Clinical Study Protocol

(Amendment 1)

Study Title	A Multicenter, Open-label, Phase I/II Dose Escalation and Expansion Clinical Study to Assess the Safety and Efficacy of MGD013 Monotherapy and in Combination with Brivanib Alaninate (ZL-2301) in Patients with Advanced Liver Cancer
Project No.	ZL-MGD013-202
Version No. and Version Date	Amendment 1/Jun30, 2020
Investigational Drug	Brivanib Alaninate (ZL-2301), MGD-013
Study Phase	Phase I/II
Sponsor	Zai Lab (Shanghai) Co., Ltd.
Principal Investigator	[redacted]

Confidentiality Statement

Confidential information of the investigational drugs involved in this protocol belongs to Zai Lab. The document is accessible to investigators, research consultants or relevant personnel, Institutional Review Board/Independent Ethics Committee only. The contents inside the document may not be disclosed to any third party without the written approval of the sponsor.

Revision History

Status	Date
Original Protocol: Version 1.1	July 24, 2019
Protocol Amendment 1	June 30, 2020

Summary of Changes in Protocol Amendment 1

ZL-MGD013-202

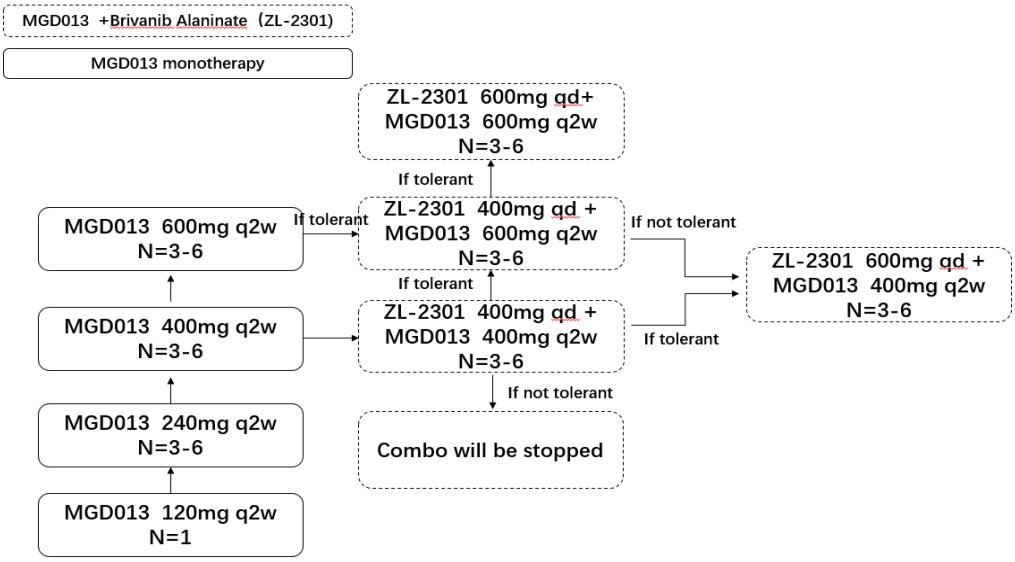
Synopsis, Section 3.1, Section 3.2.1	The starting dose of brivanib in combination therapy is revised to 400mg QD; If the dose of 400mg q2w as MGD 013 monotherapy is clear, the combination therapy will be opened from MGD013 400mg q2w+brivanib 400mg qd.
Synopsis, Section 3.1.4	Clarify the population of phase 2 is "≥2 line HCC with or without immune checkpoint inhibitor treatment"
Synopsis, section 4.1	Clarify the antiviral therapy is not required for patients with HCV infection.
Section 3.1.3	Update the DLT criteria to keep consistence with global MGD-013. Add 3 new criteria in Other ≥ Grade 3 non-hematological toxicity to exclude DLT: ● Grade 3 fever that lasts < 72 hours and is not associated with hemodynamic compromise ● Grade 3 fatigue that lasts < 72 hours ● Grade 3 skin toxicity that resolves to ≤ Grade 2 within 14 days of initiation of oral corticosteroids
Section 4.3.1	Clarify the criteria of end of treatment, including 2 additional of "death and Completion of protocol-defined therapy (MGD013 mono)"
Section 4.3.2	Clarify the criteria of End of Study ● Death ● Lost to follow up ● Withdrawn of consent ● The study is terminated
Section 5.2	Add the section of infusion preparation based on the global practice of MGD013. 5.2.1 General Guidelines and Precautions 5.2.2 Study Drug Preparation and Administration
Section 8.3.8	Update the SAE reporting process
Section 8.4.1.1	<u>Update the Management of Observed Infusion Reactions (G1 and G2)</u> Grade 1: Note: Per Section 8.4.1, the following prophylactic pre-infusion medications are required prior to all infusions of MGD013, including future infusions for patients who experience Grade 1 infusion reactions: Grade 2: For patients with Grade 2 infusion reactions, despite premedication with diphenhydramine, ranitidine or equivalent, and acetaminophen (or equivalent) and/or ibuprofen, corticosteroids (10-20 mg dexamethasone IV, or equivalent IV steroid) may be added to the

	premedication regimen for the next dosing of MGD013. Reduce corticosteroid dosing by 50% for the subsequent dose and hold thereafter, if there are no reactions

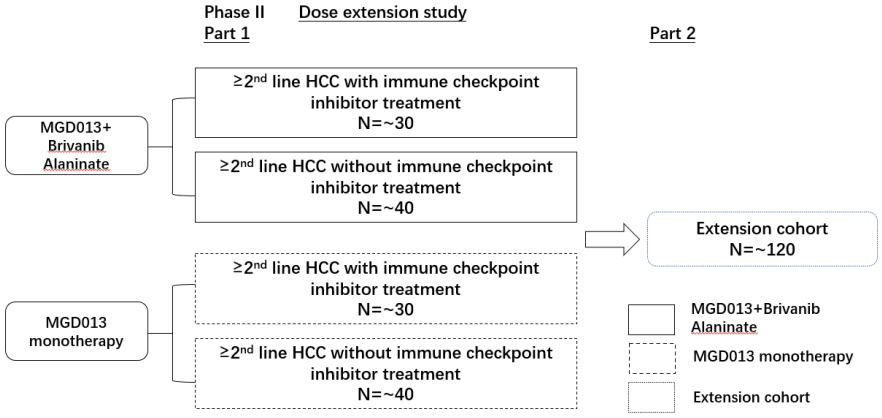
Protocol synopsis

Name of Sponsor/Company	Zai Lab (Shanghai) Co., Ltd.
Investigational Drug	MGD013 (anti-LAG-3 and PD-L1 bispecific antibody), Brivanib Alaninate (ZL-2301)
Study Title	A Multicenter, Open-label, Phase I/II Dose Escalation and Expansion Clinical Study to Assess the Safety and Efficacy of MGD013 Monotherapy and in Combination with Brivanib Alaninate (ZL-2301) in Patients with Advanced Liver Cancer
Protocol No.	ZL-MGD013-202
Investigator	[redacted]
Study Site	Approx. 25 sites
Study Duration	Approx. 3 years
Study Phase	Phase I/II
Study Objectives	This study consists of two parts: Phase I is a dose escalation study to determine the Recommended Phase II Dose (RP2D) of MGD013 monotherapy and that of MGD013 when in combination with Brivanib Alaninate (ZL-2301) in subjects with advanced liver cancer (including hepatocellular carcinoma and intrahepatic cholangiocarcinoma). Phase II is a dose expansion study and consists of two parts: Part 1 is to assess the safety and efficacy of MGD013 monotherapy and MGD013 in combination with ZL-2301 in subjects with advanced hepatocellular carcinoma (HCC); in Part 2, a therapeutic method (MGD013 monotherapy or MGD013 in combination with ZL-2301, determined by the sponsor according to the obtained data) will be selected for dose expansion study in HCC subjects who have previously failed immune checkpoint inhibitor treatment, to further evaluate the safety and efficacy of the study treatments in the specific group of subjects. **Objectives of Phase I study** **Primary Objectives** - To assess the safety of MGD013 in subjects with advanced liver cancer; - To determine the recommended phase II dose (RP2D) of MGD013 monotherapy in subjects with advanced liver cancer; - To assess the safety of MGD013 in combination with Brivanib Alaninate (ZL-2301) in subjects with advanced liver cancer; - To determine the recommended phase II dose (RP2D) of MGD013 when co-administered with Brivanib Alaninate (ZL-2301). **Secondary Objectives**

	- To assess the preliminary efficacy of MGD013 monotherapy and MGD013 in combination with Brivanib Alaninate in subjects with advanced liver cancer by investigator-assessed objective response rate (ORR) according to RECIST1.1 and irRECIST criteria respectively. **Exploratory objective** - To explore the correlation between MGD013/Brivanib Alaninate-related biomarkers and subject safety, antitumor activity. **<u>Objectives of Phase II study (Part 1)</u>** **Primary Objectives:** - To assess the safety of MGD013 monotherapy at RP2D in subjects with advanced HCC; - To assess the safety of MGD013 at RP2D in combination with Brivanib Alaninate in subjects with advanced HCC; - To assess the efficacy of MGD013 monotherapy and in combination with Brivanib Alaninate in subjects with advanced HCC, with blinded independent central review (BICR)-assessed ORR according to RECIST 1.1 as the primary efficacy endpoint. **Secondary Objectives:** - To assess the secondary efficacy endpoints of MGD013 monotherapy and in combination with Brivanib Alaninate: BICR-assessed ORR according to irRECIST, investigator-assessed ORRs (inv-ORRs) according to RECIST 1.1 and irRECIST respectively, disease control rate (DCR), time to tumor progression (TTP), duration of response (DoR), progression-free survival (PFS), survival rate at 6, 9 and 12 months, overall survival (OS). **Exploratory objective** - To explore the potential biomarker for MGD013/Brivanib Alaninate and its correlation with subject safety and antitumor activity. **<u>Objectives of Phase II study (Part two)</u>** **Primary Objectives:** - To assess the safety of the investigational drugs in subjects with advanced HCC who have previously failed immune checkpoint inhibitor treatment; - To assess the efficacy of the investigational drugs in subjects with advanced HCC who have previously failed immune checkpoint inhibitor treatment, with BICR-assessed ORR according to RECIST1.1 as the primary efficacy endpoint. **Secondary Objectives:** - To assess the secondary efficacy endpoints of the investigational drugs in subjects with advanced HCC: BICR-assessed ORR according to irRECIST, investigator-assessed ORRs (inv-ORRs) according to RECIST 1.1 and irRECIST respectively, disease control rate (DCR), time to tumor progression (TTP), duration of response (DoR), progression-free survival (PFS), survival rate at 6, 9 and 12 months, overall survival (OS).

Study Design	This is a multicenter, open-label, phase I/II clinical study. This study consists of two phases: the dose escalation study (Phase I) and the dose expansion study (Phase II). Phase II study will consist of two parts: Part 1 and Part 2. **<u>Study Design of Phase I Study</u>** Phase I study will enroll subjects with unresectable advanced HCC, intrahepatic cholangiocarcinoma and/or mixed hepatocellular-cholangiocarcinoma who have previously received at least first-line systematic treatment and recurred/not toraltable to the treatment. The dose escalation study of MGD013 monotherapy will be first conducted. After 400mg Q2w of MGD013 monotherapy is clear, the dose escalation study of the combination therapy will be conducted. The schematic diagram of the study is shown as below:  During dose escalation study of monotherapy, the starting dose escalation of MGD013 will be 120 mg Q2W with one subject. If the first dose level (120 mg Q2W) is well tolerated (without CTCAE Grade 2 or above AE within 28 days after first study drug treatment; see Section 3.1.2 for details), the dose level may escalate sequentially following traditional 3+3 dose escalation scheme. If study drug-related adverse events with CTCAE Grade 2 or above severity are observed in the subject of the initial dose group, the study will adopt traditional 3+3 dose escalation scheme from the initial dose level (120 mg Q2W), and an additional of 2 subjects will be enrolled in the initial dose group (see Section 3.1.2 for details). The highest dose level of MGD013 monotherapy will be 600 mg Q2W. Monotherapy RP2D group should enroll at least 6 evaluable subjects. The combination therapy will be initiated after the MGD013 400mg Q2w is clear. The combination dose of MGD013 could be escalated to RP2D of MGD013 after determining. Dose escalation study of the combination therapy will adopt traditional 3+3 dose escalation scheme; the dosage of Brivanib will start from 400 mg once daily (QD), and may escalate to 600 mg QD and a

	maximum of 800 mg QD (if possible). Two points should be noted: one is the combination dose of MGD 013 600mg Q2w +brivanib 400mg qd can be opened after both monotherapy RP2D of 600mg Q2w is determined and the starting dose of combination therapy is tolerant; the other is combination dose of MGD013 400mg Q2w + brivanib 600mg qd could be further explored once the starting dose of combination therapy is tolerant and the dose of MGD013 600mg Q2w+brivanib 400mg qd is not tolerant. While two or more 2 subjects experience DLT in the start dose group of the combination therapy, the combination dose level escalation will be terminated, and Phase II dose-extension study will be conducted with MGD013 alone. RP2D dose group of the combination therapy should at least enroll 6 evaluable subjects. The treatment cycle is two weeks and the observation cycle of DLT is 28 days (the first two cycles). Subjects will continue to receive study treatment until disease progression, death or the occurrence of intolerable toxicity, whichever comes first. MGD013 will be used for at most 48 cycles. If subjects do not have disease progression after 48 cycles, MGD013 will be discontinued. The treatment will be continued with Brivanib Alaninate alone. In Phase I dose escalation period, the **Safety Review Committee** (SRC) will decide whether to escalate to the next dose level or discontinue the escalation after reviewing the data from each dose group. **<u>Design of Phase II study</u>** Phase II, the dose expansion study, will only enroll subjects with HCC. There are two cohorts in Part 1, MGD013 monotherapy and MGD013 in combination with Brivanib Alaninate. After determining the RP2D of MGD013 monotherapy, dose expansion study of monotherapy will be conducted. Subjects of the combination therapy cohort will be enrolled after determining the RP2D of combination therapy in Phase I study. The schematic diagram of the dose extension study is shown as below:

	 Each cohort will enroll approximately 30 advanced HCC subjects who progressed after receiving immune checkpoint inhibitor treatment, and approximately 40 advanced HCC subjects who have not previously received immune checkpoint inhibitor treatment. The SWOG two-stage design will be employed. In the first stage, 20 advanced HCC subjects who have not previously received immune checkpoint inhibitor treatment will be enrolled. If response by image evaluation is observed in 3 or more subjects (according to RECIST 1.1), additional 20 evaluable subjects will be enrolled for the second stage. Similarly, for the cohort of advanced HCC subjects who have previously received immune checkpoint inhibitor treatment, enrollment of the second stage will initiate to have 30 evaluable subject in the cohort after 1 or more subjects in the first stage reaches response (according to RECIST 1.1) by image evaluation. Phase II Part 2 will expand the study cohort according to the safety and efficacy data obtained in Part 1. About 120 advanced HCC subjects who have progressed following immune checkpoint inhibitor treatment will be enrolled to further assess the safety and efficacy of the study treatment in the specific group of subjects. Subjects will continue to receive study treatments (MGD013 monotherapy or combination therapy) until disease progression, death or the occurrence of intolerable toxicity (whichever comes first). MGD013 will be used for at most 48 cycles. If subjects do not have disease progression after 48 cycles, MGD013 will be discontinued. Subjects of the combination therapy group may continue to take Brivanib Alaninate. Phase II study will assess the safety and efficacy of the study treatments, with BICR-assessed ORR according to RECIST 1.1 as the primary efficacy endpoint. Secondary efficacy endpoints will provide supporting data.
Number of Subjects Planning to be Enrolled	A total of 30 to 43 evaluable subjects, 158 subjects, and 120 subjects will be enrolled in Phase I, Phase II Part 1, and Phase II Part 2 respectively.
Main Inclusion Criteria:	1. Subjects who voluntarily sign the informed consent form (ICF); 2. Male or female subjects who are aged 18-75 years old; 3. Subjects with histologic, cytologic or clinical confirmed diagnosis of advanced HCC (Phase I could include intrahepatic cholangiocarcinoma or

	mixed hepatocellular-cholangiocarcinoma), and are not suitable for surgery or loco-regional therapy or have progressed following surgery and/or loco-regional therapy; 4. Subject who has at least one measurable lesion according to RECIST v1.1 criteria. 5. Phase I study: subjects who have previously received at least one line of systemic therapy, including immune checkpoint inhibitors, molecular targeted drugs or systematic chemotherapy, alone or in combination, and failed (progression confirmed by imaging) or were intolerant at the discretion of investigator; PhaseII：Advanced HCC cohort with subjects who have previously received immune checkpoint inhibitor treatment: subjects who have failed (progression confirmed by imaging) prior one line immune checkpoint inhibitor treatment, including anti-PD-1 antibody/anti-PD-L1 antibody and / or anti-CTLA-4 antibody, and/or molecular targeted therapy or systematic chemotherapy (monotherapy or in combination); Phase II: Advanced HCC cohort with subjects who have not previously received immune checkpoint inhibitor treatment: subjects who have failed (progression confirmed by imaging) or were intolerant to (at the discretion of investigator) previous molecular targeted therapy or systematic chemotherapy, without receiving immune checkpoint inhibitor treatment (including anti-PD-1 antibody, anti-PD-L1 antibody, anti-CTLA-4 antibody, and bispecific antibodies including the above targets). 6. Previous anti-tumor therapy must be completed no less than 2 weeks prior to the study treatment and all adverse events related to previous treatment must have recovered to CTCAE Grade $\leqslant$1; if subjects who have received prior immune checkpoint inhibitors have immune-related endocrinopathy, it should be controlled with hormone replacement therapy. 7. Phase I: Child-Pugh Class A; Phase II: Child-Pugh Class A or B with a score of $\leqslant$ 7; 8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; 9. Subjects with life expectancy $\geqslant$12 weeks; 10. Subjects with chronic HBV infection must have HBV-DNA <500 IU/ml, and have received at least 14 days of anti-HBV treatment (e.g. entecavir, tenofovir) prior to the initiation of study treatment and are willing to receive antiviral treatment throughout the study; Antiviral therapy is not required for patients with HCV infection and the elevation of their liver enzymes must not exceed the level of CTCAE Grade 1; 11. Adequate vital organ function as shown below: (1) Blood system function (subjects must have not received blood transfusion or stimulating growth factors within 14 days prior to screening test): neutrophil count $\geqslant 1.5\times10^9$/L, platelet count $\geqslant 75\times10^9$/L, hemoglobin $\geqslant$ 90 g/L; (2) Liver and kidney function (no albumin transfusion within 14 days

	prior to screening test): serum total bilirubin ≤ 2.5×ULN, serum albumin ≥ 29 g/L, ALT and AST ≤ 5×ULN; serum creatinine ≤ 1.5×ULN or eGFR (Cockcroft-Gault formula) ≥ 60 ml/min; (3) Coagulation function: international normalized ratio (INR)≤2.3 or prothrombin time (PT) of ≤ 6 seconds above control; (4) Left ventricular ejection fraction (LVEF) ≥50% by two-dimensional echocardiography. 12. Female subjects (except for females who have underwent surgical sterilization and those have been menopausal for more than one year) who are of childbearing potential are required to adopt a medically proven method for contraception (e.g. intrauterine contraception device, contraceptive pill or condom) throughout the study and up to 120 days after the last dose of investigational products; females who are of childbearing age and who do not underwent surgical sterilization must have negative serum or urine HCG tests within 7 days prior to enrollment; female subjects must not be breastfeeding; male subjects whose partners are of childbearing potential should use effective contraceptive methods throughout the study and up to 120 days after the last dose of investigational product. 13. Subjects who are willing to provide oncological tissues (if applicable) for biomarker test.
Exclusion criteria:	1. Subjects who have known fibrolamellar carcinoma of liver for phase I and subjects who have fibrolamellar carcinoma, mixed HCC-cholangiocarcinoma or cholangiocarcinoma for phase II; 2. Subjects with brain metastasis or leptomeningeal metastasis confirmed by brain MRI during screening period; 3. Subjects with a diagnosis of other malignant tumors within 5 years prior to first administration, except for skin basal cell carcinoma, skin squamous cell carcinoma and/or in situ cancer following radical resection; 4. Subjects who had liver or other sites loco-regional treatment (including transcatheter arterial chemoembolization (TACE), transcatheter arterial embolization (TAE), hepatic artery infusion (HAI), local radiotherapy, radioembolization, radiofrequency ablation, cryoablation or percutaneous ethanol injection) , or who had major surgery of liver or other sites within 4 weeks prior to first administration, or had minor surgical procedures (e.g. simple excision, tooth extraction) within one week prior to first administration, or had received palliative radiotherapy for bone metastasis within 2 weeks and radiotherapy-related toxicity ≥ CTCAE Grade 2. 5. Subjects who have moderate or severe ascites (detected by B-ultrasound or CT), or require therapeutic abdominal paracentesis or drainage; 6. Subjects with a history of hepatic encephalopathy; 7. Subjects with a history of unhealed wounds or ulcers or bone fractures within 3 months prior to study enrollment;

	8. Subjects who plan to have or had allogenic organ or bone marrow transplantation; 9. Subjects who are at increased risk of bleeding or have history of thrombosis: (1) Clinically significant bleeding within 3 months prior to screening or clear bleeding tendency; (2) Gastrointestinal hemorrhage within 6 months prior to screening or clear tendency of gastrointestinal hemorrhage; (3) Arterial/venous thromboembolic events within 6 months prior to screening, such as cerebrovascular accident (including transient ischemic attack), pulmonary embolism, etc.; (4) Require anticoagulation therapy with an agent such as warfarin or heparin; (5) Require chronic anti-platelet therapy (such as aspirin≥100 mg/day, clopidogrel, etc.); 10. Subjects who have clinically significant cardiovascular diseases: (1) NYHA (New York Heart Association) stage 3 and 4 congestive heart failure; (2) Unstable angina pectoris or newly diagnosed angina pectoris or myocardial infarction within 12 months prior to screening; (3) Arrhythmias requiring medications other than β-blockers; (4) Valvular heart disease of ≥ CTCAE grade 2; (5) Hypertension inadequately controlled by drugs (systolic pressure >150 mmHg or diastolic pressure >90 mmHg); 11. Subjects who have history of symptomatic pulmonary fibrosis, or have interstitial pneumonitis, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis, severe impairment of pulmonary function, or other suspicious pulmonary diseases that may interfere with drug-related pulmonary toxicity detection and treatment; 12. Subjects who have suffered active bacterial or fungal infections requiring systemic treatment within 7 days prior to screening; or active tuberculosis; 13. Subjects with active co-infection of Hepatitis B and C, confirmed by positive HBV surface antigen or HBV DNA and HCV RNA 14. Subjects who have any active, known or suspected autoimmune disease; 15. Subjects with a condition requiring systematic treatment with corticosteroids (>10 mg/day prednisone or equivalent) or other immunosuppressive drugs within 14 days before administration of the investigational drug. In the absence of active autoimmune diseases, inhalation or topical use of steroids (>10 mg/day prednisone or equivalent) is allowed; 16. Other laboratory abnormalities:

	(1) Hyponatremia, hypokalemia or hypophosphatemia that have occurred before the first administration, and failed to restore to normal level after electrolyte supplementation therapy; (2) Confirmed diagnosis of thyroid dysfunction, which cannot be maintained within normal range following thyroid hormone replacement therapy; (3) Positive Human immunodeficiency virus (HIV) test; 17. QTc interval >480 ms on two consecutive ECGs; 18. Female subjects during pregnancy or lactation; female subjects of childbearing potential or male subjects who are not willing to use contraception or contraceptive measures during the study; 19. Subjects who have previously received two lines and above tumor immune checkpiont inhibitor treatment, mainly including anti-PD-1, anti-PD-L1 and anti-CTLA-4 antibodies, etc, or bispecific antibodies including the above targets, or received anti-LAG-3 antibody; whether subjects who have previously received other tumor immunotherapy can be enrolled should be determined by the sponsor; 20. Known or suspected history of severe allergy to investigational drugs; 21. Subjects who have received live attenuated vaccines or any investigational drugs that have not been marketed in China within 4 weeks prior to first administration; 22. If subjects who have previously used immune checkpoint inhibitors (such as anti-PD-1, anti-PD-L1, anti-CTLA-4 antibodies) have the following drug-related adverse events, they will be not suitable for inclusion regardless of recovered or not: a) ⩾ Grade 3 eye-related adverse events b) Grade 4 abnormal liver function c) ⩾ Grade 3 neurotoxicity d) ⩾ Grade 3 colitis e) ⩾ Grade 3 renal toxicity f) ⩾ Grade 3 pneumonitis 23. Subjects who are not suitable for inclusion as judged by the investigators.
Investigational Drugs and Dosing Regimen	**Investigational Drugs:** ● Brivanib Alaninate: 200 mg, tablets, oral administration; ● MGD013 injection, active ingredients: PD-1x LAG-3 bispecific, tetravalent diabody DART®, 300 mg/15 mL. **Dosing Regimen:** ● MGD-013 is administered intravenously at a fixed dose according to subject's dose group, regardless of body weight or body surface area, for 60 - 75 minutes once every other week;

