confidential and should not be submitted to the Sponsor.

14.2. Publication

The results of this study can be published in core journals, and the PIs who have made significant contributions to the implementation and management of this study and those who have contributed significantly to the design, interpretation or analysis of this study can be signed.

Before publish the results of the study, 3D Medicines promises to provide the pre-pbulication article to the Investigatior for review. The Investigators must obtain the Sponsor’s agreement before submitting the academic article or abstract. The Investigators have the right to publish the results of this study, but should meet the requirements for protection of confidentiality.

The intellectual property rights of confidential information belong only to 3D Medicines. It may not be disclosed to others without the written consent of 3D Medicines, and shall not be used for other purposes except this study.

15.REFERENCES

1. Liu, M., S.-J. Wang, and Y. Ji. *The i3+ 3 Design for Phase I Clinical Trials*. Journal of Biopharmaceutical Statistics, Jul 2019; Available from: https://doi.org/10.1080/10543406.2019.1636811
2. *Cancer Facts & Figures 2019.* American Cancer Society: Atlanta, GA, USA, 2019.
3. Chen, W., et al., *Cancer statistics in China, 2015.* CA Cancer J Clin, 2016. **66**(2): p. 115-32.
4. Jiang, H., S. Wen, and G.L. Shao, *Clinical Advances of Molecular-targeted Therapy on Primary Hepatocellular Carcinoma.* Cancer Research on Prevention and Treatment, 2016. **2016, 43(5)**(R735.7): p. 427-434.
5. Qin, S.K. and LI，J., *Expert consensus on clinical application of apatinib in the treatment of gastric cancer.* Chinese Clinical Oncology, 2015. **20(9)**: p. 841-847.
6. Hu, J., G.S. Qian, and C.X. Bai, *Chinese consensus on early diagnosis of primary lung cancer (2014 version).* Cancer, 2015. **121 Suppl 17**: p. 3157-64.
7. Dienstmann, R., et al., *Genomic aberrations in the FGFR pathway: opportunities for targeted therapies in solid tumors.* Annals of Oncology, 2013. **25**(3): p. 552-563.
8. Brooks, A.N., E. Kilgour, and P.D. Smith, *Molecular Pathways: Fibroblast Growth Factor Signaling: A New Therapeutic Opportunity in Cancer.* Clinical Cancer Research, 2012. **18**(7): p. 1855.
9. Touat, M., et al., *Targeting FGFR Signaling in Cancer.* Clinical Cancer Research, 2015. **21**(12): p. 2684.
10. US-FDA, *Labeling.* Drug Approval Package: Balversa (erdafinitib), 2019(Application Number: 212018Orig1s000).
11. *The FGFR Inhibitor BGJ398 Has Activity in Tumors with FGFR Alterations*. Cancer Discovery 2017, 7: 12.
12. Nogova, L., et al., *Evaluation of BGJ398, a Fibroblast Growth Factor Receptor 1-3 Kinase Inhibitor, in Patients With Advanced Solid Tumors Harboring Genetic Alterations in Fibroblast Growth Factor Receptors: Results of a Global Phase I, Dose-Escalation and Dose-Expansion Study.* J Clin Oncol, 2017. **35**(2): p. 157-165.
13. Javle, M.M., et al., *A phase 2 study of BGJ398 in patients (pts) with advanced or metastatic FGFR-altered cholangiocarcinoma (CCA) who failed or are intolerant to platinum-based chemotherapy*, in *Gastrointestinal Cancers Symposium*. 2016， January 21-23: San Francisco, CA.
14. Saka, H., et al., *Safety, tolerability and pharmacokinetics of the fibroblast growth factor receptor inhibitor AZD4547 in Japanese patients with advanced solid tumours: a Phase I study.* Investigational New Drugs, 2017. **35**(4): p. 451-462.
15. Andre, F., et al. *Abstract LB-145: Results of a phase I study of AZD4547, an inhibitor of fibroblast growth factor receptor (FGFR), in patients with advanced solid tumors*. Cancer Research 2013 [cited 73 8 Supplement]; LB-145]. Available from: http://cancerres.aacrjournals.org/content/73/8_Supplement/LB-145.abstract.

16. Tabernero, J., et al., *Phase I Dose-Escalation Study of JNJ-42756493, an Oral Pan–Fibroblast Growth Factor Receptor Inhibitor, in Patients With Advanced Solid Tumors.* Journal of Clinical Oncology, 2015. **33**(30): p. 3401-3408.
17. Papadopoulos, K.P., et al., *A Phase 1 study of ARQ 087, an oral pan-FGFR inhibitor in patients with advanced solid tumours.* British Journal Of Cancer, 2017. **117**: p. 1592.
18. Storer, B.E., *Design and analysis of phase I clinical trials.* Biometrics, 1989. **45**(3): p. 925-937.
19. Ji, Y., et al., *A modified toxicity probability interval method for dose-finding trials.* Clinical trials (London, England), 2010. **7**(6): p. 653-663.
20. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* Am J Clin Oncol, 1982. **5**(6): p. 649-55.
21. Kalantar-Zadeh, K., L. Gutekunst, R. Mehrotra, et al., *Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease.* Clin J Am Soc Nephrol, 2010. **5**(3): p. 519-30.

16. APPENDICES

Appendix 1 The Response Evaluation Criteria In Solid Tumors (Recist) Guidelines

The text below was obtained from the following reference: Eisenhauer EA, Therese P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009; 45:228-247.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal

masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

Non-target Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are accessible by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

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

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific

guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

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

RESPONSE CRITERIA

Evaluation of Target Lesions

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

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

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

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must

achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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

Lesions that split or coalesce on treatment. When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

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

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

When the patient also has measurable disease. In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the

identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

<u>Evaluation of Best Overall Response</u>

The best overall response is the best response recorded from the start of the investigational product treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

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

Table 8 Best Overall Response

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

Any Any	PD Any	Yes or No Yes	PD PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.