	● In the combination therapy cohort, brivanib alaninate is given orally at a fixed dose according to subject's dose group once daily at a fixed time, and can be taken with or without meals; ● Both drugs are consecutively administered until disease progression, death or the occurrence of intolerable toxicity (whichever occurs first). However, MGD013 will be administered for at most 48 cycles. If subjects do not have disease progression after 48 cycles, MGD013 will be discontinued. Subjects of the combination therapy group may continue with brivanib alaninate.
Evaluation criteria	**Safety Assessment** - Vital signs, physical examination, ECOG score; - The type, occurrence time and severity of adverse events (AEs) (CTCAE 5.0 classification); - 12-lead ECG, and echocardiography (as clinically indicated); - Laboratory tests ● Hematology (complete blood count [CBC]) ● Urinalysis ● Blood biochemistry (liver and kidney function, blood glucose, electrolytes, amylase, lipase, etc.) ● Coagulation ● Thyroid function **Efficacy Assessment** **Primary Efficacy Endpoint:** Objective response rate (ORR) is the primary efficacy endpoint for both phase I and II, as assessed by investigator (Phase I) and Blinded Independent Central Review (BICR) (Phase II) according to RECIST 1.1 respectively. ORR is defined as the proportion of enrolled subjects whose best response is CR or PR. Subjects assessed as CR or PR initially are required to be confirmed at the interval of at least 4 weeks. **Secondary Efficacy Endpoints:** Phase I: irRECIST-based ORR. Phase II: secondary efficacy endpoints of phase II study include: BICR-assessed ORR according to irRECIST; Investigator-assessed ORRs according to RECIST 1.1 and irRECIST respectively; Disease control rate (DCR): defined as the proportion of enrolled subjects with best response of CR, PR or SD assessed using RECIST 1.1 and irRECIST criteria respectively. Time to tumor progression (TTP): defined as the time from the first administration to the time of radiographic disease progression under RECIST 1.1 and irRECIST criteria. Subjects without documented

	radiographic progression due to loss to follow-up or changing treatment regimen during follow-up will be censored on the last radiographic follow-up date on which no disease progression is confirmed. Duration of response (DoR): defined as the time from radiographic response to disease progression or death in subjects whose best response is CR or PR. DoR is assessed with RECIST 1.1 and irRECIST criteria respectively Progression-free survival (PFS): defined as the time from the first dose to the date of tumor progression or death due to any cause. Disease progression is assessed using RECIST 1.1 and irRECIST criteria respectively. Subjects without documented radiographic progression or death during follow-up will be censored on the last follow-up date on which no disease progression is confirmed. For subjects without progression till the date of analysis, they will be censored on the last tumor assessment date. Overall survival (OS): defined as the time from first administration to death caused by any reason. Subjects who are alive during the follow-up or are lost to follow-up without documented death will be censored on their last known alive date. For subjects alive till the date of analysis, they will be censored on their last known alive date.
Statistical Method	**Analysis Set** Statistical analysis is performed using full analysis set (FAS), per-protocol set (PPS) and safety set (SS). FAS: it includes all subjects who have received at least one dose of the investigational drug and have measurable tumors at baseline. PPS: it includes subjects with at least one post-treatment imaging assessment of tumors, good compliance, and no serious violation or deviation against the study protocol in FAS population. SS: it includes subjects who have received at least one dose of the investigational drug and undergone safety assessment. **Sample Size Determination** During phase I dose escalation study of MGD013 monotherapy, the starting dose of MGD013 will be 120 mg Q2W in one subject which has been enrolled in the group. The subsequent dose groups will adopt traditional 3+3 dose escalation scheme , with 3 - 6 evaluable subjects in each group; during dose escalation study of combination therapy, the traditional 3+3 dose escalation scheme will be used, and it is expected to have 30 - 43 subjects in total in Phase I. There will be two cohorts in Phase II Part 1. Subjects who have previously received and not received immune checkpoint inhibitor treatment will be administered with MGD013 monotherapy or MGD013 in combination with brivanib alaninate. The SWOG two-stage design will be employed. [redacted] 30 subjects are needed [redacted] There are two stages in this part. In the first stage, if response (according to RECIST 1.1 criteria) is observed radiologically in 1 or more out of 15 evaluable subjects, the

	enrollment of second stage will be open and an additional of 15 evaluable subjects will be enrolled. [redacted] 40 subjects are needed [redacted] Similarly, there are 2 stages for the cohort. At least response of 3 out of 20 evaluable subjects at the first stage will support the decision to proceed to the second stage of subject accrual till there are 40 evaluable subjects in this cohort. Each cohort will have 70 evaluable subjects. Considering 10% dropout rate, up to 158 subjects will be enrolled. According to safety and efficacy data of Phase II Part 1, a study treatment (MGD013 monotherapy or MGD013 in combination with brivanib alaninate) will be selected for Part 2 dose expansion in subjects who have previously received immune checkpoints inhibitor treatment. It is estimated to enroll 120 subjects for further assessment of its efficacy and safety. **Statistical Analysis Method** Safety Analysis Safety analysis is performed in the SS population. Safety parameters include physical examination, vital signs, AEs and laboratory tests, ECG, etc. AEs will be coded using the most updated MedDRA System Organ Class and Preferred Term. The incidence and severity of AEs, dose-limiting toxicity (DLT, phase I study), AEs leading to withdrawal from study, AEs leading to drug discontinuation, AEs leading to death, and serious adverse events (SAEs)will be summarized. For laboratory parameters and ECG, the change during the study will be summarized by descriptive analysis. The normal and abnormal laboratory values before and after treatment will be summarized using a shift table based on the lab normal range. Listing of data will be also provided. Some specified parameters will be summarized descriptively per protocol. Efficacy Analysis FAS and PPS are both used for efficacy analysis, and of which, PPS is the main analysis set and FAS analysis can provide supporting evidence. Primary efficacy endpoints: ORR. Secondary endpoints are PFS, TTP, DCR, DoR and OS. For ORR, its point estimation and the p-value (1-sided) and corresponding 95% confidence interval (95% CI) of the single-arm test will be provided. For TTP, PFS and OS, Kaplan-Meier method is adopted to estimate survival function and draw survival curve. The median TTP, median PFS, total survival rate at specific time points (at 6, 9 and 12 months) and their corresponding 95% CIs will be provided.
Study Visit Schedule and Assessments: See Table 1	

Table 1 Clinical Study Flow Chart (Each cycle = 2 weeks)

	Screening Period		Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 3 Day 1	Cycle 4 Day 1	Day 1 of each cycle	Day 1 of every two cycles	Every 8 weeks	End of Treatment[1] (EOT)	Safety Follow-up	Follow-up after treatment
Day	**D-28~0**	**D-7~0**	**D1**	**D8**	**D15**	**D22**	**D29±2d**	**D43±2d**	**±3d**	**±3d**	**±7d**	**+7d**	**30±7d**	**Every 60±7d**
weeks			**Week 1 Day 1**	**Week 2 Day 1**	**Week 3 Day 1**	**Week 4 Day 1**	**Week 5 Day 1**	**Week 7 Day 1**						
Informed consent	**X**													
Demographics	**X**													
Inclusion/Exclusion Criteria		**X**												
History of tumor treatment and other diseases	**X**													
Archival tumor tissue sample collection	**X**													
ECOG performance status	**X**		**X**		**X**		**X**	**X**	**X**			**X**		
Physical examination and body weight	**X**		**X**		**X**		**X**	**X**	**X**			**X**	**X**	
Vital signs [2]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**		
Two-dimensional echocardiography	**X**			Perform as clinically indicated										
12-Lead ECG		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**		
Adverse event evaluation[3]		←---------- **X** ----------→												
Evaluation of concomitant treatments		←---------- **X** ----------→												
HBV, HCV virological test	**X**													

	Screening Period		Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 3 Day 1	Cycle 4 Day 1	Day 1 of each cycle	Day 1 of every two cycles	Every 8 weeks	End of Treatment[1] (EOT)	Safety Follow-up	Follow-up after treatment
Day	**D-28~0**	**D-7~0**	**D1**	**D8**	**D15**	**D22**	**D29±2d**	**D43±2d**	**±3d**	**±3d**	**±7d**	**+7d**	**30±7d**	**Every 60±7d**
weeks			**Week 1 Day 1**	**Week 2 Day 1**	**Week 3 Day 1**	**Week 4 Day 1**	**Week 5 Day 1**	**Week 7 Day 1**						
HBV-DNA (when HBsAg is positive)	**X**										**X**			
HCV-RNA (when HCV antibody is positive)	**X**										**X**			
Serology HIV	**X**													
Hematology		**X**		**X**	**X**	**X**	**X**	**X**	**X**			**X**	**X**	
Blood chemistry (liver and kidney function, fasting blood glucose, electrolytes, amylase, lipase)		**X**		**X**	**X**	**X**	**X**	**X**	**X**			**X**	**X**	
AFP test		**X**									**X**	**X**		
Urinalysis		**X**			**X**		**X**	**X**	**X**			**X**		
Thyroid function		**X**					**X**			**X**		**X**		
Pregnancy test (if required)		**X**										**X**		
Coagulation		**X**		**X**	**X**	**X**	**X**	**X**	**X**			**X**		
Biomarkers (Phase I and part 1 of Phase II)[4]			**X[a]**	**X[b]**	**X[c]**		**X[d]**							
Brain MRI scan[5]	**X**			Perform as clinically indicated										
Radiographic tumor assessment[6]	**X**			Every 8 weeks until disease progression										
Brivanib alaninate (combination treatment group)			←----------QD----------→											

	Screening Period		Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 3 Day 1	Cycle 4 Day 1	Day 1 of each cycle	Day 1 of every two cycles	Every 8 weeks	End of Treatment[1] (EOT)	Safety Follow-up	Follow-up after treatment
Day	**D-28~0**	**D-7~0**	**D1**	**D8**	**D15**	**D22**	**D29±2d**	**D43±2d**	**±3d**	**±3d**	**±7d**	**+7d**	**30±7d**	**Every 60±7d**
weeks			**Week 1 Day 1**	**Week 2 Day 1**	**Week 3 Day 1**	**Week 4 Day 1**	**Week 5 Day 1**	**Week 7 Day 1**						
MGD013			**X**		**X**		**X**	**X**	**X**					
Survival and subsequent antineoplastic therapy (Phase II study)														**X**

1. The end of treatment (EOT) visit is within 7 days after the last dose (or early withdrawal); if the corresponding examination was done within 7 days, it was not necessary to repeat the examination.
2. Vital signs are only examined once at the visit in the screening period and that at EOT visit; on Cycle 1 Day 1, vital signs are examined at the following time points: prior to infusion of MGD013 (within 30 minutes prior to infusion), at 15 minutes (± 5 minutes), 30 minutes (± 5 minutes) after infusion, at the end of infusion (± 10 minutes), at 1 hour (± 10 minutes), 3 hours (± 10 minutes) after the completion of infusion. For subsequent visits vital signs are examined at the following time points: prior to infusion of MGD013 (within 30 minutes prior to infusion), at the end of infusion (± 10 minutes), at 1 hour (± 10 minutes) after the completion of infusion. Additional vital signs examination may be performed at other time points as clinically indicated.
3. Adverse events will be recorded up to 30 days after the subject's treatment ends.
4. Analysis and sampling of biomarkers: a. Serum cytokines, receptor occupancy [only in dose escalation study], cell subset and markers prior to administration of MGD013; b. serum cytokines, receptor occupancy [only in dose escalation study], cell subset and markers prior to administration; c. for analysis of serum cytokinesand receptor occupancy [only in dose escalation study], samples will be collected prior to administration of MGD013 and after the completion of infusion respectively; for analysis of cell subset and markers, samples will be collected prior to administration of MGD013; d. for analysis of serum cytokinesand receptor occupancy [only in dose escalation study], samples will be collected prior to administration of MGD013 and after the completion of infusion; for analysis of cell subset and markers, samples will be collected prior to administration of MGD013. In addition, for subjects with immune- and infusion-related reactions or cytokine release syndrome, additional sampling for analysis of serum cytokinesmay be performed.
5. MRI can only be performed in subjects who are clinically suspected of central nervous system metastasis in the screening and subsequent periods. If the subject is contradicted to MRI, cranial CT can be performed.
6. Radiographic tumor assessments (contrast-enhanced CT of the chest, enhanced CT/MRI of the abdomen and pelvis at baseline, and subsequent contrast-enhanced CT/MRI of the abdomen and pelvis and clinically indicated sites) will be performed prior to treatment (baseline) using the same radiologic imaging modalities and will be repeated every 8 weeks throughout the study, with contrast enhancement required if not medically contraindicated. Subjects who discontinued from the study due to study drug toxicity or for any reason other than unequivocal tumor progression continued to undergo tumor assessment every 8 weeks during survival follow-up until disease progression confirmed or death. Subjects radiologically assessed as CR or PR for the first time should undergo confirmation of efficacy at the interval of at least 4 weeks.

Table of Abbreviations and Definitions of Terms

Abbreviations and Special Terminology	Interpretation
AE	Adverse Event
AESI	Adverse Events of Special Interest
AFP	α-fetoprotein
ALT	Alanine aminotransferase
APTT	Active partial thromboplastin time
AST	Aspartate aminotransferase
BCLC	Barcelona liver cancer staging
BSC	Best supportive treatment
NMPA	National Medical Products Administration
Child-Pugh	Liver function grading standard
CR	Completely released
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DDI	Drug-Drug Interactions
DLT	Dose-limiting toxicity
DoR	Duration of tumor response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCC	Primary Hepatocellular Carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus (HIV)
HR	Hazard ratio
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed consent form
IEC	Independent ethics committee
ICR	Independent imaging center review
irAEI	Immune-related Adverse Events of Interest
INR	International Normalized Ratio
LVEF	Left ventricular ejection fraction
mOS	Median overall survival
mPFS	Median progression-free survival
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose

ORR	Objective Response Rate
OS	Total Survival
PD	Progressive Disease
PPS	Per Protocol Set
PFS	Progression-free survival
PR	Partial Response
PDGFR	Platelet-derived growth factor receptor
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase II Dose
Q2W	Once every 2 weeks
QD (qd)	Once a day
RPLS	Reversible posterior leukoencephalopathy syndrome
SAE	Severe adverse event
SD	Stable disease
TTP	Time to tumor progression
ULN	Upper Limit of Normal
Vss	Apparent volume of distribution at steady state

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1. Introduction

1.1 Study Background

1.1.1 Primary liver cancer

Primary liver cancer (PLC) is the sixth most common cancer and the second leading cause of cancer-related death worldwide, mainly including hepatocellular carcinoma (HCC) arising from the cells of the liver and cholangicarcinoma from the cells of bile ducts. Other rare types include fibromellar carcinoma and angiosarcoma. Among them, hepatocellular carcinoma (HCC) is most commonly seen which accounts for 85-90% of primary liver cancers (PLCs). It is the fifth most common malignancy in men and the seventh in women worldwide. Primary hepatocellular carcinoma is the third leading cause of cancer-related death after lung and gastric cancer. Globally, it is estimated that there are 782,000 new cases of HCC and causing approximate 600,000 deaths each year. Important risk factors associated with HCC include: chronic viral hepatitis (hepatitis B and C, most commonly observed), aflatoxin intake, alcoholism, and nonalcoholic steatohepatitis (NASH)[1].

There is wide geographical variability in the incidence and etiology of primary hepatocellular carcinoma. Hepatocellular carcinoma is particularly prevalent in Asian countries as compared to Western countries. Of new HCC cases worldwide, 75% occurred in Asia with 50% in China each year. China had the highest number of new cases and deaths of liver cancer in the world, with about 394,000 new cases and 326,000 deaths annually. HCC is the second leading cause of cancer-related death following lung cancer in China. Hepatitis C, alcoholic liver disease, and nonalcoholic steatohepatitis are main causes of HCC in Western countries. In contrast, a majority of HCC cases in China are associated with chronic hepatitis B (more than 80%) [2].

Due to the insidious nature of the onset of liver cancer, more than 80% of HCC patients are diagnosed at advanced stage, thus precluding potentially curative treatment. Only 5 to 15% of patients with early stage HCC have the opportunity of surgical resection. But they still have a high recurrence rate (2-year recurrence rate of 62.4% to 77.8%). Therefore, the prognosis of advanced hepatocellular carcinoma is very poor globally, with a 5-year survival rate of only 6.9% and a median overall survival of 11 months. The prognosis in Chinese patients is even worse [3].

Intrahepatic cholangiocarcinoma (ICC) is a rare malignant tumor which arises from the epithelial cells of intrahepatic bile ducts. The incidence of ICC is reported to be only about 10% of primary liver cancers. Risk factors of ICC are similar to those of HCC. Besides, they also include primary sclerosing cholangitis and primary biliary cirrhosis. For non-resectable cases, the prognosis is very poor and overall mean duration of survival is 6-10 months[4].

1.1.2 Treatment of Advanced Hepatocellular Carcinoma

For patients with unresectable or metastatic HCC, non-surgical systematic treatment is commonly used in clinical practice. Current systemic therapies for advanced hepatocellular carcinoma (HCC) in China mainly include anti-angiogenesis treatment targeting the vascular endothelial growth factor (VEGF) pathway, oxaliplatin-based systemic chemotherapy, and immunotherapy.

Three VEGFR tyrosine kinase inhibitors (TKIs) are approved to treat HCC in China: sorafenib, lenvatinib, and regorafenib. Sorafenib and lenvatinib are approved as first-line treatment of advanced HCC. The global SHARP study[5] of sorafenib and the Asia-Pacific Oriental study[6] both showed that sorafenib prolonged overall survival as compared with placebo (median overall survival (mOS) 10.7 months vs. placebo 7.9 months, HR 0.69, P <

0.001 in SHARP study; mOS 6.5 months vs.placebo 4.2 months, HR 0.68, P = 0.014 in Oriental study). However, the objective response rate (ORR) was relatively low, ranging from 2% to 3%. A phase III clinical study of lenvatinib (REFLECT study)[7] enrolled 954 patients with unresectable HCC and demonstrated non-inferiority to sorafenib in the primary endpoint of OS (mOS 13.6 months vs. 12.3 months, HR 0.92, 95% CI 0.79-1.06) with an objective response rate (as assessed by RECIST 1.1) of 18.8% (6.5% for sorafenib). Regorafenib is approved as second-line treatment for HCC patients who have progressed after sorafenib. Results of a placebo-controlled, multinational phase III study (RESORCE study)[8] showed that treatment with regorafenib improved TTP (3.2 vs. 1.5 months, HR 0.44, P < 0.0001), ORR (mRECIST, 11% vs.4%, P = 0.0047) and DCR (65% vs. 36%, P < 0.0001), and prolonged survival (10.6 vs.7.8 months, HR 0.63, P < 0.0001) as compared with placebo in sorafenib-failed HCC patients.

An open-label, randomized, controlled international multicenter phase III clinical study (EACH study) [9,10] included 371 patients with advanced HCC who were not suitable for surgery or local treatment, of which 75% were Chinese patients. The results showed that, comparing with Adriamycin alone, chemotherapy with FOLFOX4 regimen significantly prolonged mPFS (1.77 vs. 2.93 months, P < 0.001), improved ORR (2.67% vs.8.15%, P = 0.02) and DCR (31.55% vs. 52.17%, P < 0.0001) ; analysis after further follow-up for 7 months showed that OS continued to benefit in the FOLFOX4 group (6.47 vs.4.90 months, P = 0.04). In the sub-cohort of Chinese patients, mOS was significantly longer in the FOLFOX4 group (5.9 vs. 4.3 months, P = 0.0281), and mPFS, ORR, and DCR also showed a significant benefit.

Recently, the introduction of immune checkpoint inhibitors, such as PD-1 or PD-L1 antibody, into the treatment of HCC has shown promising efficacy. Nivolumab was conditionally approved by the FDA as the second line treatment of HCC. The CheckMate-040 study, which is a phase I/II open-label, multicenter, single-arm clinical study[11], indicated that the ORR (according to RECIST 1.1) of nivolumab in second-line HCC cohort (N = 145) was 14%, the 12-month overall survival rate was 60%, and the 18-month overall survival rate was 44%; the ORR in first-line cohort (N = 80) was 20%, and the 12-month and 18-month overall survival rate was 73% and 57% respectively. Pembrolizumab was also conditionally approved by the US FDA as the second-line treatment of HCC based on data from Keynote-224[12], a phase II nonrandomized, international multicenter, open-label clinical study. The ORR (as assessed by RECIST1.1) of Pembrolizumab in second-line HCC cohort (N = 104) was 17% and the 12-month overall survival rate was 54%. Currently these two drugs have not been approved for the treatment of HCC in China.

Patients with advanced ICCs who are unresectable or have progressed following loco-regional therapy are usually treated by chemotherapy agents, such as 5-fluorouracil with leucovorin, gemcitabine as a single agent, or gemcitabine plus cisplatin, irinotecan, or capecitabine. The preliminary efficacy has been demonstrated by clinical studies of immune checkpoint inhibitors in ICC patients which are ongoing. Of 24 biliary tract neoplasms with PD-L1 expression $\geqslant$ 1% in the basket study KEYNOTE-028 of pembrolizumab[13], 4 patients (17%, including 3 patients with bile duct carcinoma and 1 patient with carcinoma of gallbladder) reached partial response (PR) and 4 patients (17%) reached stable disease. It has been reported that 5 - 10% of patients with bile duct carcinoma have DNA mismatch-repair (MMR) deficiency. A study of pembrolizumab in tumor patients with MMR deficiency indicated[14] that 25% patients (1/4) with bile duct carcinoma reached partial response (PR) and the remaining 3 patients reached stable disease (SD), with a disease control rate (DCR) of 100%.

Although systemic treatments with VEGFR TKIs or oxaliplatin-based chemotherapy can prolong the overall survival of patients with advanced HCC, the objective response rate to these therapies is relatively low, and the survival benefit is also limited. The available options for advanced ICCs are limited and the prognosis is very poor. Therefore, there is still great unsatisfied medical need in patients with these two types of advanced liver cancer. The immune checkpoint inhibitors (anti PD-1/PD-L1 antibody) are expected to have better efficacy in both advanced HCCs and ICCs, but current data are limited given relevant studies are still ongoing. There is still no effective treatment or relevant study in patients who have progressed following immune checkpoint inhibitor treatment.

1.1.3 MGD013

MGD013, developed by MacroGenics (US), is a humanized PD-1 + LAG-3 bispecific, tetravalent diabody DART® molecule consisting of Fc domains, engineered as a hinge-stabilized IgG4 molecule and is designed to concomitantly bind PD-1 and LAG-3. Zai Lab obtained the exclusive right of research & development, production and sales of MGD013 in Greater China in December 2018.

1.1.3.1 Preclinical Studies

1.1.3.1.1 Pharmacology

In vitro, MGD013 bound with high affinity to human and cynomolgus monkey PD-1- and LAG-3-expressing cells. For human PD-1-expressing cells, equilibrium dissociation constant (K_D) was 0.9 nM; for cynomolgus monkey PD-1-expressing cells, K_D was 7.5 nM. In addition, K_D was 0.022 nM for human LAG-3-expressing cells and 0.190 nM for cynomolgus monkey LAG-3-expressing cells. FACS analysis showed a dose-dependent binding of MGD013 to human peripheral blood mononuclear cells (PBMCs), human T cells (and other immune cell populations), human PD-1+ NS0 Cells and human LAG-3+ NS0 Cells on modified cells and PBMCs of cynomolgus monkeys. When stimulating PBMCs with staphylococcal enterotoxin B (SEB) to induce PD-1 and LAG-3 genes expression, binding of MGD013 to human and non-human primate PBMCs was enhanced. As its specific binding characteristics, MGD013 can block PD-1/PD-L1, PD-1/PD-L2 and LAG-3/HLA (MHC-II) interactions. Co-culture reporter gene assay system indicated that MGD013 also directly blocked the PD-1/PD-L1 axis between cell lines, which was measured by enhanced T cell receptor (TCR) -mediated NFAT-driven luciferase signaling by the PD-1 expressing cell line. In addition, MGD013 can enhance human PBMC stimulated by SEB or memory T cells stimulated by tetanus toxoid (TTd) to secret interferon-γ (IFN-γ), which is beyond that observed with the combination of nivolumab and relatlimab (anti-LAG-3 monoclonal antibody [mAb]) replicas. These studies showed that MGD013 has the functional activity of intervening with PD-1/PD-L1/L2 and LAG-3/MHC-II inhibitory signal transduction pathway. Besides, binding characteristics of MGD013 are equal to nivolumab and relatlimab replicas. The functional characteristics of MGD013 are beyond those of the combination of nivolumab and relatlimab replicas, indicating that MGD013 can provide an additional effect over the antibody combination. Nivolumab and relatlimab replicas are $IgG_{4\kappa}$ molecules constructed based on public sequence by MacroGenics (MG).

1.1.3.1.2 Toxicology

The cynomolgus monkey was selected as the most appropriate animal model for nonclinical safety evaluation of MGD013 given the sequency homology of extracellular domains of cynomolgus monkey and human PD-1 and LAG-3 (96% and 92% respectively) and the ability of MGD013 to bind to both PD-1 and LAG-3 in humans and monkeys with similar affinity, and bind to PBMC in humans and monkeys following SEB stimulation to PD-1.

MacroGenics (MG) conducted single-dose and repeat-dose toxicology studies in cynomolgus monkey. MGD013 was administered at a dose range of 0 - 150 mg/kg by 1-hour intravenous infusion. They were well tolerated and there were no premature deaths. MGD013 did not induce the increase of IFN γ, IL 2, IL 4, IL 5 or TNF α levels in serum. Only transient increase in IL6 was observed. Occupancy of MGD013 receptor on PD-1^+ circulating T cells occurred. MGD013-related changes were only observed at the dose level of 150 mg/kg within 23 - 71 hours after infusion, that is, a transient decrease in circulating immune cells followed by increasing. Sporadic vomiting, and watery and/or green feces were observed clinically in some males at $\geqslant$ 40 mg/kg/dose and in some females at $\geqslant$ 100 mg/kg/dose; mild mononuclear cell infiltrates were microscopically observed in several organs of males at $\geqslant$ 10 mg/kg/dose and females at $\geqslant$ 40 mg/kg/dose at the end of the dosing phase, and showed a trend towards reversibility at the end of a 10-week recovery.

Please refer to the latest MGD013 Investigator's Brochure for more details.

1.1.3.2 Clinical Studies

At present, the phase I, first-in-human study of CP MGD013-01 is ongoing in patients with unresectable or metastatic neoplasms. This trial will characterize safety, tolerability, PK, pharmacodynamics (PD), immunogenicity, and preliminary antitumor activity of MGD013 administered intravenously.

As of November 11, 2018, the data cut-off date, a total of 36 patients with different types of solid tumors received MGD013 treatment ranging from 1 mg - 1200 mg Q2W in the dose escalation period. Subjects at each dose level are as follows: 1 patient at 1 mg, 1 patient at 3 mg, 4 patients at 10 mg, 5 patients at 30 mg, 4 patients at 120 mg, 9 patients at 400 mg, 8 patients at 800 mg and 4 patients at 1,200 mg. More patients were enrolled in the dose cohorts of 400 mg and 800 mg to obtain more data.

Of 36 patients treated with MGD013 in the dose escalation period, 33 patients (91.7%) experienced at least one adverse event (AE), irrespective of the causality. The most commonly reported AEs in $\geqslant$ 10% patients included diarrhea (n = 8 [22.2%]), lassitude and nausea (n = 7 [19.4%] each), infusion-related reaction and fever (n = 6 [16.7%] each); abdominal pain, diarrhea, vomiting, coldness, dyspnea, joint pain and back pain (n = 5 [13.9%] each); blood creatinine increased, hyponatremia, headache, cough, rash and itching (n = 4 [11.1%] each).

Most treatment-related AEs were mild to moderate (that is, grade 1 or 2). However, of 36 patients (19.4%) treated with MGD013 in the dose escalation period, 7 experienced at least one grade 3 treatment-related AE. These events included infusion-related reaction (n = 2 [5.6%]), diarrhea, vomiting, lassitude, immune-mediated hepatitis, blood bilirubin increased, transaminases increased, hypoadrenalism, hypotension, colitis, hypophosphatemia, arthritis and myalgia (n = 1 [2.8%] each). No grade 4 or 5 treatment-related AEs occurred.

Of 36 patients treated with MGD013 in the dose escalation period, only 8 (22.2%) experienced serious adverse events (SAEs). Four (11.1%) experienced treatment-related SAEs, including: immune-mediated hepatitis (n = 1, 1,200 mg); colitis (n = 1,800 mg); hypoadrenalism with hypotension (n = 1,400 mg) and ALT increased, blood bilirubin increased and hypophosphatemia (n = 1,400 mg). The SAEs which were considered unrelated to MGD013 included urinary tract infection, dyspnea, small intestine obstruction and lung hemorrhage. They were considered to be related to patients' underlying malignant tumor or concomitant disease.

Please refer to the latest MGD013 Investigator's Brochure for more details.

MGD013 showed anti-tumor effects and was generally well tolerated in the dose escalation period. Of the first 3 patients in the 1,200 mg dose cohort, 1 had an SAE and immune-mediated hepatitis meeting DLT criteria; according to 3+3 principle, 3 more patients were enrolled at the dose level and completed DLT evaluation period, without new DLTs. It did not reach the MTD (1,600 mg specified in the protocol), which would not be adopted by MacroGenics. Therefore, the cohort of 1,200 mg became the maximum dose level in the study CP-MGD013-01. While evaluating the dose level of 1,200 mg in the dose escalation period, MacroGenics will further evaluate 600 mg Q2W in the dose expansion period. The decision was made on the basis of clinical, PK data and receptor occupancy.

1.1.4 Brivanib Alaninate

Brivanib is a novel small molecule tyrosine kinase inhibitor (TKI) of the vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) receptor families. Brivanib alaninate (also known as ZL-2301) is the L-alanine ester prodrug of brivanib. This product is licensed by Zai Lab (Shanghai) Co., Ltd. (abbreviation: Zai Lab) from Bristol-Myers Squibb Company (BMS). Zai Lab has the exclusive right to develop, manufacture and market the product in China. At present, this product is proposed to be an oral small-molecule targeted drug which is being developed alone or in combination with other agents for the treatment of malignant tumours (including HCC).

1.1.4.1 Summary of Preclinical Studies

1.1.4.1.1 Pharmacology

In vitro, brivanib alaninate inhibited the proliferation of human umbilical vein endothelial cells (HUVECs) when stimulated with VEGF and basic FGF (bFGF), respectively.

In vivo, both brivanib alaninate and the active metabolite BMS540215 exhibited a broad spectrum of antitumor activity, with cytostatic effects observed in all human tumor models tested. In addition, complete tumor suppression was seen in advanced tumor xenograft models in HCC subjects.

1.1.4.1.2 Pharmacokinetics

Nonclinical pharmacokinetic (PK) and metabolic studies in mice, rats, dogs, and monkeys have shown that brivanib alaninate is rapidly converted to Brivanib (BMS-540215) by hydrolysis. Bioavailability of BMS-540215 following oral administration of brivanib alaninate ranged from 52% to 97% in mice, rats, dogs, and monkeys. BMS-540215 has the following nonclinical PK properties:

- High serum protein-binding rate
- Moderate extravascular distribution
- Low to moderate systemic clearance in each animal species studied
- Metabolized by oxidation (mainly by CYP3A4) and conjugation pathways
- Moderate inhibition of CYP3A4, CYP2C8, CYP2C9 and P-glycoprotein
- Very little potential to induce CYP3A4, CYP1A2 and CYP2B6

1.1.4.1.3 Toxicology

Single- and multiple-dose toxicity studies have been conducted in multiple animal species to evaluate the nonclinical toxicity of brivanib alaninate. Dose increase toxicity studies with brivanib alaninate in rodents (rats and mice) showed that 400 mg/kg was the highest dose at which a single oral dose was non-lethal, while single doses $\geqslant$ 800 mg/kg were lethal.

In the 30-day toxicology study, the no-observed-adverse-effect level (NOAEL) was 60

mg/kg/day in rats (mean AUC 13 to 21 μg/h/mL) and 9 mg/kg/day in monkeys (mean AUC 7 to 12 μg/h/mL). In monkeys, fatal gastrointestinal toxicity and irreversible vascular and skeletal toxicity were observed at a dose of 45 mg/kg/day (mean AUC ≥ 70 μg/h/mL).

In a 6-month oral toxicity study in rats, brivanib alaninate (mean AUC ≥ 3.63 μg/h/mL) caused dose-related, partially reversible cardiac valve changes. Other reversible (e.g., after a 30-day recovery period) toxicological findings were related to bone and teeth, hematopoietic system, blood vessels, coagulation system, and gastrointestinal tract.

In a 12-month oral toxicity study in monkeys, slight to mild increases in ALT levels and microscopic changes in the ovaries were observed at all dose levels of brivanib alaninate. At doses ≥ 20 mg/kg/day (mean AUC ≥ 45 μg/h/mL), changes in the femur and teeth, and reversible decreases in heart rate in male animals were observed, and no effect of the drug on cardiac repolarization was found on the electrocardiogram. In addition, no changes in cardiac biomarkers or histopathological changes in the heart valves were observed.

Direct genotoxicity was not observed with brivanib alaninate.

1.1.4.2 Summary of Clinical Studies

1.1.4.2.1 Clinical Pharmacokinetics

After oral administration of brivanib alaninate, at least 86% was absorbed and rapidly converted to brivanib (BMS-540215, the main active circulating moiety found in human plasma).

Two phase 1 studies (Study CA182001, CA182002) investigated PK profile of brivanib alaninate and BMS-540215 following single dose (dose ranging from 15 to 1200 mg) in healthy subjects and following both single and multiple dosing (dose ranging from 180 to 1000 mg/day) in cancer subjects. Across the dose range, PK parameters were linear with AUC increased proportionally to dose. The mean terminal half-life of BMS-540215 was 12 to 16 hours. The overall 24-hour steady-state drug exposure at 400 mg BID was similar to that at 800 mg QD, but Cmax was lower as expected.

The extent of absorption, metabolism, and clearance of [14C] -labeled brivanib alaninate after a single oral dose was evaluated in subjects with cancer. Absorption, metabolism and clearance degree of brivanib alaninate after single-dose oral administration in 4 patients with advanced cancer Most radioactivity (82%) was recovered in feces, while 12% was recovered in urine as metabolites. No pro-drug (brivanib alaninate) was detected in feces, plasma or urine.

Brivanib is primarily metabolized in the liver into several inactive metabolites through several metabolic pathways with minimal renal excretion. Population PK analyses indicated that there was no effect of race, age and gender on brivanib PK. Five drug-drug interactions studies performed in humans demonstrated that brivanib can be safely co-administered without dose adjustments with CYP3A4 substrates, with CYP2C8 substrates, with CYP3A4 inhibitors, and with P-gp substrates. There was no effect of a high-fat meal on PK parameters of brivanib alaninate.

A phase II study comparing PK, pharmacodynamic and safety profiles between two dosing regimens: 800 mg once daily and 400 mg twice daily in Chinese HCC patients is ongoing. The preliminary results showed no significant difference in the exposure between the two dosing regimens.

Sixty-eight cancer patients in a Phase I dose escalation study (CA182002) were treated with

brivanib alaninate. In the first part of the study, 18 patients received brivanib alaninate at doses of 180, 320, 600, 800, or 1,000 mg once daily. Two DLTs (mental disorder and grade 3 fatigue) occurred in the 1,000 mg group. The DLT in the 800 mg group was mild. Therefore, 800 mg daily was established as the maximum tolerated dose (MTD) of brivanib alaninate. In the second part (pharmacodynamic study), dynamic contrast-enhanced magnetic resonance imaging (MRI) revealed a significant reduction in the permeability and vascularity of the tumor in the continuous 800 mg, once daily, or 400 mg, twice daily groups. Therefore, 800 mg daily was considered as the recommended dose for further clinical trials.

1.1.4.2.2 Efficacy

Two phase II studies and four phase III clinical studies of brivanib alaninate have been conducted in patients with advanced HCC globally. Of these, BRISK-PS and BRISK-FL are main completed Phase III studies.

BRISK-FL was a multicenter, randomized, double-blind controlled study designed to compare the efficacy of brivanib alaninate and sorafenib as first-line treatment in patients with unresectable HCC. A total of 1,155 patients were recruited and randomized 1:1 to brivanib- or sorafenib-group. The study did not meet its primary objective of demonstrating non-inferiority in OS for brivanib alaninate compared to sorafenib (median overall survival was 9.5 months for brivanib alaninate and 9.9 months for sorafenib). The upper limit of 95% confidence interval (CI) around the hazard ratio (HR) didn't reached the preset non-inferiority boundary of 1.08 (HR: 1.06, 95% CI: 0.93 - 1.22, P=0.3730). In addition, there was no statistically significant difference in the median time to progression (TTP, 4.2 month vs 4.1 months, P = 0.85), objective response rate (ORR, 12% vs 9%, P = 0.057) and disease control rate (DCR, 66% vs 65%, *P*= 0.87) between the two groups. Data of TTP, ORR and DCR showed that the antitumor activity of brivanib alaninate was similar to that of sorafenib.

BRISK-PS is a multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy of brivanib alaninate and placebo as second-line treatment of unresectable HCC. A total of 395 patients were randomized in a 2:1 ratio to the brivanib alaninate group (n = 263) and the placebo group (n = 132). Compared with the placebo group, brivanib alaninate subjects showed improvement in the following response-related secondary endpoints: disease control rate (DCR) (71.2% vs 9.1%, P < 0.0001), ORR: 11.5% vs 1.9%, P = 0.0032, median time to progression (TTP): 4.2 months vs 2.7 months, P = 0.0001. However, it had no statistically significant difference in median OS between the two groups (9.4 months vs 8.2 months, *P* =0.3307). Although statistical analysis indicated that there was significant improvement in secondary endpoints, there was no statistically significant difference in the primary endpoint between the two groups. It is noteworthy that the proportion of patients with vascular invasion was higher in the brivanib alaninate-group (31%) vs 18% in placebo group. This imbalance in baseline disease characteristics may have confounded the results.

A total of 90 second-line HCC patients are enrolled in the ongoing phase II clinical study in China. As of June 2018, the interim analysis showed similar antitumor activity of brivanib alaninate among Chinese patients as compared with western patients, with the ORR of 8.3% and the median time to tumor progression (TTP) of 4.2 months in the 800 mg QD dose group (N = 36).

1.1.4.2.3 Safety

As of February 2019, a total of 2741 subjects (including 185 healthy subjects) have been treated with brivanib alaninate. A total of 14 Phase I studies, 2 Phase II studies, and 4 Phase III HCC studies have been completed, and 1 Phase II study is ongoing in China.

As a potent VEGFR inhibitor, the safety profile of brivanib alaninate reflects both class effects associated with VEGF pathway inhibition as well as AEs that are more specific to brivanib alaninate. Cumulatively calculated across all studies, the most frequently reported adverse events (> 25%) of any grade were: fatigue (54%), diarrhea (44%), anorexia (39%), nausea (35%), and vomiting (32%). The most commonly reported grade 3/4 adverse events (≥ 5%) across all studies were: fatigue (16%), ALT increased (9%), AST increased (7%), hypertension (5%), abdominal pain (5%), and diarrhea (5%).

Important identified risks (known class effect of compounds targeting the VEGF signaling pathway or identified risk in clinical studies) for Brivanib Alaninate include hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), hepatic events, hyponatremia, hypothyroidism, proteinuria, and arterial thrombotic events. Potential risks based on the mechanism of action of compounds targeting the VEGF signaling pathway or the safety profile of other VEGF inhibitors include: bleeding, venous thrombotic events, left ventricular dysfunction, gastrointestinal perforation, and impaired wound healing. (See Investigator's Brochure for a detailed list of clinical safety information.)

The important identified risks in clinical studies with brivanib alaninate are as follows:

Hepatic Events

The most common hepatic events were laboratory test abnormalities in liver enzymes (e.g. AST, ALT) and bilirubin. Since a majority of subjects treated with brivanib alaninate were reported with elevated liver enzymes or bilirubin (≥ CTCAE Grade 1), liver function should be monitored regularly throughout the study and dose interruption or reduction should be considered if abnormalities ≥ CTCAE Grade 3 occur.

As indicated by phase III studies in HCC patients, clinically important events of hepatic encephalopathy (4.6% vs.1.5%), hepatic failure (3.1% vs.1.5%), and acute hepatic failure (0.4% vs.1.5%), though slightly more common for brivanib alaninate than placebo, occurred infrequently.

Hypothyroidism

Hypothyroidism is a known event and risk in drugs with an anti-VEGFR inhibitory mechanism of action. In phase III studies of brivanib alaninate, hypothyroidism (all grades) was more commonly observed in the brivanib alaninate group than control group as indicated by reported AEs and TSH measurements > upper limit of the normal range; Grade 3/4 hypothyroidism events were infrequent (≤1%), and were rarely serious (< 1%), or required investigational drug discontinuation (< 1%).

Hyponatremia

Approximately one third of subjects treated with brivanib alaninate were reported with hyponatremia ≥ CTCAE Grade 1. CTCAE Grade 4 hyponatremia (Na < 120 mEq/L) occurred in 4% of subjects. The severity of hyponatremia is related to the degree of hepatic impairment in patients with cirrhosis.

Proteinuria

Proteinuria is a known class-effect of compounds targeting the VEGF signaling pathway. In phase III studies, the incidence of proteinuria was around 10% to 31% in the brivanib alaninate group, but few events (< 1%) were serious or led to investigational drug discontinuation.

Hypertension

Hypertension is a relatively common adverse event and was observed in 24% of subjects treated with brivanib alaninate. In addition, there is evidence of dose-effect, with hypertension reported in 21% of subjects taking 320 mg QD, 32% of subjects taking 800 mg QD, and 75% of subjects taking 1000 mg QD in clinical studies. Hypertension can be managed and treated by concomitant administration of antihypertensive drugs, dose interruption, and/or dose reduction. Through the management of hypertension, serious events of hypertension or discontinued cases from studies due to this AE were infrequently reported.

Reversible posterior leukoencephalopathy syndrome (RPLS)

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a syndrome characterized by headache, confusion, seizures and visual loss. It manifests as patchy brain tissue edema on brain MRI, and the symptoms tend to be self-limiting. Two SAEs of Grade 3 RPLS were reported during studies of brivanib alaninate, both of which were considered to be related to investigational drug, and 1 subject discontinued due to the event.

Arterial thrombotic events (ATEs)

Thromboembolic events are a known risk for drugs with anti-VEGFR mechanisms of action. Most ATEs in the HCC studies were reported as SAEs, most were considered related to study drug, and most subjects discontinued due to these events. The incidence of ATE was numerically higher in the brivanib alaninate group than the placebo group (5 subjects, 1.9%; compared to 1 subject in the placebo group, 0.8%).

1.2 Study Rationale and Risk/Benefit Assessment

1.2.1 Study Rationale

Although a variety of targeted anti-angiogenic drugs have been currently approved for the treatment of advanced HCC in China, the response rate of these drugs is relatively low and the prolongation of survival is limited. The available options for advanced ICCs are limited and the prognosis is very poor. The immune checkpoint inhibitors (anti PD-1/PD-L1 antibody) are expected to have better efficacy, but current data are limited given relevant studies are still ongoing. There is still no effective treatment or relevant study in patients who have progressed following immune checkpoint inhibitor treatment. Therefore, huge unmet medical demand for treatment of advanced liver cancer exists, and it is urgent to develop new treatments to effectively prolong patients' survival.

As an immune checkpoint molecule different from PD-1, LAG-3 also has immunosuppressive action[15]. Blockade of PD-1 and LAG-3 in animal tumor models enhanced antitumor immunity[16,17] via distinct, nonredundant signaling pathways that fostered the accumulation of functionally competent CD8+ T cells in mice. Specifically, dual targeting of PD-1 and LAG-3 may help reverse effector cell exhaustion, and increase the effectiveness of immunotherapy compared with that with single agents alone. LAG-3 positive tumor-infiltrating lymphocytes (TILs) were detected in different types of cancers in preclinical studies[18]. Internal data of Macrogenics indicated that LAG-3 was expressed in 100% (18/18) HCC samples detected through IHC, where 83.3% (15/18) were intermediate or high expression (intermediate expression is defined as 5 - 15 LAG-3 positive lymphocytes under 40X field of a microscope; high expression is defined over 15 LAG-3 positive lymphocytes), indicating LAG-3 immune inhibitory pathways may play an important role in hepatocellular carcinoma.

In the dose escalation period of the ongoing phase I, first-in-human study (CP MGD013-01) of MGD013 in patients with advanced neoplasms by Macrogenics, anti-tumor activity was observed in patients with triple negative breast cancer, pleural mesothelioma and gastric

cancer. One gastric cancer patient has progressed after receiving multiple lines of antitumor treatment including standard chemotherapy and nivolumab. Target lesions of the patient shrank by 24% at the end of the first cycle of treatment, by 76% at the end of the second cycle of treatment. The patient reached confirmed partial response, and continued the treatment. This preliminary revealed that MGD013 had antitumor effect and may be effective in cancer patients who failed prior immune checkpoint inhibitor treatment.

In recent years, except anti PD-1/PD-L1 antibody monotherapy, the combination of immune checkpoint inhibitors and anti-angiogenic agents has shown synergy in anti-tumor effect in a growing number of preclinical and clinical studies. In the tumor microenvironment (TME), elevated VEGF levels induce tumor-associated immunosuppression through the following mechanisms: 1) increased level of VEGF directly inhibits the migration, proliferation, and effector function of cytotoxic T lymphocytes (CTL); 2) VEGF inhibits the maturation and antigen presentation of dendritic cells, thus hindering the activation of T cells and T-cell-mediated anti-tumor immunity; and 3) high levels of VEGF promote the recruitment and proliferation of immunosuppressive cells, including T_{reg} cells, myeloid-derived suppressor cells (MDSCs), and M2-type tumor-associated macrophages (M2-like TAMs). 4) VEGF facilitates abnormal angiogenesis in tumors, leading to hypoxia and low pH in the tumor microenvironment, which further promotes local and systemic immunosuppression. Therefore, VEGF inhibitors can improve the immune microenvironment in tumors by inhibiting the above effects, being indicated by the normalization of tumor blood vessels, decreased number of abnormal blood vessels, and increased tumor-infiltrating lymphocytes (TIL), which in turn enhance the antitumor effect of immune checkpoint inhibitors[19].

This theory has been preliminarily verified in a number of clinical studies. The combination of VEGFR TKI and immune checkpoint inhibitor PD-1/PD-L1 antibody in clinical trials of advanced HCC has shown better efficacy than monotherapy. A phase Ib clinical study presented at the ESMO meeting in 2018 (NCT02715531) showed that the ORR (according to RECIST 1.1) of PD-L1 antibody atezolizumab in combination with a VEGF antibody bevacizumab as first-line HCC treatment (N = 68) was 34%, and the 6-month progression-free survival (PFS) rate was 71%. Other similar studies are being conducted both globally and in China, such as the study of SHR-1210 in combination with apatinib (RESCUE) and the study of pembrolizumab in combination with lenvatinib. Preliminarily data of these studies have verified the promising efficacy and acceptable safety of the combination of anti-angiogenic therapy and PD-1/PD-L1 antibody in HCC.