Note:

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

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

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

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

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

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e., in randomized trials (Phase 2 or 3) or trials where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

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

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of subjects achieving SD for a minimum period of time is an endpoint of

importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

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

APPENDIX 2 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCALE

Table 9 Eastern Cooperative Oncology Group Performance Status Scale[20]

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX 3 NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

Table 10 New York Heart Association (NYHA) Classification

Class	Limitation on Physical Activity	Status at Rest	Symptoms with Ordinary Physical Activity
I	None	Comfortable	Non
II	Slight	Comfortable	Symptomatic with greater than ordinary activities
III	Marked	Comfortable	Symptomatic with ordinary activities
IV	Unable to perform any activity	Symptomatic	Symptomatic at less than ordinary levels of activity

APPENDIX 4 CALCULATION OF THE CREATININE CLEARANCE

CrCl (male) = ([140-age] ×weight in kg)/(serum creatinine in mg/dL ×72)

CrCl (female) = CrCl (male) ×0.85

For SI units:

CrCl (male) = ([140-age] ×weight in kg)/(serum creatinine in μmol/L ×1.23)

CrCl (male) = ([140-age] ×weight in kg)/(serum creatinine in μmol/L ×1.05)

If the subject is obese (more than 30% of the ideal body weight), use the ideal weight to calculate CrCI

GFR (mL/min/1.73m^2) = CrCl (mL/min)/(BSA × 1.73)

Body Surface Area (BSA) (Dubois) = 0.007184 x (patient height in cm)$^{0.725}$ ×(patient weight in kg)$^{0.425}$ (two decimal place accuracy)

APPENDIX 5 PHOSPHORUS-RICH FOOD

Phosphorus is an important mineral element necessary for the human body. The main source of phosphorus in the human body is natural food or food phosphate additive. Phosphate is one of the most widely used and widely used food additive categories. As an important food ingredient and functional additive widely used in the processing of meat products, poultry products, seafood, fruits, vegetables, dairy products, bakery products, beverages, potato products, seasonings, convenience foods, etc.

The main source of phosphorus is diet. Therefore, controlling the intake of phosphorus in the diet is very important for the prevention and treatment of hyperphosphatemia[21].

High phosphate-rich processed foods:

- Soft drinks, soda drinks, especially cola or carbonated and fizzy lemonade
- Cordials/fruit syrup beverages
- Chocolate, candy, and anything else with a high citric acid and sugar content
- Ice-cream
- Skim milk powder (often added to processed foods)
- Biscuits, cakes
- Tomato ketchup
- Mayonnaise
- Tahini
- Fish fingers
- Processed cheese, especially soft cheese spread
- Frozen pizzas
- Hot dogs
- Processed meats
- All foods that list as an ingredient mineral salts, emulsifiers and lecithin.

High phosphate-rich natural foods:

- Egg yolks
- Milk

- Nuts
- Wheat germ
- Soybeans and their by-products
- Peas
- Beans
- Lentils
- Kidney bean
- Pinto bean
- Corn
- Walnut
- Sunflower seed
- Peanuts
- Mushrooms
- Oats
- Cocoa beans (chocolate)
- Animal organs- liver, brains, kidne

APPENDIX 6 CYP3A4 STRONG INHIBITORS AND INDUCERS, AND CYP2C8 STRONG INHIBITORS

Table 11 CYP3A4 Strong Inhibitors and Inducers, and CYP2C8 Strong Inhibitors

CYP3A4 Strong Inhibitors	Nelfinavir, Indinavir, Voriconazol, Telithromycin, Ketoconazole, Nefazodone, Itraconazole, Clarithromycin, Saquinavir, Darunavir, Posaconazole, Lopinavir, Telaprevir, Boceprevir, Idelalisib, Cobicistat, Stiripentol, Curcumin, Ritonavir, Conivaptan, Troleandomycin, Mibefradil, Doxycycline, Efavirenz, Atazanavir, Tipranavir, Naloxone, Clotrimazole, Nilotinib, Laveridine, Loperamide, Ribociclib, Danoprevir, Elvitegravir, Midostaurin, Terfenadine, Ergotamine, Econazole
CYP3A4 Strong Inducers	Nevirapine, Rifampicin, Carbamazepine, Fosphenytoin, Pentobarbital, Phenobarbital, Phenytoin, Primidone, Rifapentine, Enzalutamide, Lumacaftor, St. John's Wort, Mitotane, Apalutamide, Quinine, Rimexolone, Rifaximin, Rifamycin, Topiramate, Oxcarbazepine, Midostaurin
CYP2C8 Strong Inhibitors	Gemfibrozil, Clopidogrel, Lopinavir, Fluvoxamine, Felodipine, Mometasone furoate, Zafirlukast, Sorafenib, Erlotinib, Dabrafenib, Troglitazone, Candesartan cilexetil, Salmeterol, Cholecalciferol, Trametinib, Fluticasone, Fluticasone furoate, Fluticasone propionate, Ritonavir

https://www.drugbank.ca/categories

Subject's other concomitant medications can be judged by reference to their instructions.

APPENDIX 7 i3+3 DESIGN ALGORITHM

Similar to the 3+3 design[18], the i3+3 is rule-based design, and it is also an interval-based design similar to mTPI[19] The dose-assignment recommendation of the i3+3 design is based on the current observed DLT occurence and the relative position of the toxicity probability equivalence interval (EI). For example, if the observed DLT occurence at the current dose is below the lower limit of the equivalence interval, the i3+3 dose-assignment recommendation will be escalation "E". The specific i3+3 algorithm is as follows:

Suppose dose 'd' is the dose currently used to treat patients, 'n' is the number of patients who have been treated at dose 'd', and 'x' is the number of patients who have experienced DLTs at dose 'd'. The i3+3 dose-assignment recommendation will depend on two quantities x/n and (x-1)/n.