MGD013 is a LAG-3/PD-1 bispecific antibody and may have stronger antitumor effect than PD-1 monoclonal antibody. Brivanib alaninate is a dual tyrosine kinase inhibitor (TKI) of VEGFR and FGFR. A number of clinical trials in HCC have demonstrated similar anti-tumor activity of Brivanib to other medications with the same mechanism of action and an acceptable safety profile. On the basis of the above study data, it is expected that MGD013 monotherapy or co-administered with brivanib alaninate may have a better efficacy than PD-1 antibodies and, in particular, may be effective in patients who failed prior immune checkpoint inhibitor treatment. Therefore, the study will explore the safety and efficacy of MGD013 monotherapy or in combination with brivanib alaninate in HCC patients who failed prior immune checkpoint inhibitor treatment and those who did not receive prior immune checkpoint inhibitor treatment.

1.2.2 Dose Selection and Safety

In Phase I of the study, MGD013 monotherapy dose escalation will be conducted first in patients with advanced solid tumors at the following dose levels: 1 patient at 1 mg, 1 patient at 3 mg, 4 patients at 10 mg, 5 patients at 30 mg, 4 patients at 120 mg, 9 patients at 400 mg, 8

patients at 800 mg and 4 patients at 1,200 mg. In the dose escalation study of HCC cohort, the starting dose is 120 mg and has been escalated to 400 mg. The study is ongoing. In current study, 120 mg Q2W is the starting dose. Since 120mg Q2W has been tested and no obvious toxicity was observed in western patients with HCC, and a intermediate dose level of 240 mg is added between 120 mg and 400 mg, only single patient will be enrolled in the starting dose cohort.

Dose selection of antiangiogenic agents is an important consideration in combination therapy regarding to both safety and efficacy. Preclinical studies have suggested that[20], high dose of antiangiogenic drugs cause a reduction of blood vessels in tumors within a short period of time, resulting in further hypoxia and acidosis in the tumor microenvironment, and causing extracellular matrix deposition, which in turn promotes the infiltration of immunosuppressive cells. So high doses of antiangiogenic drugs may limit the effect of immunotherapy. By contrast, lower doses of anti-angiogenic drugs, such as one-fourth of the effective anti-angiogenic dose in animal studies, can improve the tumor immune microenvironment by inducing the normalization of tumor blood vessels and increasing tumor-infiltrating lymphocytes (TILs)[20,21].

Therefore, after 400mg q2w of MGD013 is clear, combination therapy cohort will be open and the dose of MGD 013 could be escalated to RP2D after the RP2D is determined Brivanib alaninate starts at a low dose and may escalate to higher doses. This design allows finding the optimal dose for combination treatment and reduces the safety risk posed by brivanib as well. Due to the different mechanisms of action and different safety profiles of the two drugs, no major overlapping toxicities are expected when they are used in combination. This has been preliminarily verified in the clinical studies with other combination of drugs in the same class. For example, in the phase Ib study of PD-L1 atezolizumab in combination with bevacizumab (NCT02715531), no novel emerging adverse reactions or additive toxicities beyond the toxicity of each single agent were observed. In the study of PD-1 monoclonal antibody SHR-1210 combined with apatinib (NCT02942329), the dose of SHR-1210 was fixed and the dose of apatinib escalated to its RP2D. Preliminary results of this study also suggested acceptable safety and tolerability profile of the combination, which further supports the toxicity of the combination is manageable.

In conclusion, the combination of brivanib alanine and MGD013 is expected to have synergistic activity and manageable toxicity in patients with HCC, indicationg by studies of check point inhibitor and anti-angiogenetic agent combinations, hence the risk-benefit ratio is likely to be favorable. Therefore, Zailab plans to conduct this phase I/II clinical study in Chinese patients with HCC.

2. Study Objectives

This study consists of two parts: Phase I is a dose escalation study to determine the recommended phase II dose (RP2D) of MGD013 monotherapy and that of MGD013 when in combination with ZL-2301 in subjects with advanced liver cancer (including hepatocellular carcinoma and intrahepatic cholangiocarcinoma); Phase II is a dose expansion study to assess the safety and efficacy of MGD013 monotherapy and MGD013 in combination with ZL-2301 in subjects with advanced hepatocellular carcinoma (HCC).

2.1 Objectives of Phase I study

2.1.1 Primary Objectives

- To assess the safety of MGD013 in subjects with advanced liver cancer (including hepatocellular carcinoma and intrahepatic cholangiocarcinoma);
- To determine the recommended phase II dose (RP2D) of MGD013 monotherapy in subjects with advanced liver cancer;
- To assess the safety of MGD013 in combination with brivanib alaninate (ZL-2301) in subjects with advanced liver cancer;
- To determine the recommended phase II dose (RP2D) of MGD013 when co-administered with brivanib alaninate (ZL-2301).

2.1.2 Secondary Objectives

- To assess the preliminary efficacy of MGD013 monotherapy and MGD013 in combination with brivanib alaninate in subjects with advanced liver cancer by investigator-assessed objective response rate (ORR) according to RECIST1.1 and irRECIST criteria respectively.

2.1.3 Exploratory objective

- To explore the correlation between MGD013/brivanib alaninate-related biomarkers and subject safety, antitumor activity.

2.2 Objectives of Phase II study (Part 1)

2.2.1 Primary Objectives

- To assess the safety of MGD013 monotherapy at RP2D in subjects with advanced HCC;
- To assess the safety of MGD013 at RP2D in combination with brivanib alaninate in subjects with advanced HCC;
- To assess the efficacy of MGD013 monotherapy and in combination with brivanib alaninate in subjects with advanced HCC, with blinded independent central review (BICR)-assessed ORR according to RECIST 1.1 as the primary efficacy endpoint.

2.2.2 Secondary Objectives

- To assess the secondary efficacy endpoints of MGD013 monotherapy and in combination with brivanib alaninate: investigator-assessed ORRs (inv-ORRs) according to RECIST 1.1 and irRECIST respectively, BICR-assessed ORR according to irRECIST, disease control rate (DCR), time to tumor progression (TTP), duration of response (DoR), progression-free survival (PFS), survival rate at 6, 9 and 12 months, overall survival (OS), etc.

2.2.3 Exploratory objective

- To explore the potential biomarker for MGD013/brivanib alaninate and its correlation with subject safety and antitumor activity.

2.3 Objectives of Phase II study (Part two)

2.3.1 Primary Objectives

- To assess the safety of the investigational drugs in subjects with advanced HCC who have previously failed immune checkpoint inhibitor treatment;
- To assess the efficacy of the investigational drugs in subjects with advanced HCC who have previously failed immune checkpoint inhibitor treatment, with BICR-assessed ORR according to RECIST1.1 as the primary efficacy endpoint.

2.3.2 Secondary Objectives

- To assess the secondary efficacy endpoints of the investigational drugs in subjects with advanced HCC: BICR-assessed ORR according to irRECIST, investigator-assessed ORRs (inv-ORRs) according to RECIST 1.1 and irRECIST respectively, disease control rate (DCR), time to tumor progression (TTP), duration of response (DoR), progression-free survival (PFS), survival rate at 6, 9 and 12 months, overall survival (OS).

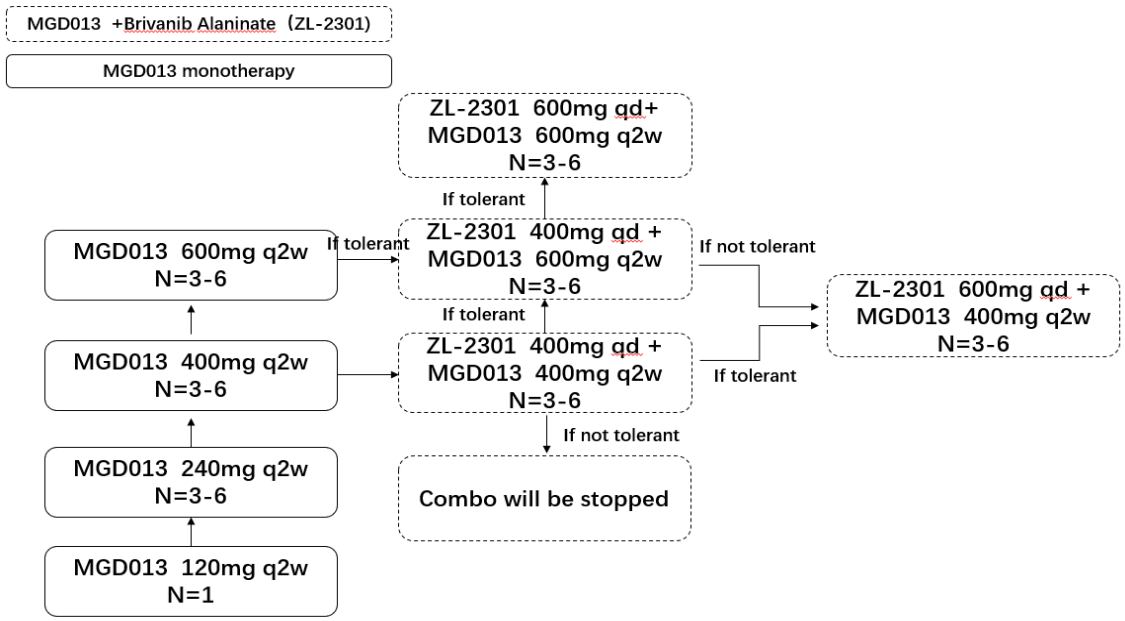
3. Study Design

3.1 Overall Design

This is a multicenter, open-label, Phase I/II clinical study, which will consist of two phases: the dose escalation study (Phase I) and the dose expansion study (Phase II). Phase II study will consist of two parts: Part 1 and Part 2.

3.1.1 Study Design of Phase I Study

Phase I study will enroll subjects with unresectable advanced HCC, intrahepatic cholangiocarcinoma and/or mixed hepatocellular-cholangiocarcinoma who have previously received at least first-line systematic treatment and recurred/not toraltable to the treatment. The dose escalation study of MGD013 monotherapy will be first conducted. After MGD013 400mg Q2w as monotherapy is clear, the dose escalation study of the combination therapy will be conducted. The schematic diagram of the study is shown as below:



MGD013 monotherapy

In Phase I study, the dose escalation study of MGD013 monotherapy will be first conducted. After determining RP2D of MGD013 monotherapy, the dose escalation study of the combination therapy will be conducted. During dose escalation study of monotherapy, the starting dose of MGD013 will be 120 mg Q2W in single subject. If no ≥ Grade 2 drug-related adverse event occurs in the DLT observation period within 28 days after the first dose, the dose may escalate sequentially. The subsequent dose groups will adopt traditional 3+3 design. If adverse events of CTCAE Grade 2 or above related to the drug are observed in the subject of the starting dose group, the study will convert to traditional 3+3 escalation scheme, and at least another 2 evaluable subjects will be enrolled in the dose group. The dose of MGD013 monotherapy will be escalated to 240 mg Q2W, 400 mg Q2W and until 600 mg Q2W successively.

MGD013 + Brivanib Alaninate (ZL-2301)

The combination therapy will be initiated after the MGD013 400mg Q2w is clear. The combination dose of MGD013 could be escalated to RP2D of MGD013 after determining.

Dose escalation study of the combination therapy will adopt traditional 3+3 dose escalation scheme; the dosage of Brivanib will start from 400 mg once daily (QD), and may escalate to 600 mg QD and a maximum of 800 mg QD (if possible). Two points should be noted: one is the combination dose of MGD 013 600mg Q2w +brivanib 400mg qd can be opened after both monotherapy RP2D of 600mg Q2w is determined and the starting dose of combination therapy is tolerant; the other is combination dose of MGD013 400mg Q2w + brivanib 600mg qd could be further explored once the starting dose of combination therapy is tolerant and the dose of MGD013 600mg Q2w+brivanib 400mg qd is not tolerant.

While two or more subjects experience DLT in the starting dose group of the combination therapy, the combination dose level escalation will be terminated, and Phase II dose-extension study will be conducted with MGD013 alone. Phase II dose-expansion study will be conducted with MGD013 alone.

The group of combination RP2D should enroll at least 6 evaluable subjects.

Definition of evaluable subject

An evaluable subject is defined as a subject who received ≥ 75% of pre-specified total dose of MGD013 and brivanib alaninate (combination treatment cohort) within the first two cycles (28 days) and has completed primary safety evaluation, **or** experiences DLT at any time within 28 days.

A cycle lasts for two weeks (14 days) in the study, and the first two cycles are the DLT evaluation period. Provided that 3 or 6 evaluable subjects in one dose group have completed the first two cycle evaluation and the dose escalation criteria is met, subsequent dose cohort is open to enroll. There will be no intra-subject dose escalations. Unevaluable subjects in Phase I will be replaced until at least 3 evaluable subjects are enrolled in each dose group. Approximately 30 ~ 43 evaluable subjects will be enrolled. The total number of subjects will depend upon the number of dose levels.

Subjects will continue treatment until disease progression, death or the occurrence of intolerable toxicity, whichever comes first. MGD013 will be used for at most 48 cycles. Subjects receiving combination therapy can continue using brivanib alaninate if there is still no disease progression after discontinuing MGD013.

3.1.2 Dose Escalation Rules

During dose escalation study of monotherapy, the starting dose of MGD013 will be 120 mg Q2W with single subject in this dose cohort. If no ≥ Grade 2 drug-related adverse events occur during the DLT observation period within 28 days after the first administration, the dose may escalate sequentially. The subsequent dose groups will adopt traditional 3+3 dose escalation scheme. If adverse events of CTCAE Grade 2 or above related to the drug are observed in the subject of the starting dose group, the study will convert to traditional 3+3 scheme for all dose groups, and at least another 2 evaluable subjects will be enrolled in starting dose group.

The study will not proceed with the 3+3 design in case of the following drug-related adverse events, that is, only one subject enrolled in the starting dose group:

- Grade 2 anemia
- Grade 2 endocrinopathy that is well controlled with hormone replacement therapy
- Grade 2 nausea, vomiting, dyspepsia, diarrhea or constipation that resolve to grade

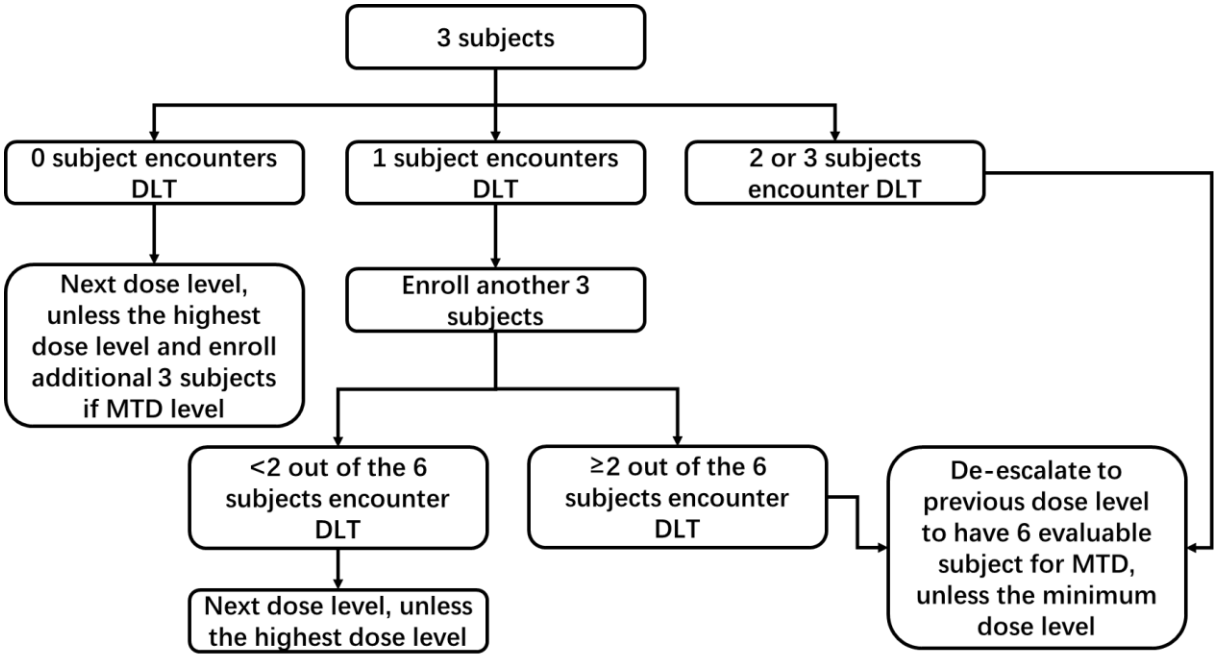
1 or baseline within 48 hours after medical intervention

- Grade 2 fatigue that resolves to grade 1 within 4 days
- Grade 2 fever or flu-like syndrome that resolves to grade 1 or baseline within 24 hours after medical intervention
- Grade 2 infection that resolves to grade 1 or baseline within 72 hours after medical intervention
- Grade 2 lymphocytes or neutrophils decreased
- Grade 2 amylase or lipase increased that resolves to Grade 1 or baseline within 72 hours
- Grade 2 electrolyte disturbance that resolves to Grade 1 or baseline within 72 hours after medical intervention
- Grade 2 cancer pain
- Grade 2 headache, cough and shortness of breath that resolve to grade 1 or baseline within 24 hours after medical intervention

Except the starting dose group of monotherapy, other dose groups and combination therapy groups will adopt traditional 3+3 dose escalation scheme. Dose escalation follows the following principles:

- If no dose-limiting toxicity (DLT) is observed in a cohort of at least 3 evaluable subjects then dose escalation may occur;
- If one subject experiences a DLT in a group of 3 evaluable subjects, then the cohort will be expanded to include 3 evaluable subjects. If only one DLT is observed in the complete cohort of 6 evaluable subjects, then dose escalation may occur;
- If 2 or more subjects experience a DLT in a group of up to 6 subjects, dose will be de-escalated to prior dose level and more subjects may be enrolled until there are 6 evaluable subjects in this dose group.
- If 2 or more subjects in the lowest-dose group experience a DLT during MGD013 monotherapy, the study will be terminated;
- If 2 or more subjects experience DLT in the starting dose group of the combination therapy (MGD013 400mg q2w+brivanib 400mg qd), the combination dose level escalation will be terminated.
- The dose of MGD013 and brivanib alaninate will not exceed 600mg Q2W and 800mg QD (monotherapy MTD).
- RP2D dose groups of the monotherapy and combination therapy should at least enroll 6 evaluable subjects.

The 3+3 dose escalation scheme is shown below.



3.1.3 Dose-Limiting Toxicity (DLT)

DLT was defined as the following adverse events (AEs) occurring within 4 weeks (the first 2 cycles, 28 days) after the investigational drugs which is at least possibly related to the study drugs:

- Hematologic Adverse Events:
  - Grade 4 neutropenia lasting ≥5 days;
  - Febrile neutropenia lasting > 48 hours or any febrile neutropenia with hemodynamic instability or an objective evidence of infection;
  - Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with obvious hemorrhage;
  - ≥ Grade 3 haemolysis
- Non-hematological adverse events:
  - ≥ Grade 3 gastrointestinal reactions and electrolyte abnormal, e.g., nausea, vomiting, diarrhea constipation and abdominal pain that persist (more than 72 hours) despite an adequate medical intervention;
  - Sustained /repeated ≥3 grade hypertension which recurred despite sufficient medical interventions (BP ≥ 150/100 mmHg means 2 measurements taken at least 24 hours (h) apart ≥ 150/100 mmHg, taken after the subject had been seated/lying quietly for 10 minutes. At least 1 week was taken to evaluate subject's response to a change in antihypertensive medication (initiation or increase in anti-hypertensive medication). Once stabilized on antihypertensives, for 1 week, a subsequent episode of ≥150/100 was to be considered the "second event").
  - Other ≥ Grade 3 non-hematological toxicity, excluding:
    - Alopecia;
    - Grade 3 infusion-related reaction or cytokine release syndrome (CRS) that resolves after medical intervention within 12 hours

- Grade 3 fever that lasts < 72 hours and is not associated with hemodynamic compromise
- Grade 3 fatigue that lasts < 72 hours
- Grade 3 skin toxicity that resolves to ≤ Grade 2 within 14 days of initiation of oral corticosteroids
- Grade 3 endocrinopathy that is well controlled with hormone replacement therapy
- Grade 3 amylase or lipase increased without clinical or radiographic evidence of pancreatitis
- Grade 3 tumor inflammatory reaction (local inflammatory response at tumor or metastasis focuses attributed to an antitumor effect of drug, e.g., swelling, pain, fever) that resolves to ≤ Grade 2 within 7 days

➢ ≥ Grade 2 ocular pain or vision decreased that does not resolve to Grade 1 by topical therapy within 14 days, or that requires systemic treatment;

➢ Hepatic dose-limiting toxicity:

- For subjects with ≤ grade 2 baseline transaminases increased (≤ 3 × ULN):
  - Transaminases increased > 8 × the upper limit of normal (ULN);
  - Grade 3 elevated total bilirubin (> 5 × ULN);
  - Transaminases increased (5 × ULN to 8 × ULN) that does not resolve to Grade 2 within 7 days and Grade 1 or baseline within 14 days. Oral steroids must be tapered to ≤ 10 mg of prednisone or equivalent dose within14 days.
  - Increased total bilirubin (3× ULN to 5× ULN) that does not resolve to Grade 2 within 7 days and Grade 1 or baseline within 14 days. Oral steroids must be tapered to ≤ 10 mg of prednisone or equivalent dose within 14 days.
- For subjects with Grade 2 baseline transaminases increased (3 × ULN to 5 × ULN), the DLT is defined as:
  - Elevation of one or more transaminases (> 10 × ULN) with increased total bilirubin (≥ 1 grade, for example: Grade 0 to 1, or Grade 1 to 2);
  - Elevation of one or more transaminases (> 10 × ULN) that does not recover to Grade 2 with steroids within 14 days or that requires another immunosuppressive agent.
  - Elevation of one or more transaminases (> 15 × ULN);
  - Grade 3 increased total bilirubin (> 5 × ULN).

➢ Any other adverse events which in the judgment of the investigator required discontinuation from the study.

Definition of maximum tolerated dose (MTD)

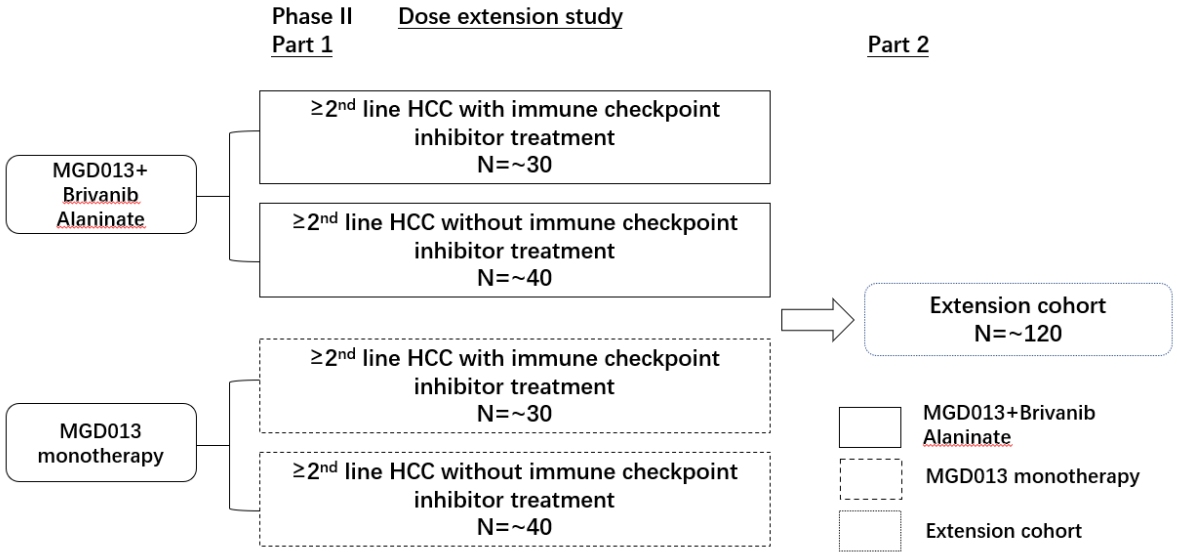
It is defined as the maximum dose at which <33% subjects suffer from DLTs; if 2 or more DLTs occur in a certain dose group, this dose is considered as intolerable, its prior dose level is defined as the maximum tolerated dose (MTD). There must be at least 6 evaluable subjects in the MTD dose group.

In Phase I dose escalation period, the **Safety Review Committee** (SRC) will decide whether to escalate to the next dose level or discontinue the escalation after reviewing the data from each dose group.

3.1.4 Design of Phase II study

In the Phase II dose expansion study, Part 1 will enroll two cohorts, MGD013 monotherapy and MGD013 in combination with brivanib alaninate. After determining the RP2D of MGD013 monotherapy, dose expansion study of monotherapy will be conducted **without** waiting for the completion of the dose escalation study of the combination treatment. Subjects of the combination therapy cohort will be enrolled after determining the RP2D of combination therapy in Phase I study.

Schematic diagram of the study:



Each cohort will enroll approximately 30 evaluable advanced HCC subjects who progressed after immune checkpoint inhibitor treatment, and approximately 40 evaluable advanced HCC subjects who have not previously received immune checkpoint inhibitor treatment. The SWOG two-stage design will be employed. In the first stage, 20 advanced HCC subjects who have not previously received immune checkpoint inhibitor treatment will be enrolled. If response is observed in 3 or more subjects (according to RECIST 1.1), the enrollment of second stage will be open and an additional of 20 evaluable subjects will be enrolled. The enrollment of advanced HCC subjects who have previously received immune checkpoint inhibitor treatment will be similar, there are 2 stages for the group and the response (according to RECIST 1.1) of 1 and more out of 15 evaluable subjects at the first stage will support the decision to proceed to the second stage of subject accrual until there are 30 evaluable subjects in this group. If the response in any treatment group is found less than the above standard in the first period, the enrollment of second stage will be terminated.

In Phase II study, 2 weeks (14 days) will be defined as a cycle, and subjects will continue to receive study treatment until disease progression (according to irRECIST), death or the occurrence of intolerable toxicity (whichever comes first). MGD013 will be administered for

at most 48 cycles. If subjects do not have disease progression after discontinuing MGD013, subjects of the combination therapy group may continue brivanib alaninate.

Phase II Part 2 will expand the cohort study according to the safety and efficacy data obtained in Part 1. When at least 6 responders are observed among 30 evaluable patients (observed ORR=20%) in the post checkpoint inhibitor cohort in Part 1, the enrollment of Part 2 will be initiated. The treatment (MGD013 monotherapy or MGD013 in combination with Brivanib) that meets above criteria will proceed to Part 2. If both monotherapy and combination therapy achieve at least 6 responders in the post checkpoint inhibitor cohort, the decision of which treatment to proceed to Part 2 depends on the totality of safety and efficacy data from Part 1, and will be made by Safety Review Committee (SRC) after reviewing the data. About 120 advanced HCC subjects who have progressed following immune checkpoint inhibitor treatment will be enrolled to further assess the safety and efficacy of the study treatment. Decision on the study treatment (MGD013 monotherapy or in combination with brivanib alaninate) in Part 2 will be made by the sponsor according to the obtained data from Part 1.

The primary efficacy endpoint in Phase II study is BICR-assessed ORR according to RECIST1.1. Investigators will also evaluate objective anti-tumor efficacy and disease progression based on target lesions, non-target lesions and new lesions according to RECIST 1.1 and irRECIST criteria. The radiological responses that determine whether treatment groups in Part 1 will enter the second period after the completion of the first period of the study will be evaluated by investigators according to RECIST1.1. **The subjects will be managed and evaluated for a disease progression that requires the discontinuation of the investigational drug by the investigators preferably according to irRECIST.**

3.2 Discussion of Study Design

3.2.1 Dose Selection for Phase I Study

In Phase I of the study, MGD013 monotherapy dose escalation will be conducted first. MGD013 is a humanized PD-1 + LAG-3 bispecific, tetravalent diabody DART® molecule consisting of Fc domains, engineered as a hinge-stabilized IgG4 molecule and is designed to concomitantly bind PD-1 and LAG-3. As of November 2018, in the Phase I dose-escalation study (CP-MGD013-01), 36 patients with different types of solid tumors were administered MGD013 at a dose ranging from 1 mg to 1,200 mg Q2W, while single-patient dose escalation was adopted at dose levels of 1, 3 and 10 mg and 3+3 design was adopted at dose levels of 30 mg, 120 mg, 400 mg, 800 mg and 1,200 mg. They are generally well tolerated by the patients. Preliminary data indicated that the safety profile of MGD013 was similar to that of known immune checkpoint inhibitors. The common AEs included constipation, fatigue, nausea, infusion-related reaction, fever, abdominal pain, diarrhea, vomiting, chills, dyspnea, joint pain, back pain, blood creatinine increased, hyponatremia, headache, cough, rash and itching. Most treatment-related AEs were mild to moderate (i.e. Grade 1 or 2). Seven (19.4%) experienced at least one grade 3 treatment-related AE. No grade 4 or 5 treatment-related AEs occurred. Of the first 3 treated patients in the 1,200 mg dose cohort, 1 experienced a SAE and immune-mediated hepatitis meeting DLT criteria; 3 more patients were enrolled at the dose level and completed DLT evaluation period, without new DLTs; It did not reach the MTD (1,600 mg specified in the protocol), which would not be adopted. Therefore, the cohort of 1,200 mg became the maximum dose level in the study CP-MGD013-01. While evaluating the dose level of 1,200 mg in the dose escalation period, MacroGenics will further evaluate 600 mg Q2W in the dose expansion period.

MacroGenics chose 120 mg Q2W as the starting dose in HCCs for dose escalation. None of the 3 patients experienced DLT at the starting dose. As of April 1, 2019, enrollment of the

dose group of 400 mg Q2W has been started. In this study, 120 mg Q2W was also used as the starting dose in one HCC patient since it has been validated safe in overseas studies, and a dose level of 240 mg was added between 120 mg and 400 mg. If no ≥ grade 2 drug-related adverse reactions occurred, it can be escalated to the next dose level. It will not be more than the RP2D (600 mg Q2W) that has been confirmed in other dose escalation studies of solid tumors for the monotherapy dose escalation.

After determining the RP2D of MGD013 monotherapy, it will be co-administered with brivanib alaninate at that RP2D. A multicenter, phase I, open-label clinical trial of brivanib alaninate (CA182002) is a dose escalation study in patients with tumors. In Part 1 of the study, the starting dose of brivanib alaninate was 180 mg, and the dose sequentially escalated to 320, 600, 800, and 1,000 mg once daily. Two DLTs (Mental disorder and grade 3 fatigue) occurred in the 1,000 mg group. Therefore, 800 mg QD was established as the maximum tolerated dose (MTD) of brivanib alaninate. 800 mg QD will be used in subsequent studies. In combination therapy of the study, the starting dose of brivanib alaninate is as low as 400 mg QD, to lower the risks of subjects. If the first dose is safe and well tolerated when in combination with MGD013, the dose may escalate sequentially to 600 mg, and 800 mg (if possible). If ≥2 patients experience a DLT in the first dose group of the combination therapy when MGD013 is administered at RP2D with brivanib alaninate (400mg QD), the dose of MGD013 will be de-escalated to the next level at which it will be combined with brivanib alaninate (400 mg QD). If there are still ≥ 2 DLTs, it indicates that there is a toxic multiply and the study will be terminated, and Phase II dose-extension study will be conducted with MGD013 alone.

3.2.2 Study Patient Population

In current clinical practice in China, the medications that are used as the first-line treatment of advanced HCC include: VEGFR TKIs, such as sorafenib, lenvatinib, or systemic chemotherapy with oxaliplatin-based single agent or in combination with other agents, such as the FOLFOX4 regimen. Other options include systemic oxaliplatin-based chemotherapy in combination with sorafenib, or arsenious acid chemotherapy, or traditional Chinese medicine. Immune checkpoint inhibitors (for example anti-PD-1 antibody nivolumab) were conditionally approved by the US FDA as the treatment of HCC patients who have progressed after sorafenib treatment. These drugs have not been approved in China for indications of HCC, but they have been widely used in clinical studies or off-label treatments.

Intrahepatic cholangiocarcinoma (ICC) is a rare malignant tumor which arises from the epithelial cells of intrahepatic bile ducts. The incidence of ICC is reported to be only about 10% of primary liver cancers. Unresectable advanced ICCs are usually treated by chemotherapy agents, such as 5-fluorouracil with leucovorin, gemcitabine as a single agent, or gemcitabine plus cisplatin, irinotecan, or capecitabine. For non-resectable cases, the prognosis is very poor and overall mean duration of survival is less than 6 months. Combining lenvatinib (Lenvima) with PD-1 inhibitors showed promising efficacy in patients with advanced intrahepatic cholangiocarcinoma (ICC) who have failed prior treatments with an ORR of 21.4% (3/14) and a median PFS of 5.0 months, according to preliminary data from a single-center study [22] reported at the 2018 Gastrointestinal Cancers Symposium.

In Phase I of the study, besides HCC subjects who progressed after or were intolerant to toxicity of one or more systemic treatments, ICC or mixed HCC-ICC subjects will be also enrolled to explore the initial efficacy of monotherapy or combination therapy in these subjects. These subjects may receive prior first-line or above immune checkpoint inhibitor treatment, VEGFR inhibitors or systemic chemotherapy.

Phase II Part I will only enroll HCC subjects. Study population in the HCC cohort that has failed prior immune checkpoint inhibitors has radiologically confirmed disease progression following anti-PD-1 antibody, anti-PD-L1 antibody or CTLA-4 antibody that have been approved or are in the clinical research & development period. These subjects can only be previously treated with first-line immune checkpoint inhibitors, e.g., PD-1/PD-L1 antibody monotherapy, PD-1/PD-L1 antibody in combination with anti-CTLA-4 antibody or one targeted antiangiogenic drug, or systemic chemotherapy. The molecular targeted antiangiogenic drugs and chemotherapeutic drugs are only allowed to be co-administered. In the cohort that has not previously treated with immune checkpoint inhibitors, subjects have failed or are intolerant to toxicities of targeted antiangiogenic drug and/or systematic chemotherapy without receiving PD-1/PD-L1 antibody or CTLA-4 antibody and other immune checkpoint drugs. Phase II Part 2 will only enroll HCC subjects who have previously treated with immune checkpoint inhibitors to further evaluate the efficacy and safety of the investigational drugs in these subjects.

3.2.3 Selection of Efficacy Endpoints

The primary efficacy endpoint of the phase II study was objective response rate (ORR) according to RECIST 1.1. Secondary endpoints included ORR, TTP, PFS, OS, etc. according to irRECIST for immunotherapy, which could provide supportive evidence for clinical benefit.

Current radiologic evaluation criteria that can be applied to HCC include RECIST 1.1 criteria, mRECIST criteria, and irRECIST criteria for immunotherapy. Primary phase III clinical studies of immunotherapy in HCC adopted the RECIST 1.1 criteria (e.g., Checkmate-040 study, study of Atezolizumab in combination with Bevacizumab). The mRECIST criteria have not been fully validated for immunotherapy. Therefore, the ORR assessed according to RECIST 1.1 criteria was used as the primary efficacy endpoint for comparing with other studies. Provided that the characteristics of immunotherapy have been fully considered and a better rationality than RECIST 1.1 in terms of subject management (e.g., discontinuation of investigational drugs after reaching PD), it should be subject to irRECIST in case of investigator-assessed progressive disease and discontinuation of the investigational drugs.

4. Study Population

4.1 Inclusion criteria

1. Subjects who voluntarily sign the informed consent form (ICF);
2. Male or female subjects who are aged 18-75 years old;
3. Subjects with histologic, cytologic or clinical confirmed diagnosis of advanced HCC (phase I could include intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma), and are not suitable for surgery or loco-regional therapy or have progressed following surgery and/or loco-regional therapy;
4. Subject who has at least one measurable lesion according to RECIST v1.1 criteria.
5. Phase I study: subjects who have previously received at least one line of systematic therapy, including immune checkpoint inhibitors, molecular targeted drugs or systematic chemotherapy, alone or in combination, and failed (progression confirmed by imaging) or were intolerant at the discretion of investigator;

   Phase II Advanced HCC cohort with subjects who have previously received immune checkpoint inhibitor treatment: subjects who have failed (progression confirmed by imaging) prior first-line immune checkpoint inhibitor treatment, including anti-PD-1 antibody/anti-PD-L1 antibody and / or anti-CTLA-4 antibody, and/or molecular targeted therapy or systematic chemotherapy (monotherapy or in combination);

   Phase II Advanced HCC cohort with subjects who have not previously received immune checkpoint inhibitor treatment in Phase II study: subjects who have failed (progression confirmed by imaging) or were intolerant to (at the discretion of investigator) previous molecular targeted therapy or systematic chemotherapy, without receiving immune checkpoint inhibitor treatment (including anti-PD-1 antibody, anti-PD-L1 antibody, anti-CTLA-4 antibody, and bispecific antibodies including the above targets).
6. Previous anti-tumor therapy must be completed no less than 2 weeks prior to the study treatment and all adverse events related to previous treatment must have recovered to CTCAE Grade $\leqslant$1; if subjects who have received prior immune checkpoint inhibitors have immune-related endocrinopathy, it should be controlled with hormone replacement therapy.
7. Phase I: cirrhotic status of Child-Pugh Class A; Phase II: cirrhotic status of Child-Pugh Class A or B with a score of 7;
8. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1.
9. Subjects with life expectancy $\geqslant$12 weeks;
10. Subjects with chronic HBV infection must have HBV-DNA <500 IU/ml, and have received at least 14 days of anti-HBV treatment (e.g. entecavir, tenofovir) prior to the initiation of study treatment and are willing to receive antiviral treatment throughout the study; Antiviral therapy is not required for patients with HCV infection and the elevation of their liver enzymes must not exceed the level of CTCAE Grade 1;
11. Adequate organ function as outlined below:
    (1) Blood system function (subjects must have not received blood transfusion or stimulating growth factors within 14 days prior to screening test): neutrophil count $\geqslant 1.5\times10^9$/L, platelet count $\geqslant$ 75×10^9/L, hemoglobin $\geqslant$ 90 g/L;
    (2) Liver and kidney function (no albumin transfusion within 14 days prior to

screening test): serum total bilirubin ≤ 2.5×ULN, serum albumin ≥ 29 g/L, ALT and AST ≤ 5×ULN; serum creatinine ≤1.5×ULN or eGFR (Cockcroft-Gault formula) ≥ 60 ml/min;

(3) Coagulation function: international normalized ratio (INR)≤2.3 or prothrombin time (PT) of ≤ 6 seconds above control;

(4) Left ventricular ejection fraction (LVEF) ≥50% by two-dimensional echocardiography.

12. Female subjects (except for females who have underwent surgical sterilization and those have been menopausal for more than one year) who are of childbearing potential are required to adopt a medically acceptable contraceptive measure (such as intrauterine device, contraceptive pill or condom) throughout the study and up to 120 days after the last dose of investigational products; females must have negative serum or urine HCG tests within 7 days prior to enrollment; female subjects must not be breastfeeding; male subjects whose partners are of childbearing potential should use effective contraceptive methods throughout the study and up to 120 days after the last dose of investigational product.
13. Subjects who are willing to provide oncological tissues (if applicable) for biomarker test.

4.2 Exclusion criteria

1. Subjects who have known fibrolamellar carcinoma of liver for phase I and subjects who have fibrolamellar carcinoma, mixed HCC- cholangiocarcinoma or cholangiocarcinoma for phase II;
2. Subjects with brain metastasis or leptomeningeal metastasis confirmed by brain MRI during screening period;
3. Subjects with a diagnosis of other malignant tumors within 5 years prior to first administration, except for skin basal cell carcinoma, skin squamous cell carcinoma and/or in situ cancer following radical resection;
4. Subjects who had liver or other sites loco-regional treatment (including transcatheter arterial chemoembolization (TACE), transcatheter arterial embolization (TAE), hepatic artery infusion (HAI), local radiotherapy, radioembolization, radiofrequency ablation, cryoablation or percutaneous ethanol injection) , or who had major surgery of liver or other sites within 4 weeks prior to first administration, or had minor surgical procedures (such as simple excision, tooth extraction, etc.) within one week prior to first administration, or had received palliative radiotherapy for bone metastasis within 2 weeks and radiotherapy-related toxicity ≥ CTCAE Grade 2.
5. Subjects who have moderate or severe ascites (detected by B-ultrasound or CT), or require therapeutic abdominal paracentesis or drainage;
6. Subjects with a history of hepatic encephalopathy;
7. Subjects with a history of unhealed wounds or ulcers or bone fractures within 3 months prior to study treatment
8. Subjects who plan to have or had allogenic organ or bone marrow transplantation
9. Subjects who are at increased risk of bleeding or have history of thrombosis:

(1) Clinically significant bleeding within 3 months prior to screening or clear bleeding

tendency;

(2) Gastrointestinal hemorrhage within 6 months prior to screening or clear tendency of gastrointestinal hemorrhage;

(3) Arterial/venous thromboembolic events within 6 months prior to screening, such as cerebrovascular accident (including transient ischemic attack), pulmonary embolism, etc.;

(4) Require anticoagulation therapy with an agent such as warfarin or heparin;

(5) Require chronic anti-platelet therapy (such as aspirin≥100 mg/day, clopidogrel, etc.);

10. Subjects who have clinically significant cardiovascular diseases:

(1) NYHA (New York Heart Association) stage 3 and 4 congestive heart failure;

(2) Unstable angina pectoris or newly diagnosed angina pectoris or myocardial infarction within 12 months prior to screening;

(3) Arrhythmias requiring medications other than β-blockers;

(4) Valvular heart disease of ≥ CTCAE Grade 2;

(5) Hypertension inadequately controlled by drugs (systolic pressure >150 mmHg or diastolic pressure >90 mmHg);

11. Subjects who have history of symptomatic pulmonary fibrosis, interstitial pneumonitis, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis, or severe impairment of pulmonary function, or other suspicious pulmonary diseases that may interfere with drug-related pulmonary toxicity detection and treatment

12. Subjects who have suffered active bacterial or fungal infections requiring systematic treatment within 7 days prior to screening; or active tuberculosis;

13. Subjects with active co-infection of Hepatitis B and C, confirmed by positive HBV surface antigen or HBV DNA and HCV RNA;

14. Subjects who have any active, known or suspected autoimmune disease

15. Subjects with a condition requiring systematic treatment with corticosteroids (>10 mg/day prednisone or equivalent) or other immunosuppressive drugs within 14 days before administration of the investigational drug. In the absence of active autoimmune diseases, inhalation or topical use of steroids (>10 mg/day prednisone or equivalent) is allowed;

16. Other laboratory abnormalities:

(1) Hyponatremia, hypokalemia or hypophosphatemia that have occurred before the first administration, and failed to restore to normal level after electrolyte supplementation therapy;

(2) Confirmed diagnosis of thyroid dysfunction, which cannot be maintained within normal range following thyroid hormone replacement therapy;

(3) Positive Human immunodeficiency virus (HIV) test;

17. QTc interval >480 ms on two consecutive ECGs;

18. Female subjects during pregnancy or lactation; female subjects of childbearing potential or male subjects who are not willing to use contraception or contraceptive measures

during the study;

19. Subjects who have previously received two lines and above tumor immune checkpiont inhibitor treatment, mainly including anti-PD-1, anti-PD-L1 and anti-CTLA-4 antibodies, etc, or bispecific antibodies including the above targets, or received anti-LAG-3 antibody; whether subjects who have previously received other tumor immunotherapy can be enrolled should be determined by the sponsor;
20. Known or suspected history of severe allergy to investigational drugs;
21. Subjects who have received live attenuated vaccines or any investigational drugs that have not been marketed in China within 4 weeks prior to first administration;
22. If subjects who have previously used immune checkpoint inhibitors (such as anti-PD-1, anti-PD-L1, anti-CTLA-4 antibodies) have the following adverse events related to immune checkpoints, they will be not suitable for inclusion regardless of recovered or not:
    a) ≥ Grade 3 eye-related adverse events
    b) Grade 4 abnormal liver function
    c) ≥ Grade 3 neurotoxicity
    d) ≥ Grade 3 colitis
    e) ≥ Grade 3 renal toxicity
    f) ≥ Grade 3 pneumonitis
23. Subjects who are not suitable for inclusion as judged by the investigators.

4.3 Discontinuation of Subjects from Treatment

4.3.1 End of Treatment

Subjects may discontinue treatment at any time during the study. End of Treatment Visit (EOT) should be performed within 7 days of decision date to discontinue treatment.

Study drug shall be permanently discontinued in any of the following cases:

- Adverse Event
    - Occurrence of any CTCAE (V5.0) grade 3 or 4 treatment-related adverse event, which fails to recover to CTCAE Grade 1 or below within 4 weeks (28 days) (unless the investigator believes that the subject may continue to benefit from treatment and the continuation requires the permission from sponsor's medical monitor);
    - CTCAE Grade 3 or 4 treatment-related adverse event recurs in combination treatment group despite dose reduction of brivanib alaninate;
    - Myocardial ischemia and/or infarction;
    - Evidence for abnormal cardiac valve function ≥ CTCAE Grade 2;
    - LVEF decrease by > 10% from baseline-ECHO and LVEF < 45%;
    - QTc > 500 milliseconds on 3 consecutive ECGs performed during the same visit and in the absence of possible causes other than study therapy;

- Torsade de pointes or sustained ventricular tachycardia;
- Hemorrhage ⩾ CTCAE Grade 3;
- Gastrointestinal perforation;
- Arterial thromboembolic event;
- Venous thromboembolic events of CTCAE Grade 3 or 4;
- Hypertensive crisis;
- Immune-related adverse events of grade 4.

- Disease progression according to irRECIST criteria
- Risk to the subject as judged by the investigator and/or sponsor
- Critical violation to the protocol as judged by the investigator and/or sponsor
- Subject's decision
- Pregnancy
- Death
- Completion of protocol-defined therapy (MGD013 monotherapy)

If the reason for treatment discontinuation is not disease progression, death, withdrawal of informed consent or loss to follow-up, radiologic tumor assessments will still be performed at protocol-specified intervals until disease progression by irRECIST or the starting of subsequent antitumor therapy (Phase II).

4.3.2 End of Study

Patients who are no longer on treatment but are still followed on the study can be terminated from the study for the following reasons:

- Death
- Lost to follow up
- Withdrawn of consent
- The study is terminated

5. Study Treatment

5.1 Investigational Products

Investigational products of this study are shown in the table below:

Table 2. Investigational Products for Clinical Study

Name of investigational drug	Brivanib alaninate Tablets	MGD013 injection
Appearance	Light yellow to yellow biconvex oblong film-coated tablets	Sterile injection
Strength	200mg	300 mg/15 mL
Administration route	Oral administration	Intravenous infusion

Brivanib alaninate is given orally at the dose according to subject's dose group once daily at a fixed time, and can be taken with or without meals; If subject vomits after a dose or misses a dose, additional dose should not be taken on the same day.

In the dose escalation period, the starting dose of MGD013 was 120 mg IV on day 1 of each cycle, once every two weeks; the dose sequentially escalated to 240 mg, 400 mg and 600 mg IV, Q2W; MGD013 may be administered at a level or frequency beyond the above examples according to safety data obtained from the study and other studies.

Before intravenous infusion, MGD013 at each dose level must be diluted with 0.9% sodium chloride injection, USP (normal saline) 100 mL or 250 mL of infusion bags. The final concentration of MGD013 for infusion after dilution with normal saline must be between 0.12 mg/mL and 6.4 mg/mL. It is administered for 60 - 75 minutes. A 0.2 μm sterile and pyrogen-free inline filter made of polyether sulfone (PES) with a low protein-binding rate must be adopted for IV infusion since there may be visible semi-transparent protein particles in the solution.

5.2 Infusion preparation

5.2.1 General Guidelines and Precautions

MGD013 should not be administered as an IV push or bolus. All doses of MGD013 will be diluted in normal saline and administered as an IV infusion with a commercially available infusion instructions, see Pharmacy Manual for details. The final concentration of MGD013 for infusion after dilution with normal saline must be between 0.12 mg/mL and 6.4 mg/mL. It is administered for 60 - 75 minutes. All infusion instructions must be calibrated in accordance with the institutional standards, policies, and procedures to ensure consistent, accurate delivery of MGD013.