- If x/n is below the EI, escalate (E) and enroll patients at the next higher dose (d +1);
- If x/n is inside the EI, stay (S) and continue to enroll patients at the current dose d;
- If x/n is above the EI, there are two scenarios,
  - If (x-1)/n is below the EI, stay (S) and continue to enroll patients at the current dose d;
  - Else, de-escalate (D) and enroll patients at the next lower dose (d −1)

According to the above i3+3 algorithm and the preset EI, the i3+3 dose-assignment recommendation can be summarized in a decision table (Figure 1).

APPENDIX 8 SIMULATION TEST FOR i3+3 AND 3+3 DESIGNS

Simulation setup

We conducted a simulation trial using U-Design v1.1.5 (udesign.laiyaconsulting.com). The statistical performance of the i3+3 and 3+3 (Storer, 1989) designs was compared according to the study setup of the 3D185 phase 1 clinical trial in China. In this study, there are 7 escalating dose levels will be evaluated, the first two dose levels will use accelerated titration dose-escalation design, and the remaining five dose levels will use i3+3 dose escalation design. If a Grade ≥ 2 drug-related AE occurs during the accelerated titration phase, the current dose level will become the initial dose level in the i3+3 phase. Therefore, the initial dose of the i3+3 may have three different conditions: 100 mg (Cohort 3), 50 mg (Cohort 2), or 25 mg (Cohort 1). And the maximum sample size in each condition will be 30, 36, and 42, respectively. Each cohort will enroll 3 subjects. The MTD target toxicity probability pT = 25%, the choice of ε1 is 0.09, and the choice of ε2 is 0.05, so the EI is (16%, 30%). We simulated six different scenarios (Table 12) and three different starting dose settings, and performed 1,000 simulations for each of the "Scenario* Starting Dose".

Table 12 Scenarios Settings

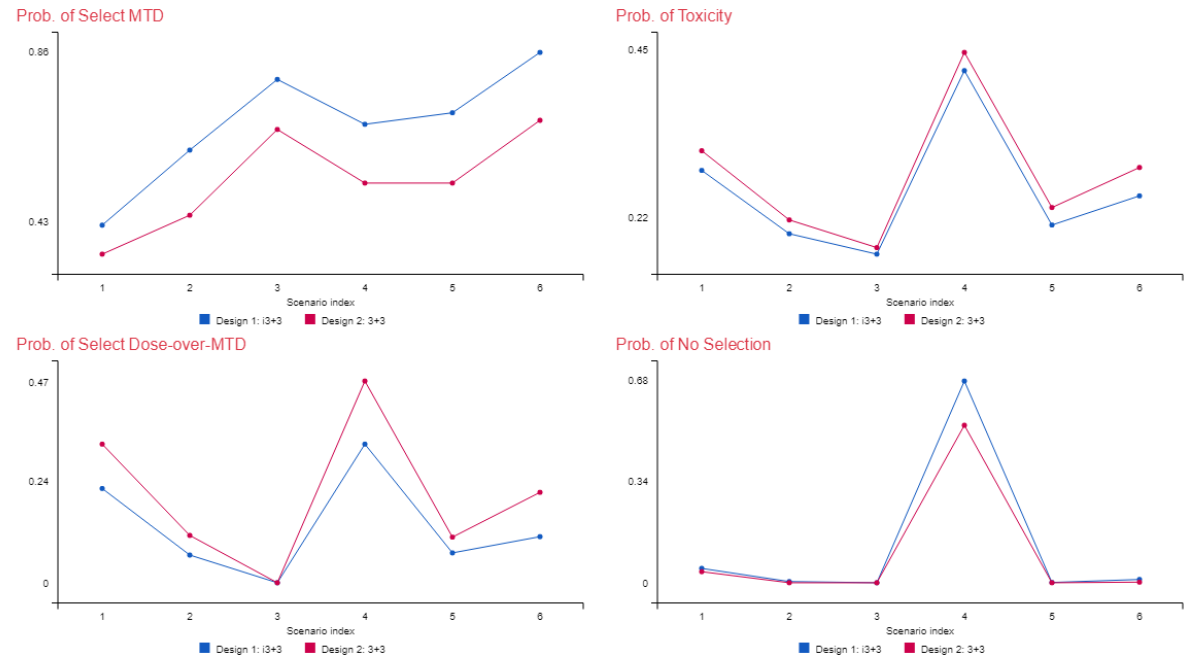
Scenarios	pT (%)	Times	True Toxicity Probability of Each Dose						
			Dose 1	***Dose 2***	***Dose 3***	***Dose 4***	***Dose 5***	***Dose 6***	***Dose 7***
1	0.25	1000	0.1	0.25	0.35	0.45	0.55	0.65	0.75
2	0.25	1000	0.04	0.08	0.13	0.2	0.25	0.35	0.5
3	0.25	1000	0.04	0.08	0.12	0.16	0.2	0.24	0.28
4	0.25	1000	0.38	0.43	0.48	0.53	0.58	0.63	0.68
5	0.25	1000	0.04	0.08	0.12	0.16	0.45	0.55	0.65
6	0.25	1000	0.05	0.1	0.42	0.49	0.57	0.64	0.7

Simulation results (i3+3 vs 3+3)

The simulation results of the six scenarios were summarized in Figure 2-4 and Table 13-14. Figure 2 and Table 13 summarized the simulation results for the initial dose of Dose 3. Figure 3 and Table 14 summarized the simulation results for the initial dose of Dose 2. Figure 4 and Table 15 summarized the simulation results for the initial dose of Dose 1. For example, in Table 13,

each scenario included two sub-tables. The upper sub-table contained 4 parts. The first part listed the target toxicity probability pT, the dose level, and true toxicity probabilities. The next three parts listed the selection probability, number of subjects treated, and the number of toxicities. The lower sub-table summarized four indicators that reflect the safety and reliability of the study, including the probability of selecting the true MTD, the probability of toxicity (proportion of subjects who have experienced DLT), the probability of select dose over-MTD, and the probability of no selection. Figure 2 showed these four indicators for all scenarios and all design methods in Table 13 by line graph.

Figure 2-4 and Table 13-14 showed that the i3+3 design has superior operating characteristics compared to the traditional 3+3 design. For example, in most scenarios, i3+3 has a higher probability of select true MTD, while having a smaller probability of select dose over-MTD.



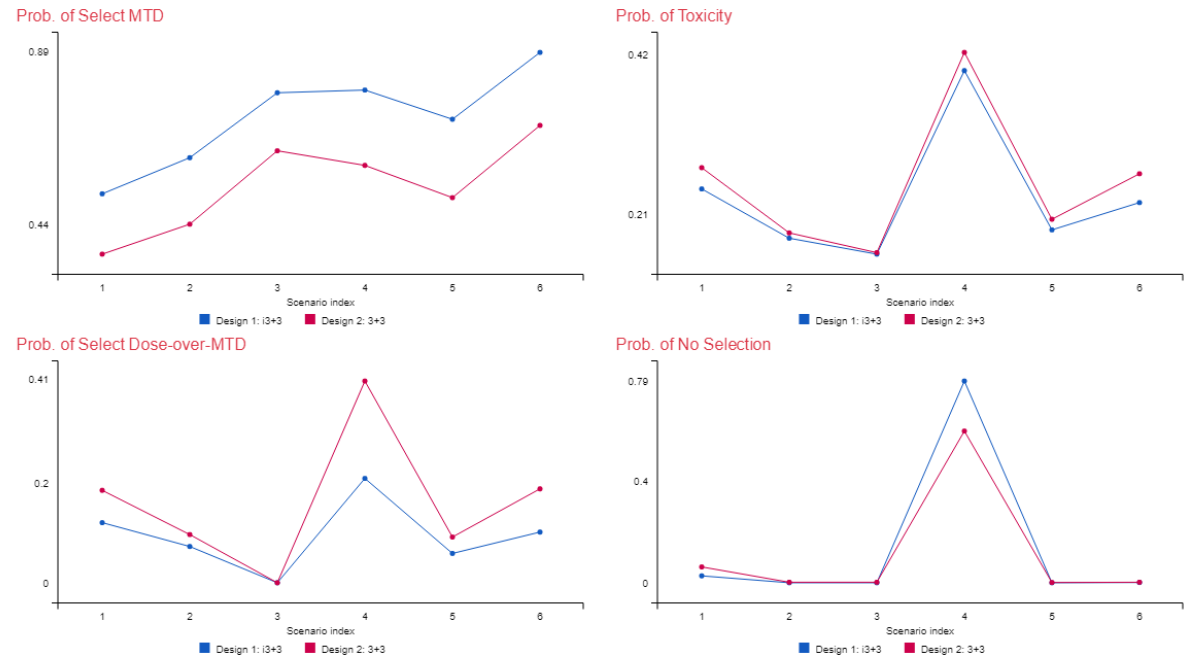
Summary of Performance

	Design 1 (i3+3)	Design 2 (3+3)
Prob. of Select MTD	0.672 ± 0.151	0.533 ± 0.128
Prob. of Toxicity	0.262 ±0.091	0.279 ± 0.095
Prob. of Select Dose-over-MTD	0.134 ±0.122	0.205 ± 0.171
Prob. of No Selection	0.122 ±0.267	0.094 ± 0.212

* Mean ± Standard deviation. The statistics are calculated given by the current scenario and design setting.

Figure 2 Comparison of the i3+3 design with the 3+3 design (starting at Dose 3).

Design 1 was an i3+3 design with a maximum sample size of 30 (blue line) and design 2 was a 3+3 design (red line). The mean ±standard deviation of the statistical indicators for all simulation scenarios was summarized below the line graph. The probability of select true MTD was the percentage of trials that correctly select the true MTD in all 1000 simulation trials. The higher the value, the better the reliability of the design. The probability of toxicity was the percentage of subjects who developed DLT in all the 1000 simulated trials, and the lower the number, the better the safety of the design. The probability of select dose over-MTD in all the 1000 simulated trials, the study design selected a dose higher than the true MTD as the percentage of the MTD. The lower the value, the better the safety of the design. The probability of not selecting any dose indicates that in all the 1000 simulated trials, no dose was selected as the percentage of the MTD. If this scenario does not exist real MTD, the higher value the better.