Infusion or allergic reactions may occur with the infusion of mAbs and other protein-based therapeutics. Precautions for anaphylaxis should be observed during MGD013 administration. Supportive measures may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen. Please refer to Section 8.4.1 for specific guidelines regarding the management of infusion reactions. Supportive care measures consistent with optimal patient care will be provided throughout the study according to institutional standards.

5.2.2 Study Drug Preparation and Administration

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. Return the vial if the solution is cloudy, there is pronounced discoloration (solution may have pale-yellow or pale brown color), or there is foreign particulate matter.
Instructions on the preparation of the study drugs for IV infusion are detailed in the Pharmacy Manual.
Do not mix the study drug with, or administer as an infusion with, other medicinal products.
The study drugs do not contain preservatives. Once diluted in normal saline, the dose solution is stable up to 4 hours at room temperature or 24 hours stored refrigerated at 2° to 8°C with minimal exposure to light. If the dose solution is stored at 2° to 8°C, it should be removed from the refrigerator at least 30-60 minutes prior to administration to allow the dose solution to reach room temperature. Precautions should be taken to minimize the time between dose preparation and IV infusion.

5.3 Concomitant medication

Any medication the subject takes other than the study treatment, including prescribed, non-prescribed, Chinese herbal medicine and dietary supplements, should be considered as concomitant medication.

All previous and concomitant medications must be recorded in the eCRF. It must include: generic name, route of administration, start and completion time, dosage and indications related to each concomitant medication. Any changes to the product of concomitant medication should also be recorded in the eCRF. At Screening, subjects will be asked what medications they have taken during the last 30 days. At each subsequent study visit, subjects will be asked what concomitant medications they are currently taking.

5.3.1 Prohibited Medications

- Other anti-tumor therapies, such as chemotherapy, immunotherapy, therapeutic radiation, experimental anticancer drugs or loco-regional therapy, are not allowed while the subject is using the investigational drug; palliative radiotherapy is allowed for non-target lesions that are present prior to enrollment with uncontrolled pain that cannot be relieved by local or systemic analgesics, provided that there is no disease progression.
- Corticosteroids should be limited because MGD013 has a mechanism of action dependent upon the engagement of T lymphocytes. Chronic use of corticosteroids > 10 mg/d of prednisone or equivalent are prohibited other than for the management of drug-related adverse reactions. Corticosteroids for topical (e.g., ophthalmic, inhaled, or nasal) administration are allowed.
- The concomitant use of rifampin (and its analogues);
- Hypericum perforatum or traditional Chinese medicines with indications for the treatment of liver cancer (including but not limited to Xiaoaiping, Kanglaite, Cinobufotalin, Elemene and Delisheng Injection) is not allowed.
- Vaccination with live vaccines is not allowed within 28 days prior to the first dose and during the study.
- Prophylactic use of stimulating factors (eg, granulocyte colony-stimulating factor) is not allowed during the first cycle of therapy.
- Anticoagulation therapy such as warfarin or heparin is not allowed when the subjects are administrated with the investigational products.

5.3.2 Drug-drug Interactions

Drug-drug interactions of MGD013 have not been evaluated in clinical studies. Bispecific antibodies to MGD013, for example, are not substrates for cytochrome P450s or drug transporters and are not likely to be cytokine modulators. No PK DDI is expected between MGD013 and small molecule drugs.

In five drug-drug interaction (DDI) studies in human, no drug-drug interactions were detected in humans when brivanib alaninate was co-administered with CYP3A4 substrates, CYP2C8 substrates, CYP3A4 inhibitors, and P-gp substrates without dose adjustment. Concomitant Rifampin should be avoided for it can significantly lower the exposure to Brivanib.

5.3.3 Best supportive care

All subjects participating in this clinical study are allowed to receive best supportive care (BSC). The BSC will be defined according to the institutional standards of the participating clinical centers. In general, BSC should be understood as a multi-professional focus on the overall physical, psychosocial, spiritual and cultural needs of the subjects at all stages of disease. This concept is applicable to the subjects of all ages and is independent of the intent of any anticancer therapy (EORTC Pain and Symptom Control Work Team). Based on the physical health status of HCC subjects participating in this study, BSC may include, but is not limited to: (1) analgesics, including non-steroidal anti-inflammatory drugs, opioids, etc.; (2) antiemetics; (3) vitamins and nutritional support; (4) hepatoprotective and choleretic therapy; (5) bisphosphonates for bone metastases, etc. Loco-regional radiation therapy is allowed to reduce symptoms, such as the pain caused by non-target lesions, as long as the total dose of treatment is within the palliative range specified by institutional standards. Palliative radiotherapy to the target lesion is not allowed if the subject is taking investigational drug. If jaundice is caused by obstruction of the biliary tree, percutaneous intrahepatic biliary drainage may be adopted.

5.4 Treatment Compliance

Brivanib alaninate is dispensed to subjects by trained medical personnel. It will be dispensed at the study center pharmacy and will be self-administered by subjects. Subjects must record the investigational drug administration information in the study diary provided by the Sponsor. At each visit, subjects must bring back the diary as well as all unused investigational drug and empty packing boxes or bottles. Compliance will be assessed by the investigator and/or study staff through the count of tablets and information provided by the subjects or caregivers. At each visit, the administration information of investigational drug (including planned administration dose, actual administration dose, dose change, administration interruption, etc.) must be recorded in the source documents and in the eCRF.

Each dose of MGD013 will be administered at the study site and will be prepared and infused by trained medical staffs. The administration information of MGD013 (administration dose, infusion time, whether there is infusion reaction, etc.) should also be recorded in the source documents and in the eCRF.

It is investigator’s and site staff's responsibility to evaluate and analyze potential noncompliance (such as AEs or missing dose) at the beginning and during the study with the sponsor's monitor, and to consider and implement strategies for improving medication compliance in advance.

5.5 Investigational Drug Management

5.5.1 Packaging and Storage

Brivanib alaninate tablets are supplied in tightly closed high-density polyethylene (HDPE) bottles with desiccant canisters. The bottles are heat-induction sealed with child-resistant

closures. MGD013 is supplied in 20 mL (single-dose) Type I USP and EP borosilicate clear glass vial, which is capped with a 20 mm FluroTec®-coated 4023/50 gray butyl rubber stopper. It is sealed with a 20 mm aluminum-plastic lid. Brivanib alaninate shall be stored at 10 - 30 °C in a tightly closed container. MGD013 should be stored at 2℃ - 8℃. All investigational drugs for treatment must be stored in accordance with sponsor and manufacturer's instructions. They will be placed in access control places with locks that meet storage conditions and comprehensive safety precautions.

All investigational drugs will be numbered according to the requirements of Good Manufacturing Practice (GMP). The label text should include drug name, strength, package, sponsor name, batch no., and expire date, protocol no., and administration and so on.

5.5.2 Responsibilities for Reception, Storage, and Management of Investigational Drugs

It is the responsibility of the investigator to manage the investigational products and equipment on its study site that are provided by the sponsor. The investigational products and supplies must be recorded accurately in accordance with the protocol and national laws and regulations, supplied as required by the study at any time and maintained, stored, dispensed, used and disposed according to the regulations. A specialized person should be designated by the investigator to receive, store, dispense and return all investigational products during the study, and to record the dispensing accurately. Drug dispensing management form should include subjects' identification number, random number, number of the dispensed, number of drug bottles and number of the returned. Drugs returned from subjects to study sites must be marked with "returned" to distinguish them from those that are not dispensed.

All dispensing and management records should be accessible to the Sponsor for review. Study monitors will verify according to drug dispensing management form and stored drugs. Designated drug managers will dispense the investigational drugs according to the study protocol and drug management manual and cooperate with monitors' audit.

6. Visit Schedule and Assessments

6.1 Study visits and assessments

6.1.1 Screening Period (Day-28 to Day0)

The following examinations or tests are required to be completed during the screening period:

- Signing ICF;
- Recording demographics: date of birth, gender, race, tobacco use, alcohol intake history, etc.;
- Medical history and physical examination;
  - Medical and surgical history
  - Past and present medical history of HCC, including the date of first diagnosis, pathological type of tumor, BCLC stage of initial diagnosis, history of surgical or loco-regional treatment, systematic treatment history, cause of disease, BCLC stage at enrollment, Child-Pugh liver function classification, etc.
  - Physical examination and vital signs (within 7 days before administration), including height, weight and systemic examination; ECOG performance status score;
- Hematologic test (complete blood cell count, CBC differential count): within 7 days before administration;
- Serum biochemistry (within 7 days before administration): including liver function (total bilirubin, alanine aminotransferase, aspartate aminotransferase, γ-GT, alkaline phosphatase, lactate dehydrogenase, serum total protein and albumin, etc.), renal function (urea nitrogen or urea, creatinine), electrolytes (K, Na, Cl, Ca, serum phosphorus, serum magnesium), fasting blood glucose, amylase, lipase;
- Thyroid function (TSH, free T3, free T4), within 7 days before administration;
- Coagulation (TT, PT, APTT and INR), within 7 days before administration;
- AFP test within 7 days before administration;
- Urinalysis (urine protein, urine occult blood, urine red blood cell, urine glucose, white blood cell, urine specific gravity, PH value), within 7 days before medication;
- 12-lead ECG, within 7 days before administration;
- Echocardiography (performed during the screening period, and whether examinations are required at subsequent visits is determined according to clinical needs);
- Blood or urine HGG for female subjects with childbearing potential (except females who have underwent surgical sterilization or those have been menopausal for more than one year) to exclude pregnancy (within 7 days before administration);
- Hepatitis B serologic test, and HBV-DNA (only when HbsAg is positive);
- Anti-HCV antibody, HCV-RNA (only when HCV antibody is positive);
- HIV serology;
- RECIST 1.1 assessment (During the screening period, contrast-enhanced CT on the chest as well as contrast-enhanced CT/MRI on the abdomen and pelvis are

required; contrast-enhanced CT/MRI on the abdomen and other clinically indicated sites are performed for subsequent assessments);

- Brain MRI (To rule out brain metastasis as indicated clinically);
- Assessment of previous and concomitant medications (it is required to collect the medication history within 30 days prior to signing the ICF);
- Evaluation of adverse events;
- Eligibility assessment based on inclusion and exclusion criteria (review on results of diagnostic examination, and assessment of inclusion and exclusion criteria);

6.1.2 Cycle 1

6.1.2.1 Cycle 1, Day 1

- Physical examination (to assess the changes since screening period) and body weight
- Vital signs (respiratory rate, Blood Pressure (BP), heart rate, body temperature) : on Cycle 1 Day 1, vital signs are examined at the following time points: prior to infusion of MGD013 (within 30 minutes prior to infusion), at 15, 30 minutes (± 5 minutes) after infusion, at the end of infusion (± 10 minutes), at 1, 3 hours (± 10 minutes) after the completion of infusion.
- ECOG body performance status score
- 12-lead ECG
- Evaluation of adverse events
- Evaluation of concomitant medication
- Dispense investigational drug and medication diary
- Completion of intravenous infusion of MGD013 at study sites
- Administration of the first dose of brivanib alaninate (combination therapy group)

6.1.2.2 Cycle 1, Day 8

- Vital signs (respiration, blood pressure, heart rate, body temperature)
- 12-lead ECG
- Hematology
- Serum biochemistry
- Coagulation
- Evaluation of adverse events
- Evaluation of concomitant medication

6.1.3 Cycle 2

6.1.3.1 Cycle 2, Day 1

- Physical examination (to assess the changes since screening period) and body weight
- Vital signs (respiration, BP, heart rate, temperature): prior to infusion of MGD013 (within 30 minutes prior to infusion), at the end of infusion (± 10 minutes), at 1

hour (± 10 minutes) after the completion of infusion.

- ECOG body performance status score
- 12-lead ECG
- Hematology
- Serum biochemistry
- Coagulation
- Urinalysis
- Evaluation of adverse events
- Evaluation of concomitant medication
- Return Investigational Drug and Review Medication Diary
- Completion of intravenous infusion of MGD013 at study sites
- Dispensing of the investigational drugs and medication diary (combination therapy group)

6.1.3.2 Cycle 2, Day 8

- Vital signs (respiration, blood pressure, heart rate and body temperature)
- 12-lead ECG
- Hematology
- Serum biochemistry
- Coagulation
- Evaluation of adverse events
- Evaluation of concomitant medication

6.1.4 Day 1 of subsequent cycles

- Physical examination (changes since the previous assessment) and body weight
- Vital signs (respiratory rate, BP, heart rate, body temperature): prior to infusion of MGD013 (within 30 minutes prior to infusion), at the end of infusion (± 10 minutes), at 1 hour (± 10 minutes) after the completion of infusion.
- ECOG body performance status score
- 12-Lead ECG
- Hematology
- Urinalysis
- Coagulation test
- Serum biochemistry
- Serum AFP: once every 8 weeks (±7 days) until disease progression, test corresponding to radiographic assessment
- Assessment according to RECIST 1.1 and irRECIST: once every 8 weeks (± 7 days) until disease progression, tumor evaluation of pelvic and abdominal cavity and other sites as clinically indicated

- Thyroid function: once every two cycles (±3 days)
- HBV-DNA (HBsAg positive subjects), once every 8 weeks (± 7 days)
- HCV-RNA (HCV antibody positive subjects), once every 8 weeks (± 7 days)
- Evaluation of adverse events
- Evaluation of concomitant medication
- Dispense investigational drug and recover medication diary (combination therapy group)
- Completion of intravenous infusion of MGD013 at study sites (for at most 48 cycles)

6.2 End of Study Treatment (completion of visits within 7 days after last dose of investigational drugs/withdrawal)

- Physical examination and body weight
- Vital signs (respiration, blood pressure, heart rate, body temperature)
- ECOG body performance status score
- 12-Lead ECG
- Hematology
- Urinalysis
- Coagulation test
- Blood or urine pregnancy test (for female with childbearing potential)
- Serum biochemistry
- Serum AFP
- Thyroid function
- Evaluation of AEs (un-recovered or new AEs need to be assessed and recorded after this visit until 30 days after the last dose of investigational drug; in case of serious AEs or AESIs, the subject will be followed continuously until recovery or stabilization of the adverse event.)
- Evaluation of concomitant medication
- Return the investigational drugs and medication dairy (combination therapy group)

Note: If the corresponding laboratory tests or examinations are performed within 7 days, it is not necessary to repeat them.

6.3 Safety Follow-up (30 days ± 7 days after end of study treatment)

- Physical examination
- Hematology
- Blood chemistry
- Evaluation of AEs (investigational drug-related SAEs after this visit should be evaluated and recorded)
- Evaluation of concomitant medication

6.4 Post-Treatment Assessments (Subjects in phase II are not required to have visits in the study site)

- Subjects will receive survival follow-up and subsequent treatment follow-up to collect
  - the information (including commencement date of subsequent first anti-tumor treatment) of first anti-tumor treatment (including chemotherapy) after the end of study treatment every 60 days (± 7 days)
  - Subjects will receive survival follow-up after discontinuation of study treatment every 60 days (± 7 days) to collect the information of new malignant tumors
- Monitoring of SAEs and irAEs: study treatment-related SAEs or irAEs ⩾ grade 3 occurring within 30 days after the last dose should be recorded and evaluated.
- Tumor imaging assessments and serum AFP: If the subject is withdrawn from the treatment for reasons other than radiographic progression, the subject will still need to undergo imaging scans and AFP testing every 8 weeks (± 1 week) after discontinuation of study treatment until tumor progression is confirmed or subsequent antineoplastic therapy is initiated

7. Study Endpoints

7.1 Safety Assessments

7.1.1 Laboratory Tests

The laboratory tests will be performed at the study site in accordance with the schedule of study visits in Table 1. Table 3 listed required laboratory tests of this study. Specific items included in hemotology, biochemistry, coagulation tests and urinalysis could be adjusted based on local practice of each site.

Females subjects (except females who have underwent surgical sterilization and those have been menopausal for more than one year) of childbearing potential should undergo pregnancy test. The frequencies of all laboratory tests will be determined according to the schedule of study visits, but unscheduled tests may be added according to the clinical judgment by the investigator. All test results should be filed in the original case report and recorded in the eCRF.

Table 3. Laboratory tests

Haematological examination (CBC)	**Clinical Chemistry (Serum) and Coagulation**	**Urinalysis**
Red cell count	Blood urea nitrogen or urea, creatinine	Specific Gravity
Hemoglobin	Albumin, total protein	White blood cell
Packed cell volume	LDH, blood glucose	Occult blood, red blood cell
Classification of leukocytes and absolute count (neutrophils, basophils, eosinophils, lymphocytes, monocytes)	Alkaline phosphatase (ALP), GGT, ALT, AST, total bilirubin	Glucose
Platelet count	Sodium, potassium, calcium, magnesium, chloride	Protein, PH
	Amylase, lipase	
	Activated partial thromboplastin time APTT, international standardization ratio INR	

7.1.2 Electrocardiogram Assessment

12-lead ECG examination will be performed according to Table 1 Schedule or at the time when any cardiac-related adverse event occurs during the study. Examination should be performed after the subject has rested in the supine position for at least 10 minutes prior to the specified time point. Each examination should be performed in the same position and all ECGs should be recorded. At each time point, the record of 2 ECGs with 2 minutes apart, should be obtained. A standardized electrocardiograph machine should be used, and the same device should be used throughout the study if possible.

All ECG assessment items will include parameters such as heart rate, QRS complex, QT interval, QTc, and RR interval. ECG results will be assessed by the investigator or specialist and will be recorded in the eCRF. If a clinically significant abnormality is found at baseline (screening), it should be recorded in the subject's medical history; if a clinically significant abnormality is reported during treatment, it will be reported as an AE.

7.1.3 Physical examination

A standard physical examination (including appearance, skin, eyes, ears/nose/throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, nervous system, and other body systems, as applicable) will be performed according to Table 1 schedule of study visits. Height is measured at the screening visit only.

7.1.4 Vital signs

Vital signs (respiratory rate, heart rate, blood pressure, and body temperature) will be measured according to Table 1 schedule of study visits. Vital sign should be measured in a sitting position after at least 10-minute's rest. Vital signs are only examined once at the visit in the screening period and that at the end of study; on Cycle 1 Day 1, vital signs are examined at the following time points: prior to infusion of MGD013 (within 30 minutes prior to infusion), at 15, 30 minutes (± 5 minutes) after infusion, at the end of infusion (± 10 minutes), at 1, 3 hours (± 10 minutes) after the completion of infusion. For subsequent visits, vital signs are examined at the following time points: prior to infusion of MGD013 (within 30 minutes prior to infusion), at the end of infusion (± 10 minutes), at 1 hour (± 10 minutes) after the completion of infusion. Additional vital signs examination may be performed at any other time points as clinically indicated.

7.1.5 Eastern Cooperative Oncology Group (ECOG) Performance Status Score

ECOG performance status scoring will be evaluated according to Table 1 schedule of study visits. Refer to Table 4 for scoring.

Table 4. ECOG score

Description of physical status	Score
Completely normal, being able to perform work before illness without restriction	0
Not able to carry out heavy physical work, but be able to walk around and carry out light physical work such as light housework or office work	1
Can move around, capable of self-care, but unable to carry out any work-related activities, confined to bed for less than 50% of the day	2
Self-care can only be achieved to a limited extent, with more than 50% of the daytime spent in bed rest or chair sitting	3
Complete loss of activity of daily living, unable to achieve selfcare, confined to bed or wheelchair	4

7.1.6 Echocardiography

Echocardiogram for LVEF is to be done at baseline, and then performed as clinically indicated (e.g. cardiac symptoms, or abnormal ECG findings with clinical significance).

7.2 Efficacy assessments

Contrast-enhanced CT or MRI of abdomen, pelvic and contrast-enhanced CT of lungs are required at baseline. During the follow-up visit, the same method of radiologic assessment on abdomen, pelvic cavity and other clinically indicated sites should be used. All baseline tumor imaging assessments must be performed within 28 days prior to the start of study medication. If subjects receive scanning before signing an informed consent form, as long as the scanning imaging is within the time limit specified by the protocol, the test method meets the requirements for image collection, and the data are obtained, it can be used for study analysis.

Radiologic examination should be conducted on abdomen, pelvic cavity and other clinically indicated sites every 8 weeks (±7 days) dated from the first day of the first cycle until disease progression. All imaging of Phase II study must be evaluated by independent central review.

Tumor assessment should be carried out in strict accordance with the study plan. If imaging assessment occurs beyond the planned visits and there is no disease progression, subsequent tumor assessments should still be carried out **according to the original plan**.

The investigator will also evaluate imaging response by RECIST 1.1 and irRECIST criteria, and classify the objective tumor response by target lesion assessment into: CR, PR, SD, PD and NE. For the subjects with initial response as PR or CR, **the response should be confirmed at an interval of at least 4 weeks**. subjects should be administered until PD confirmed according to irRECIST.

7.2.1 Blinded independent central review (BICR) procedures

In case of disease progression / treatment discontinuation at the investigator's discretion, or at other time points specified by the sponsor, all imaging films should be submitted to the center for review. Imaging assessment based on RECIST 1.1 and irRECIST will be conducted by two independent imaging experts, assisted by an adjudicator if necessary. Reviewers are blinded to treatment cohorts of subjects.

7.3 Exploratory study

In Phase I and Phase II Part 1, an exploratory study of biomarkers will be conducted. Subjects participating in the study should submit archived or the latest formalin-fixed and paraffin-embedded (FFPE) tumor tissues or about 20 unstained paraffin sections (if any) during the screening period, which will be sent to the central laboratory designated by the sponsor. Collection, handling, storage and transportation procedures of samples will be addressed in the laboratory manual of the central laboratory. The tumor tissues will be tested as follows:

- Detect immune cell infiltration (including T cell infiltration), expression of PD-1, PD-L1, LAG-3, MHC-II and fibrinoid protein (FGL1) in tumor tissues through immunohistochemistry (IHC).

In addition, blood will be also sampled and tested in Phase I and Phase II Part 1. The peripheral blood will be tested for:

- Cytokines in serum, including but not limited to IFN-γ, IL-2, IL-6, IL-10 and TNF-α.
- Receptor occupancy of MGD013 on PBMC using multiparameter flow cytometer [only limited to phase I];
- Characterization of immune cells using multiparameter flow cytometer, including the percentage of B cells, T cells (T cell subsets), NK cells and monocytes in peripheral blood and T cell subsets; the markers of T cell activation and / or T cell exhaustion in PBMCs and markers of cytolytic activity (including but not limited to PD-1, CTLA-4, LAG-3, TIM-3, CD25, CD69 and granzymeB)
- Exploration of safety-related biomarkers, including but not limited to IFN-γ, IL-2, IL6, IL-10 and TNFa

The above blood analyses will be prioritized based on the degree of subjects' response to drugs

and the number of FFPE sections. In addition, for subjects with immune- and infusion-related reactions or cytokine release syndrome, additional sampling for analysis of serum cytokines. Exploratory study results will be reported separately other than in the clinical study report (CSR).

8. Safety Monitoring, Reporting and Management

8.1 Definition of adverse event (AE)

In clinical study, adverse event refers to any untoward medical occurrence in a clinical investigation subject administered a investigational product. The event does not necessarily have to have a causal relationship with study treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an invetsigatonal product, whether or not considered related to the investigational product. Adverse events include serious adverse events (SAE) and non-serious adverse events.

8.2 Definition of Serious Adverse Event (SAE)

Serious adverse event refers to an adverse event which occurs during clinical trial and meets any of the following criteria:

- Results in death;
- Is life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient or prolonged hospitalization (Note: Common usage of "inpatient hospitalization" generally would include being treated by a physician in a hospital for at least a 24 hour period. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).);
- Results in persistent or significant disability/malfunction/incapacity;
- Results in congenital abnormality or birth defect;

Other important medical event (defined as an event events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical intervention to prevent one of above listed outcomes. These should also usually be considered serious. Example of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.).
Note: The following scenarios will **not** be reported as SAEs:

- Any results, including death, caused by progressive disease of tumor as assessed by investigator.
- A hospitalization or prolonged hospitalization due to economic issue or for purpose of reimbursement only.

- A hospitalization admission is pre-planned (ie, elective or scheduled surgery arranged prior to the start of the study).