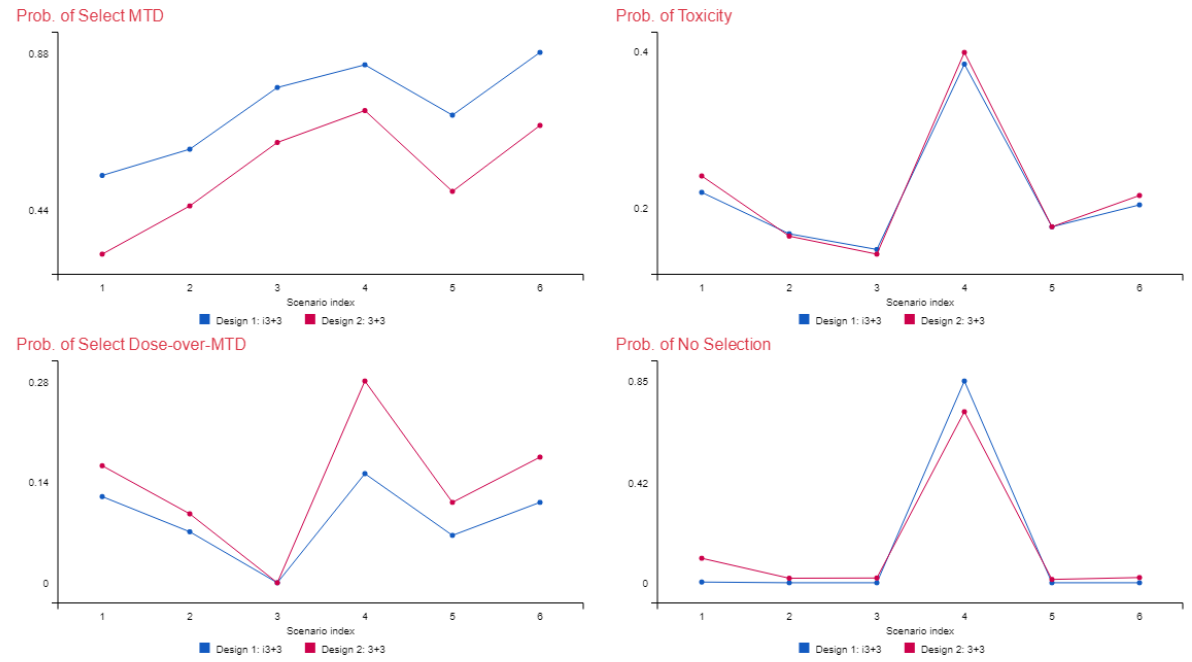
Summary of Performance

	Design 1 (i3+3)	Design 2 (3+3)
Prob. of Select MTD	0.715 ±0.1 32	0.54 ± 0.125
Prob. of Toxicity	0.239 ±0.088	0.251 ± 0.095
Prob. of Select Dose-over-MTD	0.097 ±0.075	0.162 ± 0.139
Prob. of No Selection	0.134 ±0.315	0.111 ± 0.238

* Mean ± Standard deviation. The statistics are calculated given by the current scenario and design setting.

Figure 3 Comparison of the i3+3 design with the 3+3 design (starting at Dose 2).

Design 1 was an i3+3 design with a maximum sample size of 36 (blue line) and design 2 was a 3+3 design (red line). The mean ±standard deviation of the stati stical indicators for all simulation scenarios was summarized below the line graph. The probability of select true MTD was the percentage of trials that correctly select the true MTD in all 1000 simulation trials. The higher the value, the better the reliability of the design. The probability of toxicity was the percentage of subjects who developed DLT in all the 1000 simulated trials, and the lower the number, the better the safety of the design. The probability of select dose over-MTD in all the 1000 simulated trials, the study design selected a dose higher than the true MTD as the percentage of the MTD. The lower the value, the better the safety of the design. The probability of not selecting any dose indicates that in all the 1000 simulated trials, no dose was selected as the percentage of the MTD. If this scenario does not exist real MTD, the higher value the better.



Summary of Performance

	Design 1 (i3+3)	Design 2 (3+3)
Prob. of Select MTD	0.727 ±0.1 36	0.547 ± 0.155
Prob. of Toxicity	0.224 ±0.085	0.223 ± 0.094
Prob. of Select Dose-over-MTD	0.088 ±0.054	0.138 ± 0.094
Prob. of No Selection	0.141 ±0.344	0.15 ± 0.281

* Mean ± Standard deviation. The statistics are calculated given by the current scenario and design setting.

Figure 4 Comparison of the i3+3 design with the 3+3 design (starting at Dose 1).

Design 1 was an i3+3 design with a maximum sample size of 42 (blue line) and design 2 was a 3+3 design (red line). The mean ±standard deviation of the statistical indicators for all simulation scenarios was summarized below the line graph. The probability of select true MTD was the percentage of trials that correctly select the true MTD in all 1000 simulation trials. The higher the value, the better the reliability of the design. The probability of toxicity was the percentage of subjects who developed DLT in all the 1000 simulated trials, and the lower the number, the better the safety of the design. The probability of select dose over-MTD in all the 1000 simulated trials, the study design selected a dose higher than the true MTD as the percentage of the MTD. The lower the value, the better the safety of the design. The probability of not selecting any dose indicates that in all the 1000 simulated trials, no dose was selected as the percentage of the MTD. If this scenario does not exist real MTD, the higher value the better.

Table 13 Comparison of i3+3 and 3 + 3 designs (starting at Dose 3 [100 mg])

The i3+3 design was marked in blue with a maximum sample size of 30 and a 3+3 design marked in red. The orange line represented the dose of the true MTD. A dose level without an orange marker indicated that this dose was not a true MTD and should not be selected as the MTD.

Scenario 1							
		Selection Prob.		# of Subjects Treated		# of Toxicities	
Dose Level	True Tox Prob.	i3+3	3+3	i3+3	3+3	i3+3	3+3
1	0.10	0.31	0.29	4.329	1.926	0.441	0.201
2	0.25	0.42	0.348	10.827	3.714	2.665	0.959
3	0.35	0.201	0.266	11.733	5.043	4.069	1.775
4	0.45	0.019	0.054	2.691	1.863	1.235	0.856
5	0.55	0.001	0.005	0.375	0.396	0.209	0.228
6	0.65	0	0	0.027	0.033	0.018	0.018
7	0.75	0	0	0	0.006	0	0.002
		i3+3		3+3			
Prob. of Select MTD		0.42		0.348			
Prob. of Toxicity		0.288		0.311			
Prob. of Select Dose-over-MTD		0.221		0.325			