8.3 Collection, Record, Follow-up and Report of Adverse Events

8.3.1 Time Limit for Collection of Adverse Events

The collecting and recording of adverse events will be throughout the clinical trial, from the

signing of the informed consent form (ICF) to the end of the trial (AE will be collected until 30 days after the last dose of investigational drugs). AEs and SAEs that occur following the signing of the ICF but before the first dose treatment should be recorded on Medical History page of eCRF form as pretreatment symptoms and signs, and not collected as AEs on the AE eCRF page, but if deteriorates (higher than a grade) after administration the investigational drug, such events should be recorded as AEs

8.3.2 Follow-up of Adverse Events

Investigators must follow up all adverse events until their disappearance or recovery to baseline, up to disease stable in case of permanent injury; if an adverse event is not recovered at the last visit of the study, investigators must continue to follow up the adverse event until disappearance or recovery to baseline level, or clinical stability. Subsequent follow-up may not be recorded in the eCRF, but the sponsor has the right to ask investigators to provide more information where necessary.

8.3.3 Elements of Adverse Event Collection

- Selection of AE term: The disease diagnosis is preferred as AE term if a unifying diagnosis is available; if not, the associated symptoms and signs are to be captured and recorded using standard medical terminology. Once the diagnosis is confirmed with the follow up information, the symptoms and sign should be replaced with diagnosis accordingly. One single event term to be recorded should only contain a sole event, such as a single diagnosis, sign and/or symptom. For example, if a subject experiences “vomiting and diarrhea”, then it need to be captured separately as two AEs rather than one, namely “vomiting” and “diarrhea”.

- Onset date/Stop date of AE: In general, the date when first signs and/or symptoms appear is captured as onset date rather than the time of confirmed diagnosis, to prevent missing safety information or underestimating safety hazards. If the date when first signs and/or symptoms appear cannot be determined based on the available information, then the time of disease diagnosis will be used as the event onset date.

- AE severity (CTCAE Grade 1-5): AE severity is graded from 1 to 5 according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0); for those reported without assigned CTCAE Grade, the terms including “mild”, “moderate” and “severe” that used to describe the event severity can be converted to the corresponding CTCAE Grade by referring to the defined CTCAE criteria. Serious adverse events (SAEs) are different from severe AEs: SAEs are determined based on clinical outcome or medical intervention as described in Chapter 8.2, while the severity of AE refers to the event intensity which is usually evaluated and graded according to the CTCAE. A severe AE is not necessarily an SAE, e.g. nausea lasting for several hours may be graded as severe in CTCAE grading however probably not a SAE. Conversely, a stroke that caused partial disability may only be mild based on CTCAE grading; however, it is generally reported as a SAE.

- The investigator should evaluate and provide causal relationship between the investigational drug and the AE, for the details please refer to 8.3.4.

- Action taken with the investigational drug in response to AEs (e.g., whether the AE led to drug discontinuation or dose reduction, etc.).

- Concomitant medication: It should be indicated whether the concomitant medication is for treatment of a specific AE/SAE, or part of clinical routine diagnosis and treatment, which should be clarified and recorded in the SAE report.
- Event outcome: Outcomes of AE include complete recovery, events not yet resolved, recovery with sequelae, death and unknown.

8.3.4 Causality Assessment

The investigator's assessment of causality must be provided for all AEs to determine if there is a reasonable possibility that the investigational product caused or contributed to an AE. "Yes" or "No" will be provided. Generally, the following factors should be considered in performing causality assessment:

- Temporal relationship with investigational drug treatment;
- Whether the symptoms and signs are consistent with the pharmacological action of the drug's active ingredients;
- Alternative medical reasons other than the investigational drug treatment;
- De-challenge results; if symptoms/signs relieved or improved upon reduction or withdrawal of the investigational drug;
- Re-challenge results; if symptoms/signs recurred or worsened upon re-introduction of the investigational drug treatment;
- Evidence of previous, similar incidents from literature search.

In case of insufficient information which does not allow for a comprehensive assessment, the AEs could be conservatively assessed as related to the investigational drug and the reason need to be documented.

8.3.5 Adverse Events based on Laboratory Examinations and Tests

The laboratory test, vital signs, ECGs and any other safety relevant test specified in the study will be summarized in the clinical study report. The change of value from the baseline is reported as an AE only if it is medically significant. For example, worsened by 1 grade or higher in CTCAE grading, led to discontinuation, dose adjustment or interruption of study treatment or the investigator believes that this abnormality should be reported as an AE.

When the abnormal findings in laboratory test/examinations, vital signs, ECG and other safety relevant test are considered related to a clinical diagnosis, then only this clinical diagnosis need to be reported as AE and those abnormal findings are handled as additional safety information related to the corresponding diagnosis. In this case, the investigator should use clinical terminology (e.g. anemia) rather than laboratory terminology (e.g. hemoglobin decreased) as applicable.

8.3.6 Progressive Disease

Events due to progression of the neoplasm disease which under investigation should not be reported as AEs or SAEs.

8.3.7 Death

All deaths occurring during the study, including deaths occurring within 30 days after the last

dose of the investigational drug administration, should be reported by investigators as follows:

- If death is caused by disease progression, the investigator should notify the Sponsor's monitor of the event in the next site monitoring visit and record it in corresponding moduleof eCRF, but it will not be reported as a SAE.
- If it is not clear whether the death is caused by disease progression, the death should be reported as a SAE, informed to the monitor and reported to the relevant parties within 24 hours (refer to 8.3.9); the SAE report should evaluate whether the disease progression jointly contributed to the death of the subject and identify the main cause of death and other related factors, as appropriate;
- Death cases with unknown causes must be reported as SAE, and the cause of death should be clarified with every effort. Autopsy may be conductive to assessment on the cause of death. If an autopsy is performed, the Sponsor should be notified of the autopsy report.

If adverse events occurred beyond the above collection time limit:

- Deaths caused by disease progression do not need to report as SAEs;
- If the death is determined to be related to the investigational drug by the investigator, monitors and concerned parties should be notified within 24 hours (see 8.3.8)

8.3.8 SAE Reporting

Any SAE occurring during the study, regardless of causal relationship to investigational drug, should be reported by following the SAE reporting procedures required by competent regulatory authorities or Independent Ethics Committee.

The investigator should:

(1) Immediately take appropriate medical measures, if necessary;

(2) Record SAEs in the AE Form, SAE Form and source documents of eCRF.

(3) The investigator should immediately (within 24 hours of becoming aware of the event) send the singed and dated SAE Form to Drug Safety Department of the Sponsor (email as follows).

Please send SAE report to the email mailbox of Drug Safety Department of Zai Lab: [redacted]

The SAE reporting period starts from when the subject signs the ICF until 30 days after the last dose treatment. Collection and follow up on SAEs that are related to the investigational drugs which occurring after 30 days of the last dose will be pursued until they disappeared, or recovered to the baseline level or clinically stable, even if the ICF is withdrawn.

8.3.9 Adverse Event of Special Interest (AESI)

Given the mechanism of action and summary of the aggregate data from a set of preclinical and clinical studies previously conducted, the event listed as follows are selected as AESIs of brivanib alaninate in this trial:

- Important identified risks: hypertension, RPLS, hepatic events, hypothyroidism, hyponatremia, proteinuria, arterial thrombotic events;
- Important potential risks: hemorrhage, venous thrombotic events, left ventricular dysfunction, gastrointestinal perforation, and impaired wound healing;

If an AESI meets SAE criteria, then it should be reported as such according to the standard SAE reporting procedure as specified in protocol. Otherwise, AESIs will be recorded on eCRF only for periodic review and analysis by the sponsor.

AESIs of MGD013 include ≥Grade 3 infusion-related reactions and any immune-related adverse events (irAEs) leading to discontinuation and interruption of MGD013. See 8.4.1.

All occurrences of AESIs of MGD013 must be reported to the Sponsor within 24 hours of awareness. The investigator should complete the "AESIs Report Form" within 24 hours of awareness and report the events to the sponsor by email. If an AESI meets SAE criteria, then it should be reported directly in accordance with standard SAE reporting procedures as specified.

8.3.10 Pregnancy

Effective contraception is required for both male and female subjects of childbearing potential during the study and within 120 days after discontinuation of investigational drug treatment. Once pregnancy is found to be pregnant following initiation of study treatment, the investigational drug will be permanently discontinued and the female subject will be withdrawn from the trial. If a female subject or a male subject's partner becomes pregnant during the study or within 4 months after the last dose of investigational drug adminstration, the investigator should be notified immediately. The pregnancy must be recorded on “Pregnancy Reporting Form” and reported by the investigator to the Sponsor via email within 24 hours of becoming aware of the event. At the same time, the pregnancy also must be recorded on eCRF. All pregnancies must be followed until the end of pregnancy, and the sponsor should be informed of the pregnancy outcome information. If the outcome of the pregnancy meets SAE criteria (e.g., spontaneous abortion/miscarriage or therapeutic abortion with any detected congenital anomaly, stillbirth, neonatal death, or birth defect), it will be reported as SAE. The investigator should send the completed “SAE Reporting Form” to the Sponsor via email within 24 hours of becoming aware of the event. All pregnancies during the trial or within 120 days after the last dose of investigational drug should be handled in accordance to the procedure described in this section.

8.3.11 Overdose

Overdose is defined as any condition where the maximum dose recommended specified in the protocol is exceeded, including infusion dose in unit time. At present, there is no human data on overdose of MGD013 and no known antidote have been obtained. In the event of MGD013 overdose, the intravenous infusion should be immediately discontinued and the subject should be closely monitored and treated symptomatically.

In the entire brivanib alaninate clinical program, there have been a total of 49 reports of overdose reports. Among these 49 reports, 20 of them were randomized to either placebo or comparator group, and 29 were randomized to brivanib group. The reported overdose was as high as 2 times (1,600 mg) the normal daily dose of brivanib alaninate or the comparator. Most reported cases were reported as one-time accidental overdose. There were no clinical sequelae reported for any overdose with one exception. One subject experienced one

accidental overdose of brivanib alaninate (1,600 mg) on day 1 of the study treatment, but no overdose-related AE was reported. The subject continued to receive blinded drug therapy with a correct dose. The subject developed toxic dermatitis 3 weeks later. Although it was possibie that the study treatment with brivanib may have played a participative role in the development of toxic dermatitis, the toxic dermatitis was not considered to be related to accidental overdose. In another case, a subject with overdose of 1,600 mg for a week experienced extremely severe ALT/AST elevation. After study unblinding, the subject was found to be assigned to comparator group.

There is no known antidote for overdosage of brivanib alaninate. In case of overdosage, the subject should be monitored, and supportive treatment should be administered, including supportive medical interventions to treat the presenting clinical manifestations.

8.4 Management of study drug-related adverse events

8.4.1 Prevention and treatment of MGD013-related adverse events

8.4.1.1 Infusion-related reactions, including cytokine release syndrome (CRS)

Infusion-related reactions related to mAbs or DARTs (including CRS) should be controlled according to standard practice for drugs. General guidelines for the management of such reactions are provided in this section; however, severe reactions may require more intensive interventions (e.g., steroids, anti–TNF-α antibodies, and/or IL-6 inhibitors).

Subjects should be monitored closely for the development of infusion-related reactions during the MGD013 infusion. Medications and supportive measures for severe hypersensitivity reactions should be available for immediate intervention of an infusion reaction during administration of study drug and may include, but are not limited to: subcutaneous (SC) epinephrine (0.3 to 0.5 mL of a 1:1000 solution), antihistamines (e.g., diphenhydramine 25 to 50 mg IV), corticosteroids (e.g., hydrocortisone 20 to 40 mg IV push or equivalent, dexamethasone 10 to 20 mg IV), IV fluids, vasopressors, oxygen supplementation, bronchodilators, and antipyretics. In addition, resuscitation equipment and other supplies for the emergency management of an allergic/toxic reaction must be available. The subject should be treated according to the best available local practices and procedures. All supportive measures consistent with optimal subject care will be provided throughout the study according to institutional standards.

Should symptoms of fever or chills develop, it may be difficult to distinguish among potential causes of the symptoms including emerging infection or infusion reaction. Subjects should be evaluated carefully for the presence of infection, with the acquisition of cultures and/or implementation of empiric antibiotic therapy, as appropriate, based on the assessment of the Investigator. Management guidelines for infusion-related reaction are as follows.

Grading and Management of Infusion-related Reactions

- Grade 1: Mild transient reaction; infusion interruption or intervention not indicated;
- Grade 2: Therapy or infusion interruption indicated with immediate response to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours;
- Grade 3: Prolonged (e.g., not rapidly responsive to medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates);

- Grade 4: life-threatening consequences; vasopressors or ventilatory support indicated;
- Grade 5: Death.

It is considered appropriate for grading all infusion reactions in this study, irrespective of the underlying mechanism of the reaction for the above CTCAE v5.0 grading scale for CRS is nearly identical to that for infusion reaction and allergic reaction. The Sponsor's monitor or designated personnel should be contacted immediately if questions arise from the grading.

Premedication and Prophylaxis for Infusion-related Reactions

Prophylactic pre-infusion guidelines should be followed to mitigate the occurrence or severity of potential infusion reactions with study drug. Prior to the infusion of MGD013, the pre-medications are as follows:

- Acetaminophen(or equivalent) 650-1000 mg or ibuprofen 400 mg per os (PO)
- Diphenhydramine 50 mg or appropriate dose of equivalent H1 antagonist PO or IV
- Ranitidine 300 mg PO or 50 mg IV; or appropriate dose of equivalent H2 antagonist at the discretion of the investigator

For subjects who had infusion reactions following the first dose of MGD013 that were not adequately controlled with the above pre-medications, IV corticosteroids may be added to the pre-medication for subsequent administration. Dexamethasone 10-20 mg IV, or equivalent IV steroids, may be used as pre-medication in addition to acetaminophen, diphenhydramine, and ranitidine if the subject experiences a > Grade 2 infusion reaction with the first infusion. Premedication with steroids should be reduced by 50% with subsequent dose and discontinued thereafter, if there are no infusion reactions.

Management of Observed Infusion Reactions

$\geqslant$ Grade 3 infusion reactions should be reported as AESIs and/or SAEs, as applicable.

The following are treatment guidelines (which may be modified as needed by the investigator according to the best practices of drugs) for infusion reactions:

Grade 1:

- Slow the study drug infusion rate by 50%
- Monitor the subject for worsening of condition
- Continue at 50% of infusion rate and recover to the original rate after 30 minutes if the initial rate is tolerated. The subsequent infusions can be from 50% rate, which can be increased if tolerated by the subjects.
- Note: Per Section 8.4.1, the following prophylactic pre-infusion medications are required prior to all infusions of MGD013, including future infusions for patients who experience Grade 1 infusion reactions::
  - Diphenhydramine 25 to 50 mg (or equivalent) PO/IV
  - Acetaminophen (or equivalent) 650-1000 mg PO and/or ibuprofen 400 mg PO
  - Ranitidine 300 mg PO or 50 mg IV, or equivalen.

Grade 2:

- Stop the infusion.

- Administer diphenhydramine hydrochloride 25 to 50 mg IV.
- Acetaminophen (or equivalent) 650-1000 mg PO or ibuprofen 400 mg PO for fever.
- Oxygen inhalation and bronchodilators for mild bronchospasm.
- Resume at 50% of the initial rate once the infusion reaction has resolved or decreased to Grade 1. The initial rate can be resumed after 30 minutes if tolerated. The subsequent infusions can be from 50% rate, which can be increased if tolerated by the subjects.
- Monitor for worsening condition. If symptoms recur, discontinue the infusion; no further study drug will be administered at that visit.
- For patients with Grade 2 infusion reactions, despite premedication with diphenhydramine, ranitidine or equivalent, and acetaminophen (or equivalent) and/or ibuprofen, corticosteroids (10-20 mg dexamethasone IV, or equivalent IV steroid) should be added to the premedication regimen for the next dosing of MGD013. Reduce corticosteroid dosing by 50% for the subsequent dose and hold thereafter, if there are no reactions.

Grade 3:

- Discontinue the infusion and disconnect the infusion tubing from the subject.
- To avoid exacerbation of infusion reaction or CRS: do not flush the tubing, and withdraw residual drugs from the lumen.
- Diphenhydramine hydrochloride 25 to 50 mg IV, dexamethasone 10- 20 mg IV (or equivalent), and other medications/treatment as medically indicated. Higher doses of corticosteroids (e.g., methylprednisolone 2 to 4 mg/kg IV or the equivalent) may also be considered for acute management.
- Tocilizumab (an IL6 receptor antagonist) 4 mg/kg IV considered.
- Intravenous fluids replacement, oxygen supplementation, and bronchodilators should be considered as appropriate.
- If a Grade 3 infusion reaction occurs with MGD013, it will be discontinued for that day. If the symptom has resolved to baseline within 12 hours, MGD013 may be resumed at the next scheduled dose, with 50% of infusion rate. In addition, subjects should be pre-medicated with the following drugs (diphenhydramine hydrochloride 25 to 50 mg IV; acetaminophen 650-1000 mg PO and/or ibuprofen 400 mg PO; corticosteroids may be considered as well (dexamethasone 10 to 20 mg IV, or equivalent IV steroids)) for this re-challenge and for any subsequent doses of MGD013. Reduce corticosteroids by 50% for the subsequent dose and withhold thereafter, if there are no reactions.
- Subjects who have a Grade 3 infusion reaction that does not resolve within 12 hours despite medical management should not receive further MGD013 treatment.
- Subjects who experience a second Grade 3 infusion reaction at the time of rechallenge of the investigtional drugs will permanently discontinue MGD013.

Grade 4:

- Discontinue the infusion and disconnect the infusion tubing from the subject.
- To avoid exacerbation of infusion reaction or CRS: do not flush the tubing.

- Diphenhydramine hydrochloride 50 mg IV, dexamethasone 20 mg IV (or higher doses of steroids, e.g., methylprednisolone 2 to 4 mg/kg IV or the equivalent, as considered appropriate).
- Tocilizumab (an IL6 receptor antagonist) 4 mg/kg IV considered.
- Epinephrine or bronchodilators as indicated.
- Supported ventilation and vasopressor as indicated.
- Subjects who have a Grade 4 infusion reaction should not receive any further doses of MGD013.

All changes in the infusion of MGD013, including interruption of the infusion and its duration as well as reductions in infusion rate and duration, must be recorded.

8.4.1.2 Immune-related Adverse Events

Blockade of immune checkpoints has been associated with several immune mediated adverse events that develop as a result of disruption of immune tolerance in normal tissues. They include but are not limited to pneumonitis, autoimmune hepatitis, glomerulonephritis, diarrhea or colitis, encephalitis, hypophysitis, thyroiditis, or other autoimmune endocrinopathies (e.g., pancreatitis and diabetes), myocarditis, and Stevens Johnson syndrome/toxic epidermal necrolysis. The occurrence of any of these events may indicate interruption or discontinuation of MGD013, and they should be evaluated and reported to the Sponsor as AESIs. Most low-grade immune-related AEs (irAEs) can be managed symptomatically. Persistent low grade or moderate toxicities may require treatment with corticosteroids or in refractory cases other immunosuppressive agents such as mycophenolate or infliximab may be required. Severe immune-related toxicities will, in almost all cases, require treatment with high-dose corticosteroids.

General guidelines for management of specific immune-related toxicity / event are provided below. All events will be graded according to NCI CTCAE v5.0.

Diarrhea or Colitis

Diarrhea that develops in subjects while receiving MGD013 treatment may reflect immune reactivity against normal colonic epithelium and careful monitoring for potential immune-related colitis should be instituted. Subjects should be monitored closely for evidence of diarrhea or other change in bowel habits as well as other signs and symptoms suggestive of colitis. Subjects who develop signs or symptoms including abdominal pain, abdominal distension, nausea, vomiting, diarrhea, or blood in the stool should be evaluated carefully for potential colitis.

- Grade 1 diarrhea - Closely monitor the diarrhea until resolution.
- Grade 2 diarrhea - Increase frequency of monitoring until resolution. For management of symptoms:
  - Loperamide/diphenoxylate
  - Low-dose steroids if clinically indicated
  - Consider management of prolonged Grade 2 diarrhea lasting more than 5 to 7 days or relapsed diarrhea as Grade 3 diarrhea (see below)
- Grade 3 diarrhea - withhold MGD013. Hospitalize subject promptly for further evaluation and management, including the following:
  - Bowel rest

- Intravenous fluids replacement with close monitoring of body fluid and electrolytes status
- Monitor frequency of bowel movements
- Consider imaging to rule out bowel obstruction or perforation
- Consideration of colonoscopy as appropriate
- Implementation of preliminarily empirical immune suppression consisting of IV corticosteroids using methylprednisolone at a dose of 2 mg/kg/day (or equivalent) divided twice daily. As tolerated, subjects may be converted to oral corticosteroids (i.e., prednisone 2 mg/kg/day divided twice daily) and tapered as appropriate guided by the subjects' clinical status.
- Taper corticosteroids as clinically indicated
- For subjects with severe colitis or those who do not respond to corticosteroids, additional immune suppression with anti-TNF-α antibodies (i.e., infliximab) should be considered early in the course.
- The MGD013 should be resumed if:
    - It has been confirmed there is no colitis and an alternative cause of diarrhea is found, and
    - Diarrhea resolves to ≤ Grade 1 within 14 days

- Grade 4 diarrhea - discontinue MGD013 and treat as for Grade 3.

Hepatotoxicity

Transaminases increased

Management guidelines for subjects experiencing hepatic toxicity are as follows:

- Grade 1 transaminases increased - No specific therapy required.
- Grade 2 transaminases increased - For transaminases increased (3 to 5 × ULN), rule out viral and other etiologies. Consider imaging examinations such as ultrasound or CT scan and liver biopsy to ascertain etiology of hepatosis. Consider starting oral prednisone 60 mg/day divided twice daily, and withhold MGD013.
    - If it doesn't recover to ≤ Grade 1 within 48 hours, IV steroids such as methylprednisolone at 2 mg/kg/day divided twice daily or oral steroids such as prednisone 60 to 120 mg/day divided twice daily should be considered.
    - Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.
    - Taper corticosteroids as clinically indicated with improvement in liver function
    - Resume MGD013 at the next scheduled dose if no more than two doses were missed.
    - If an improvement to ≤ Grade 1 does not occur within 14 days, discontinue MGD013.
- Grade 3 transaminases increased - withhold MGD013.
    - For transaminases increased > 8 × ULN, permanently discontinue MGD013.

- Begin immediate IV steroids; it is suggested to use methylprednisolone (2 mg/kg/day divided twice daily).
- Consider additional immune suppression with mycophenolate for subjects who do not respond to corticosteroids within 3 to 5 days.
- Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.

- If transaminases increased > 5× ULN and ⩽ 8 × ULN:
  - Begin immediate IV steroids; it is suggested to use methylprednisolone (2 mg/kg/day divided twice daily).
  - Consider additional immune suppression with mycophenolate for subjects who do not respond to corticosteroids within 3 to 5 days.
  - Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.
  - If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue MGD013.
  - Resume MGD013 if:
    - Laboratory elevations improved to ⩽ Grade 2 within 7 days and improved to ⩽ Grade 1 or baseline within 14 days.
    - Steroids have been tapered to ⩽ 10 mg/day of prednisone or equivalent.
    - On resuming MGD013, laboratory tests of AST, ALT, and total and direct bilirubin will be evaluated at least once per week for 3 consecutive weeks.
- Permanently discontinue MGD013 in the case of a second increase of AST or ALT to ⩾ Grade 3.

- Grade 4 transaminases increased - Discontinue MGD013 and treat as for Grade 3 elevation.

Increased Total Bilirubin

Management guidelines for subjects experiencing increased total bilirubin are as follows:

- Grade 1 increased total bilirubin - No specific therapy required.
- Grade 2 increased total bilirubin - Withhold MGD013 until improvement to ⩽ Grade 1 or baseline.
  - Rule out viral and other etiologies. Consider imaging examinations such as ultrasound or CT scan and liver biopsy to ascertain etiology of hepatosis. Consider oral steroids.
  - If an improvement to ⩽ Grade 1 does not occur within 14 days, discontinue MGD013 and begin oral steroids.
- Grade 3 increased total bilirubin - withhold MGD013.