Prob. of No Selection		0.049			0.037		
Scenario 2							
		Selection Prob.		**# of Subjects Treated**		**# of Toxicities**	
Dose Level	**True Tox Prob.**	**i3+3**	**3+3**	**i3+3**	**3+3**	**i3+3**	**3+3**
1	**0.04**	0.004	0.014	0.084	0.084	0.004	0.006
2	**0.08**	0.043	0.144	1.587	0.936	0.128	0.08
3	**0.13**	0.274	0.285	10.002	4.572	1.335	0.607
4	**0.20**	0.353	0.229	9.576	4.059	1.925	0.855
5	**0.25**	0.255	0.217	5.91	3.012	1.461	0.743
6	**0.35**	0.064	0.089	2.343	1.803	0.824	0.659
7	**0.5**	0.003	0.022	0.48	0.531	0.252	0.282
		i3+3			**3+3**		
Prob. of Select MTD		0.608			0.446		
Prob. of Toxicity		0.198			0.216		
Prob. of Select Dose-over-MTD		0.067			0.111		
Prob. of No Selection		0.004			0		

Scenario 3							
		Selection Prob.		# of Subjects Treated		# of Toxicities	
Dose Level	True Tox Prob.	i3+3	3+3	i3+3	3+3	i3+3	3+3
1	0.04	0.002	0.008	0.057	0.048	0	0.002
2	0.08	0.03	0.131	1.176	0.834	0.077	0.066
3	0.12	0.18	0.199	8.895	4.347	1.089	0.537
4	0.16	0.283	0.196	8.52	3.975	1.366	0.651
5	0.20	0.258	0.178	6.039	3.204	1.204	0.656
6	0.24	0.158	0.143	3.276	2.325	0.76	0.535
7	0.28	0.089	0.145	2.037	1.287	0.575	0.397
		i3+3		3+3			
Prob. of Select MTD		0.788		0.662			
Prob. of Toxicity		0.169		0.178			
Prob. of Select Dose-over-MTD		0		0			
Prob. of No Selection		0		0			

Scenario 4				
	Selection Prob.		# of Subjects Treated	# of Toxicities

Dose Level	True Tox Prob.	i3+3	3+3	i3+3	3+3	i3+3	3+3
1	0.38	0.251	0.164	12.045	3.423	4.546	1.354
2	0.43	0.06	0.177	7.122	4.137	3.062	1.769
3	0.48	0.021	0.119	6.327	4.563	3.06	2.187
4	0.53	0.003	0.01	0.924	0.873	0.468	0.469
5	0.58	0	0.003	0.108	0.099	0.07	0.058
6	0.63	0	0	0.006	0.021	0.003	0.009
7	0.68	0	0	0	0.006	0	0.002

	i3+3	3+3
Prob. of Select MTD	0.665	0.527
Prob. of Toxicity	0.422	0.446
Prob. of Select Dose-over-MTD	0.335	0.473
Prob. of No Selection	0.665	0.527

Scenario 5

		Selection Prob.		# of Subjects Treated		# of Toxicities	
Dose Level	True Tox Prob.	i3+3	3+3	i3+3	3+3	i3+3	3+3
1	0.04	0.002	0.007	0.057	0.042	0	0.003

2	**0.08**	0.03	0.13	1.179	0.822	0.077	0.073
3	**0.12**	0.194	0.229	9.033	4.365	1.106	0.519
4	**0.16**	0.702	0.527	12.36	4.806	1.971	0.813
5	**0.45**	0.067	0.098	6.609	3.135	2.982	1.401
6	**0.55**	0.004	0.008	0.702	0.708	0.361	0.394
7	**0.65**	0	0.001	0.06	0.072	0.046	0.048

	i3+3	**3+3**
Prob. of Select MTD	0.702	0.527
Prob. of Toxicity	0.218	0.233
Prob. of Select Dose-over-MTD	0.071	0.107
Prob. of No Selection	0.001	0

Scenario 6

		Selection Prob.		**# of Subjects Treated**		**# of Toxicities**	
Dose Level	**True Tox Prob.**	**i3+3**	**3+3**	**i3+3**	**3+3**	**i3+3**	**3+3**
1	**0.05**	0.025	0.101	0.765	0.618	0.038	0.026
2	**0.10**	0.849	0.685	12.828	4.65	1.288	0.514
3	**0.42**	0.106	0.177	14.844	4.779	6.19	2.017

4	**0.49**	0.006	0.033	1.422	1.299	0.724	0.637
5	**0.57**	0	0.001	0.132	0.225	0.076	0.132
6	**0.64**	0	0.001	0.009	0.012	0.006	0.007
7	**0.70**	0	0	0	0.003	0	0.002
		i3+3			**3+3**		
Prob. of Select MTD		0.849			0.685		
Prob. of Toxicity		0.277			0.288		
Prob. of Select Dose-over-MTD		0.112			0.212		
Prob. of No Selection		0.014			0.002		

Table 14 Comparison of i3+3 and 3 + 3 designs (starting at Dose 2 [50 mg])

The i3+3 design was marked in blue with a maximum sample size of 36 and a 3+3 design marked in red. The orange line represented the dose of the true MTD. A dose level without an orange marker indicated that this dose was not a true MTD and should not be selected as the MTD.

Scenario 1							
		Selection Prob.		**# of Subjects Treated**		**# of Toxicities**	
Dose Level	**True Tox Prob.**	**i3+3**	**3+3**	**i3+3**	**3+3**	**i3+3**	**3+3**
1	**0.10**	0.333	0.389	7.677	2.679	0.766	0.298
2	**0.25**	0.516	0.363	19.479	5.151	4.853	1.26

3	**0.35**	0.117	0.141	7.23	2.967	2.533	1.098
4	**0.45**	0.008	0.042	1.404	1.068	0.638	0.479
5	**0.55**	0	0.003	0.171	0.27	0.092	0.151
6	**0.65**	0	0	0.003	0.015	0.002	0.01
7	**0.75**	0	0	0	0	0	0

	i3+3	**3+3**
Prob. of Select MTD	0.516	0.363
Prob. of Toxicity	0.247	0.271
Prob. of Select Dose-over-MTD	0.125	0.186
Prob. of No Selection	0.026	0.062

Scenario 2

		Selection Prob.		**# of Subjects Treated**		**# of Toxicities**	
Dose Level	**True Tox Prob.**	**i3+3**	**3+3**	**i3+3**	**3+3**	**i3+3**	**3+3**
1	**0.04**	0.002	0.074	0.366	0.456	0.016	0.024
2	**0.08**	0.057	0.15	6.999	3.999	0.573	0.342
3	**0.13**	0.254	0.236	10.128	4.197	1.353	0.546
4	**0.20**	0.363	0.208	9.732	3.765	1.925	0.776
5	**0.25**	0.251	0.233	5.976	2.835	1.525	0.657

6	**0.35**	0.068	0.078	2.268	1.74	0.801	0.647
7	**0.5**	0.005	0.019	0.531	0.474	0.259	0.244
		i3+3			**3+3**		
Prob. of Select MTD		0.614			0.441		
Prob. of Toxicity		0.179			0.185		
Prob. of Select Dose-over-MTD		0.073			0.097		
Prob. of No Selection		0			0.002		
Scenario 3							
		Selection Prob.		**# of Subjects Treated**		**# of Toxicities**	
Dose Level	**True Tox Prob.**	**i3+3**	**3+3**	**i3+3**	**3+3**	**i3+3**	**3+3**
1	**0.04**	0.002	0.061	0.36	0.378	0.016	0.017
2	**0.08**	0.041	0.141	6.621	3.987	0.54	0.319
3	**0.12**	0.174	0.164	8.811	4.014	1.055	0.513
4	**0.16**	0.301	0.191	8.691	3.651	1.396	0.579
5	**0.20**	0.246	0.182	5.979	3.024	1.221	0.611
6	**0.24**	0.141	0.114	3.462	2.223	0.846	0.566
7	**0.28**	0.095	0.145	2.076	1.134	0.577	0.323
		i3+3			**3+3**		

Prob. of Select MTD	0.783	0.632
Prob. of Toxicity	0.157	0.159
Prob. of Select Dose-over-MTD	0	0
Prob. of No Selection	0	0.002

Scenario 4

		Selection Prob.		**# of Subjects Treated**		**# of Toxicities**	
Dose Level	**True Tox Prob.**	**i3+3**	**3+3**	**i3+3**	**3+3**	**i3+3**	**3+3**
1	**0.38**	0.187	0.193	17.322	3.927	6.532	1.523
2	**0.43**	0.035	0.181	8.214	4.749	3.517	2.021
3	**0.48**	0.001	0.03	1.512	1.242	0.751	0.629
4	**0.53**	0	0.001	0.186	0.222	0.099	0.119
5	**0.58**	0	0	0.012	0.024	0.007	0.012
6	**0.63**	0	0.001	0	0.006	0	0.001
7	**0.68**	0	0	0	0.003	0	0.002

	i3+3	**3+3**
Prob. of Select MTD	0.777	0.594
Prob. of Toxicity	0.4	0.423
Prob. of Select Dose-over-MTD	0.223	0.406

Prob. of No Selection		0.777			0.594		
Scenario 5							
		Selection Prob.		**# of Subjects Treated**		**# of Toxicities**	
Dose Level	**True Tox Prob.**	**i3+3**	**3+3**	**i3+3**	**3+3**	**i3+3**	**3+3**
1	**0.04**	0.002	0.058	0.36	0.354	0.016	0.018
2	**0.08**	0.042	0.145	6.633	3.987	0.541	0.315
3	**0.12**	0.183	0.194	8.985	4.089	1.083	0.511
4	**0.16**	0.715	0.51	12.666	4.398	2.051	0.744
5	**0.45**	0.055	0.082	6.753	2.955	3.082	1.359
6	**0.55**	0.003	0.01	0.549	0.609	0.307	0.349
7	**0.65**	0	0	0.054	0.078	0.029	0.05
		i3+3			**3+3**		
Prob. of Select MTD		0.715			0.51		
Prob. of Toxicity		0.197			0.203		
Prob. of Select Dose-over-MTD		0.058			0.092		
Prob. of No Selection		0			0.001		
Scenario 6							
		Selection Prob.		**# of Subjects Treated**		**# of Toxicities**	

Dose Level	True Tox Prob.	i3+3	3+3	i3+3	3+3	i3+3	3+3
1	**0.05**	0.009	0.111	0.816	0.678	0.039	0.031
2	**0.10**	0.885	0.698	18.192	5.466	1.865	0.567
3	**0.42**	0.1	0.154	15.366	4.176	6.463	1.8
4	**0.49**	0.005	0.032	1.467	1.14	0.739	0.544
5	**0.57**	0	0.002	0.153	0.198	0.087	0.112
6	**0.64**	0	0.001	0.006	0.033	0.005	0.017
7	**0.70**	0	0	0	0.003	0	0.002

	i3+3	3+3
Prob. of Select MTD	0.885	0.698
Prob. of Toxicity	0.256	0.263
Prob. of Select Dose-over-MTD	0.105	0.189
Prob. of No Selection	0.001	0.002

Table 15 Comparison of i3+3 and 3 + 3 designs (starting at Dose 1 [25 mg])

The i3+3 design was marked in blue with a maximum sample size of 42 and a 3+3 design marked in red. The orange line represented the dose of the true MTD. A dose level without an orange marker indicated that this dose was not a true MTD and should not be selected as the MTD.

Scenario 1

		Selection Prob.		# of Subjects Treated		# of Toxicities	
Dose Level	True Tox Prob.	i3+3	3+3	i3+3	3+3	i3+3	3+3
1	0.1	0.34	0.42	13.764	4.782	1.353	0.493
2	0.25	0.536	0.314	19.29	4.569	4.779	1.17
3	0.35	0.106	0.125	7.02	2.571	2.452	0.928
4	0.45	0.015	0.035	1.623	0.933	0.71	0.425
5	0.55	0	0.003	0.183	0.228	0.1	0.127
6	0.65	0	0	0.012	0.018	0.007	0.012
7	0.75	0	0	0	0	0	0

	i3+3	3+3
Prob. of Select MTD	0.536	0.314
Prob. of Toxicity	0.224	0.241
Prob. of Select Dose-over-MTD	0.121	0.163
Prob. of No Selection	0.003	0.103

Scenario 2

		Selection Prob.		# of Subjects Treated		# of Toxicities	
Dose Level	True Tox Prob.	i3+3	3+3	i3+3	3+3	i3+3	3+3
1	0.04	0.002	0.061	4.434	3.456	0.197	0.129

2	**0.08**	0.05	0.152	6.588	3.957	0.5	0.321
3	**0.13**	0.267	0.222	11.106	4.143	1.495	0.567
4	**0.2**	0.363	0.233	10.431	3.672	2.109	0.707
5	**0.25**	0.246	0.217	6.204	2.916	1.552	0.734
6	**0.35**	0.071	0.077	2.835	1.59	1.011	0.611
7	**0.5**	0.001	0.019	0.402	0.495	0.201	0.25

	i3+3	3+3
Prob. of Select MTD	0.609	0.45
Prob. of Toxicity	0.168	0.164
Prob. of Select Dose-over-MTD	0.072	0.096
Prob. of No Selection	0	0.019

Scenario 3

		Selection Prob.		**# of Subjects Treated**		**# of Toxicities**	
Dose Level	**True Tox Prob.**	**i3+3**	**3+3**	**i3+3**	**3+3**	**i3+3**	3+3
1	**0.04**	0.002	0.064	4.422	3.522	0.194	0.149
2	**0.08**	0.038	0.132	6.327	3.906	0.487	0.32
3	**0.12**	0.176	0.155	9.408	3.909	1.171	0.495
4	**0.16**	0.272	0.191	8.823	3.585	1.419	0.562

5	**0.2**	0.252	0.183	6.447	3.099	1.256	0.626
6	**0.24**	0.163	0.101	4.017	2.118	0.97	0.534
7	**0.28**	0.097	0.154	2.556	1.17	0.701	0.311

	i3+3	3+3
Prob. of Select MTD	0.784	0.629
Prob. of Toxicity	0.148	0.141
Prob. of Select Dose-over-MTD	0	0
Prob. of No Selection	0	0.02

Scenario 4

		Selection Prob.		# of Subjects Treated		# of Toxicities	
Dose Level	**True Tox Prob.**	**i3+3**	**3+3**	**i3+3**	**3+3**	**i3+3**	**3+3**
1	**0.38**	0.149	0.218	22.062	4.908	8.333	1.831
2	**0.43**	0.007	0.047	2.409	1.641	1.038	0.736
3	**0.48**	0	0.015	0.372	0.426	0.183	0.201
4	**0.53**	0	0	0.045	0.096	0.025	0.05
5	**0.58**	0	0.001	0	0.012	0	0.006
6	**0.63**	0	0	0	0.003	0	0.002
7	**0.68**	0	0	0	0	0	0

	i3+3	3+3
Prob. of Select MTD	0.844	0.719
Prob. of Toxicity	0.385	0.399
Prob. of Select Dose-over-MTD	0.156	0.281
Prob. of No Selection	0.844	0.719

Scenario 5

		Selection Prob.		# of Subjects Treated		# of Toxicities	
Dose Level	**True Tox Prob.**	i3+3	3+3	i3+3	3+3	i3+3	3+3
1	**0.04**	0.002	0.056	4.422	3.48	0.194	0.143
2	**0.08**	0.038	0.128	6.327	3.951	0.487	0.324
3	**0.12**	0.188	0.199	9.588	4.071	1.188	0.509
4	**0.16**	0.705	0.491	13.497	4.395	2.161	0.731
5	**0.45**	0.065	0.102	7.389	2.988	3.306	1.34
6	**0.55**	0.002	0.009	0.726	0.642	0.38	0.367
7	**0.65**	0	0.001	0.051	0.063	0.038	0.04

	i3+3	3+3
Prob. of Select MTD	0.705	0.491
Prob. of Toxicity	0.185	0.176

Prob. of Select Dose-over-MTD		0.067			0.112		
Prob. of No Selection		0			0.014		
Scenario 6							
		Selection Prob.		**# of Subjects Treated**		**# of Toxicities**	
Dose Level	**True Tox Prob.**	**i3+3**	**3+3**	**i3+3**	**3+3**	**i3+3**	**3+3**
1	**0.05**	0.005	0.126	5.127	3.741	0.283	0.178
2	**0.1**	0.883	0.677	18.99	5.4	1.872	0.572
3	**0.42**	0.105	0.151	16.335	4.155	6.847	1.753
4	**0.49**	0.007	0.022	1.413	1.029	0.694	0.524
5	**0.57**	0	0.002	0.129	0.171	0.074	0.099
6	**0.64**	0	0	0.006	0.024	0.004	0.011
7	**0.7**	0	0	0	0	0	0
		i3+3		**3+3**			
Prob. of Select MTD		0.883		0.677			
Prob. of Toxicity		0.233		0.216			
Prob. of Select Dose-over-MTD		0.112		0.175			
Prob. of No Selection		0		0.022			