- For increased total bilirubin > 5 × ULN, permanently discontinue MGD013 and initiate IV steroids (it is suggested to use methylprednisolone 2 mg/kg/day divided twice daily).
    - If no response to corticosteroids is observed within 3 to 5 days, an additional immune suppression therapy with mycophenolate is considered.
    - Monitor liver function testing at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until total bilirubin has returned to Grade 1 or baseline.
- If increased total bilirubin> 3.0 - ≤ 5 × ULN:
    - Begin immediate IV steroids; it is suggested to use methylprednisolone (2 mg/kg/day divided twice daily). Consider additional immune suppression with mycophenolate for subjects who do not respond to corticosteroids within 3 to 5 days.
    - Monitor liver function tests including total bilirubin at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until total bilirubin has returned to Grade 1 or baseline.
    - If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue MGD013.
    - Resume MGD013 if:
        - Laboratory elevations improved to ≤ Grade 2 within 7 days and improved to ≤ Grade 1 or baseline within 14 days.
        - Steroids have been tapered to ≤ 10 mg/day of prednisone or equivalent.
    - On resuming MGD013, laboratory tests of AST, ALT, and total bilirubin will be evaluated at least once per week for 3 consecutive weeks.
    - Permanently discontinue MGD013 in the case of a second increase of total bilirubin to ≥ Grade 3.

- Grade 4 increased total bilirubin - Discontinue MGD013 and treat as for Grade 3 elevation.

Non-infectious Pneumonitis

Management guidelines for subjects experiencing pneumonitis are as follows:

- Grade 1 pneumonitis - No specific therapy required; close monitoring of lung function and imaging.
- Grade 2 pneumonitis - Withhold MGD013.
    - Consider corticosteroids: 1 to 2 mg/kg/day of oral prednisone or equivalent divided twice daily.
    - Taper over 4 weeks as clinically indicated.
    - Resume MGD013 at next scheduled dose if pneumonitis resolves to ≤ Grade 1 within 5 days with or without treatment.
- Grade 3 and 4 pneumonitis - Permanently discontinue MGD013.

- Hospitalization
- Recommend a pulmonary specialist consult/diagnostic evaluation including chest X-ray and CT scan.
- Initiate maximal supportive care including IV corticosteroids (it is suggested to use methylprednisolone 2 to 4 mg/kg/day divided twice daily). Higher doses may be used in consultation with the Sponsor's Monitor.
- If no response to corticosteroids is observed within 3 to 5 days, additional immune suppression therapy (i.e., infliximab, etc.) can be considered.

Skin Toxicity

Management guidelines for subjects experiencing skin toxicity are as follows:

- Grade 1 or 2 skin reactions
  - Symptomatic treatment with low-dose topical corticosteroids (betamethasone 0.1% or hydrocortisone 1%) or antihistamines (diphenhydramine).
  - Persistent Grade 1 or 2 rash should be managed with higher dose topical corticosteroids and/or oral prednisone (1 to 2 mg/kg/day) if there is no improvements with topical therapies or the rash is accompanied by other dermal toxicities such as pruritus.
- Grade 3 skin reactions – Withhold MGD013.
  - Initiate oral corticosteroids (oral prednisone 1 to 2 mg/kg/day).
  - MGD013 may be restarted at the next scheduled dosing if symptoms resolve to ≤ Grade 2 within 14 days.
  - A Grade 3 skin toxicity that does not resolve to ≤ Grade 2 within 14 days after oral corticosteroids requires permanent discontinuation of MGD013.
- Grade 4 skin reactions - Discontinue MGD013.
  - Initiate oral corticosteroids (oral prednisone 1 to 2 mg/kg/day).
  - Consideration should be given to start IV corticosteroids (methylprednisolone 1-2 mg/kg/day) for Grade 4 skin toxicities; methylprednisolone should be tapered over 30 days if resolved to < Grade 2.

Nephritis

Management guidelines for subjects experiencing nephritis are as follows:

- Grade 1 nephritis - No specific therapy required; close monitoring of renal function.
- Grade 2 nephritis - Withhold MGD013.
  - Consider nephrology consultation and renal biopsy to confirm interstitial nephritis.
  - Initiate corticosteroids: 1 to 2 mg/kg/day of oral prednisone or equivalent divided twice daily. Taper over 4 weeks as clinically indicated.
  - Resume MGD013 at next scheduled dose if:
    - Nephritis resolves to ≤ Grade 1 within 14 days with or without treatment

- Grade 3 and 4 nephritis - Permanently discontinue MGD013.
  - Consider hospitalization, nephrology consultation, and renal biopsy to confirm interstitial nephritis.
  - Initiate corticosteroids: 2 to 4 mg/kg/day of oral or IV methylprednisolone or equivalent divided twice daily. Taper over 4 weeks as clinically indicated.

Immune-Mediated Hypophysitis

Management guidelines for subjects experiencing hypophysitis are as follows:

- Grade 1 hypophysitis - No specific therapy required.
- Grade ≥ 2 hypophysitis - Withhold MGD013.
  - Consult endocrinologist.
  - Consider hospitalization.
  - Consider a short course of high dose IV corticosteroids: e.g., methylprednisolone 2-4 mg/kg/day IV (or equivalent) divided twice daily.
  - Initiate hormonal replacement therapy as indicated.
  - MGD013 may be resumed as allowed by protocol when:
    - Endocrinopathy is controlled with appropriate replacement therapy.
    - Corticosteroids reduced to ≤ 10 mg/day prednisone or equivalent.
  - Brain MRI recommended.

Thyroid Toxicity

Thyroid disorders may occur at any time during treatment with MGD013. Monitor subjects for changes in thyroid function and for clinical signs and symptoms of thyroid disorders per protocol and as indicated by clinical evaluation. Isolated hypothyroidism may generally be managed with replacement therapy without treatment interruption or corticosteroids, and treatment guidelines for hyperthyroidism are recommended below:

- Grade 1 hyperthyroidism - No specific therapy required.
- Grade 2 hyperthyroidism - Withhold MGD013.
  - Consider initiating oral corticosteroids.
  - A short course of corticosteroids such as methylprednisolone 1 to 2 mg/kg/day IV (or equivalent) divided twice daily.
  - MGD013 will be resumed if it is reduced to ≤ 10 mg/day prednisone or equivalent and stable on hormone replacement therapy (if necessary).
- Grade 3 or 4 hyperthyroidism - Withhold MGD013.
  - Consider hospitalization and consulting endocrinologist.
  - IV corticosteroids such as methylprednisolone 2 to 4 mg/kg/day IV (or equivalent) divided twice daily.
  - Initiate hormonal replacement therapy as indicated.
  - Consider restarting MGD013 when complete resolution or disease stable on hormone replacement therapy within 14 days and it is reduced to ≤ 10

mg/day prednisone or equivalent.

8.4.2 Brivanib Alaninate-related Adverse Reactions

Management of Hypertension

In case of hypertension during treatment with angiogenesis inhibitors, investigators should take measures according to the best practices of drugs. The following treatment guideline may be adopted according to experience of previous antiangiogenic therapy. Consider cardiologist consultation to recommend the optimal dose and combination regimen in case of uncontrollable hypertension.

- Persistent mild hypertension (systolic pressure: 140 - 149 and / or diastolic pressure: 90-99 mmHg)
  - Treatment:
    - Initiate or add one antihypertensive agent at a stating dose (recommendation: enalapril or hydrochlorothiazide). Increase the dose gradually until blood pressure (BP) is under control.
    - No dose adjustment of study drugs
- Persistent moderate hypertension (systolic pressure: 150 - 179 and / or diastolic pressure 100 - 109 mmHg)
  - Treatment:
    - Initiate or add one long-acting antihypertensive agent, which gradually increases to the maximum until improvement to mild hypertension.
    - Add the second drug if BP is partially controlled or not controlled, increase the dose gradually to the maximum until BP is under control.
    - Add the third antihypertensive agent if BP is not controlled or partially controlled within the moderate range, increase the dose gradually to the maximum until BP is under control.
    - When it is controlled to mild hypertension, it can be de-escalated to the next level according to the dose of brivanib alaninate.
- Persistent severe hypertension (systolic pressure >180 and / or diastolic pressure: >110 mmHg)
  - Treatment with symptoms:
    - Discontinue the investigational drug
    - Monitor BP closely. Beware of hypotension while discontinuing the investigational drug
    - Consider hospitalization for close monitoring and IV treatment
    - Treat as a hypertensive crisis.
  - Treatment if there is no symptom:
    - Suspend the investigational drug and monitor BP closely
    - Initiate or add two antihypertensive agents, which gradually increase to the maximum until BP is under control.
    - If BP is not controlled, but there is no symptom, add one drug that increases

gradually to the maximum until BP is controlled.

- When it is controlled to mild hypertension, resume the investigational drug that is considered to be de-escalated to the next level according to the dose taken by the subject
- Discontinue the investigational drug if it is still not controlled with three antihypertensive drugs at the maximum dose

- Hypertensive crisis (diastolic pressure > 120 mmHg; systolic pressure > 180 mmHg or CNS, cardiovascular and kidney involvement)

- Treatment:
  - Discontinue the investigational drug
  - Immediate treatment

Management of Hyponatremia

In the study of brivanib alaninate, about 1/3 subjects experienced > Grade 1 hyponatremia. In addition, hyponatremia is a common complication of hepatic cirrhosis and ascites. Therefore, blood biochemistry and renal and liver function should be monitored periodically in advanced HCC subjects receiving brivanib alaninate. It is recommended to adopt medical interventions in case of CTCAE Grade 1 hyponatremia.

Table 5: Management of Hyponatremia Related to Brivanib Alaninate

Electrolytes		
Hyponatremia CTCAE Grade 3: <130-120 mmol/L	The first occurrence	Continue the investigational drug and begin medical intervention until blood sodium ≥ 130 mmol/L
	Last for ≥ 7 days or occur for the second time	Suspend the investigational drug and begin medical intervention Resume the investigational drug if blood sodium ≥ 130 mmol/L, consider to reduce the dose to level -1
	The third occurrence	Discontinue the investigational drug or discuss with medical monitors
Hyponatremia CTCAE Grade 4: <120 mmol/L	The first occurrence	Suspend the investigational drug and begin medical intervention Resume the investigational drug if blood sodium ≥ 130 mmol/L, consider to reduce the dose to level -1
	The second occurrence	Discontinue the investigational drug or discuss with medical monitors

8.4.3 Toxicity and Management of Combination Toxicity

No new AEs other than toxicity related to single drug are anticipated for the combination of MGD013 and brivanib alaninate for they have different mechanism of action. However, some adverse reactions, e.g., thyrotoxicity and hepatotoxicity, may overlap. The combination medication group should be closely monitored for AEs. Both investigational drugs should be discontinued in case of any adverse events with CTCAE Grade 3 to 4 and causally related to study treatment. Before the study drug is resumed, the appropriate medical intervention should be applied until the AE is resolved to CTCAE Grade ≤1 (or baseline level if the event severity is higher than CTCAE Grade 1 at baseline). If the AE fails to be resolved to CTCAE Grade ≤1 within 28 days upon event onset, both study drugs should be

permanently discontinued and the subject should be withdrawn from the study.

When study treatment is to be resumed, if the investigator considers that the AE is related to brivanib alaninate, the treatment can be restarted at the original dose or dose reduced to next lower level as pre-defined, depending on the dose originally administered and event severity (See 8.4.2). In Phase I study, dose reduction is not allowed during the DLT observation period and permitted at most once for the remaining period. If treatment-related AE of CTCAE Grade 3-4 occurs again after dose reduction, the study treatment will be discontinued (except hyponatremia and hypertension that can be controlled by drugs, see 8.4.2). Once reduced, the dose should be maintained at lower level and dose escalation is never allowed.

Given the mechanism of action of MGD013, it is anticipated that activation of cellular immune system can be manifested as immune-related AEs (irAEs). The fundamental principles of managing irAEs are suspension of the immune checkpoint inhibitor (ICI), a course of corticosteroids and routine supportive measures are given based upon the severity of Grade 1 - 2 irAEs, and restart the treatment without adjusting the dose after adverse events are resolved; discontinue MGD013 in case of drug-related Grade 3 adverse events and restart the drug after resolving to ≤ Grade 1 or baseline; permanently discontinue MGD013 and terminate the study in case of any drug-related Grade 4 adverse events. Guidelines for irAE management are available through the American Society of Clinical Oncology and National Comprehensive Cancer Network [23](https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf) or the European Society of Medical Oncology [24](https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy). In the study, clinical management of MGD013-related adverse events is shown in 8.4.1.

9. Statistical Analysis

9.1 Analysis Set

Statistical analysis is performed using full analysis set (FAS), per-protocol set (PPS) and safety set (SS).

FAS: it includes all subjects who have received at least one dose of the investigational drug and have measurable tumors at baseline.

PPS: it includes subjects with at least one post-treatment imaging assessment of tumors, good compliance, and no serious violation or deviation against the study protocol in FAS population.

SS: it includes subjects who have received at least one dose of the investigational drug and undergone safety assessment.

9.2 Sample Size Determination

During Phase I monotherapy dose escalation study, the starting dose group (MGD013 120 mg Q2W) will adopt single-subject dose escalation and one subject will be enrolled. Subsequent dose groups and combination treatment will adopt the traditional 3+3 dose escalation scheme , with 3 - 6 evaluable subjects each, 30 - 43 subjects in total.

Phase II Part 1 is a single-arm, SWOG two-stage design study with ORR as its primary efficacy endpoint. [redacted] 40 subjects are needed [redacted] There are 2 stages for the 2nd line cohort and the radiological response (according to RECIST1.1 criteria) of 3 and more out of 20 evaluable subjects at the first stage will support the decision to proceed to the second stage of subject accrual until there are 40 evaluable subjects in this cohort. Assuming the dropout rate is 10%, 34 subjects will be enrolled.

[redacted] 30 subjects are needed [redacted] Similarly, the study has two stages. In the first stage, if response (according to RECIST 1.1 criteria) is observed radiologically in 1 or more out of 15 evaluable subjects, the enrollment of second stage will be open and an additional of 15 evaluable subjects will be enrolled. Assuming the dropout rate is 10%, 45 subjects will be enrolled.

Phase II Part 2 is a expansion study and it is estimated to enroll 120 subjects to further assess the safety and efficacy of the investigational drug.

9.3 Statistical Analysis Method

9.3.1 Safety Analysis

Safety analysis is performed in the SS. Safety parameters include: physical examination, vital signs, AEs and laboratory tests, ECG, etc. AEs will be coded using MedDRA System Organ Class and Terminology.

The incidence rates and severity levels of adverse events, dose-limiting toxicity (DLT), adverse events leading to withdrawal from the study, adverse events leading to discontinuation, adverse events leading to death, and serious adverse events will be summarized. A line listing of AEs will be provided.

Each laboratory should examine the indicators and ECG, describe their changes during the study, use a cross-classification table to describe the normal and abnormal changes before and after treatment and provide a data list. Some specified parameters will be summarized descriptively per protocol.

9.3.2 Efficacy Analysis

FAS and PPS are both used for efficacy analysis, and of which, PPS is the main analysis set and FAS analysis can provide supporting evidence.

Analysis method of the primary efficacy endpoint: summary of BICR-assessed objective response rate (ORR) after administration according to RECIST1.1. The secondary endpoints include investigator-assessed ORR, BICR-assessed ORR according to irRECIST, progression-free survival (PFS), time to tumor progression (TTP), disease control rate (DCR), duration of response (DoR), survival rate at fixed time points (6, 9, 12 months) and overall survival (OS).

For the objective response rate (ORR), the point estimate, p-value of one-sided test and its 95% confidence interval (95% CI) will be provided. Kaplan-Meier method was used to estimate the survival functions for time to tumor progression (TTP), progression-free survival (PFS), and overall survival (OS), respectively, and their survival curves plots, the median TTP, median PFS, Survival rate at fixed time points and their respective 95% confidence intervals (95% CI) will be provided.

See the statistical analysis plan (SAP) for the details of Statistical Analysis.

10. Clinical Trial Management

10.1 Statement

This clinical study shall be implemented and reported in accordance with the *Declaration of Helsinki*, Chinese Good Clinical Practice, ICH GCP and local appropriate regulations.

10.2 Ethical Considerations

Before initiating a trial, the investigator should obtain approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, informed consent form and any other written information to be provided to subjects.

Before initiation of the clinical trial, approval must be obtained from the Ethics Committee. The approval issued by the Ethics Committee shall be made available to the investigator in written form. The investigator is obligated to provide the sponsor of a copy of the approval. The Ethics Committee approval should clearly list all the committee members involved in the review with their respective responsibilities.

During the clinical study, any of issues related to the subject safety of the clinical study, such as changes in the clinical study protocol or subject informed consent form as well as serious adverse events in the clinical study, must be reported to the Ethics Committee in a timely manner. The completion or termination of the clinical study must also be reported to the Ethics Committee.

10.3 Source Data Verification

The investigator must properly handle all the data obtained during the clinical study, so as to ensure the rights and privacy of the subjects participating in the clinical study. The investigator must permit the monitor/auditor/inspector to consult and review required clinical study data to verify accuracy of original data and learn about study progress. If the original records cannot be verified, the investigator should agree to assist to further validation of data with them.

10.4 Quality Assurance and Auditing

The quality of all drugs and materials used in the clinical study must be controlled. The sponsor, personnel authorized by the sponsor or related medical management institutions have the right to audit the clinical study in order to ensure the authenticity of the clinical study data and abide by the provisions of the clinical study protocol. Subjects participating in the clinical study will be informed of the audit, but the privacy and data of subjects will be strictly protected.

10.5 Informed consent form

The investigator has the responsibility to explain to each subject the purpose, methods, benefits and potential risks of this clinical study. Signed informed consent must be obtained before conducting any study-specific procedures. Informed consent should be expressed in written form. The informed consent must be dated and signed by the subject him/herself. For those subjects who could not sign the informed consent form by themselves for any reasons, their parents, legal guardians, or protectors should sign the informed consent form. The original signed informed consent form and the process of obtaining informed consent should be preserved and documented in the case report form and relevant trial source documents by the investigator.

By signing the informed consent form, the subject must also agree to allow the sponsor, the drug approval authorities, and the auditor and (or) the monitor to check and verify the

obtained source data and materials related to clinical study, and all parties mentioned above must comply with confidentiality statement.

10.6 Protocol Amendment

Upon finalization of the study protocol, any changes to the protocol must be filed in details, which should be at least jointly signed and dated by the investigator and the sponsor, with version numbers indicated.

The changes should involve the sponsor and the investigator. The revised contents should not be implemented before obtaining the approval of the Ethics Committee.

10.7 Case Report Form (CRF)

The CRO working on behalf of Zailab is responsible for data management, so as to ensure the authenticity, integrity, privacy and traceability of the clinical study data.

Information has been entered by the investigator and its authorized personnel to the eCRF, and only the investigator with a physician qualification certificate can sign on the clinical/safety evaluation conclusion. Any changes to the eCRF will be automatically recorded in the system after the input of source data.

10.8 Monitoring

The Sponsor will designate a monitor for on-site monitoring. Monitors should operate in compliance with the company's standard operation procedure (SOP). They should perform regular visits from the start to the end of study.

The monitors will have access to relevant source data of the clinical study, and review CRF according to SOP to confirm information completeness, accuracy and consistency with original data.

CRFs, copies of lab tests and medical tests must be accessible to clinical monitors, auditors and health authorities for review at any time. Monitors should review all CRFs and informed consent forms.

10.9 Confidentiality Agreement and Subject Privacy

The Investigator must ensure that the confidentiality of the information about the Sponsor and the investigational drug provided or disclosed by the Sponsor for the clinical study, and such information can only be used upon authorization by the Sponsor.

The commitment is independent, effective and sustained until the permission of the Sponsor.

The Investigator also commits to keep confidentiality to a third party for any confidential information provided or disclosed by the Sponsor and the investigational products. Any intention to use such information must be approved by the Sponsor and agreed upon.

Investigators are obligated to protect the privacy of subjects participating in clinical study. In all the documents submitted to the sponsor, the identity of any subject in the clinical study will be coded by the subject number, while the subject's name, admission number should not show up. The investigator must appropriately keep name and address of clinical trial subjects, as well as enrollment table corresponding to clinical study subject number. These enrollment tables will be strictly kept confidential and stored by the investigator.

11. Publication of study protocol and results

Zai Lab (Shanghai) Co., Ltd., as the sponsor, has exclusive rights to this study. The manuscript and publication will reflect the cooperation among investigators and investigator's institution and Zai Lab. Authors will be identified before drafting of the manuscript. Many study institutions and investigators are participating in this study, unless prior consent has been obtained from Zai Lab, individual participating institution or investigator shall not publish any data related to the clinical study. Zai Lab has the final right to determine how the manuscript and its relevant publication will be disclosed.

12. Data Archival

According to the requirements of relevant laws and regulations, the investigator should properly keep source records related to the clinical study. Copies of all clinical study data must be retained for at least 5 years after approval for marketing. It is the responsibility of the Sponsor to inform the Investigator/Study Site of when it is no longer necessary to further retain such data.

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14. Appendix

Appendix A Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Guideline

1. Overview of Evaluation Process

Tumor burden will be recorded at the baseline. First, the reviewer will determine lesions suitable for repeated quantitative evaluations ("measurable" lesions). Among measurable lesions, the reviewer will select a set of lesions for quantitative follow-up throughout the study ("target" lesions). RECIST 1.1 recommends method maximizing the measurement reproducibility or reliability to measure target lesions and calculate the tumor burden of target lesions (sum of diameters). All tumor lesions not selected for quantitative evaluation will be recorded and qualitatively followed up as "non-target" lesions.

At each follow-up visit, the reviewer will evaluate the target lesion, by measuring and calculating the sum of diameters in an appropriate method, to compare with baseline value (for observing partial response) and with the minimum value observed before this time point (also referred to as the "minimum", for observing disease progression). The reviewer will also qualitatively evaluate non-target lesions and look for new lesions, to provide overall response of the subject at a specific visit by combining the information of target lesions, non-target lesions, and new lesions. The relevant efficacy endpoints will be evaluated based on overall response in the sequential visits and corresponding dates.

2. Baseline Tumor Measurement

2.1 Measurement of Lesions

All lesions should be measured in metric unit and with a caliper when clinical evaluation is required. All baseline assessments should be as close to the initiation of treatment, up to a maximum of 4 weeks prior to the initiation of treatment.

Lesions other than lymph nodes are measured by CT or MRI scan for the longest diameter. Typically, it is measured from the axial plane. Lymph nodes, even though not affected by tumor, have normal anatomical structures in imaging examination. At baseline and subsequent visits, only the short diameter of lymph nodes is required to calculate the sum of diameters of target lesions.

At baseline assessment, tumor lesions and/or lymph nodes will be classified as measurable or unmeasurable lesions as follows:

2.1.1. Measurable Tumor Lesions

Tumor lesions can be accurately measured, and the longest diameter on the measurable plane should be the following minimum size at least:

- CT scan: 10 mm (CT scan slice thickness $\leqslant$5 mm)
- MRI scan: 10 mm or twice the slice thickness plus any interval thickness, whichever is greater
- At least 10 mm measured by caliper in the clinical examination (lesions that cannot be accurately measured by caliper are unmeasurable lesions)
- Chest X-ray: 20 mm

Malignant lymph nodes: pathologically enlarged and measurable, the short diameter of lymph nodes must be $\geqslant$15 mm in CT scan (recommended CT scan slice thickness $\leqslant$5 mm). At baseline and follow-ups, only short diameters are measured and followed up. The size of lymph

node is generally reported in two-dimensional data on the image plane (CT as the axial plane and MRI as the coronal or sagittal plane). For example, the short diameter of a 20 mm × 30 mm abdominal lymph node is 20 mm, and it can be considered as a malignant, measurable nodule. In this case, 20 mm is the measurement of lymph node as a target lesion.

2.1.2. Unmeasurable Tumor Lesions

Unmeasurable tumor lesions include small lesions (the longest diameter <10 mm or short diameter of pathological lymph node ≥10 mm while <15 mm) and truly unmeasurable lesions. Truly unmeasurable lesions include: leptomeningeal lesions, ascites, pleural or pericardial effusions, breast inflammatory lesions, cutaneous or pulmonary lymphangitis, peritoneal metastases, and abdominal mass/enlargement of abdominal organs identified in the physical examination but cannot be measured by repeatable imageology.

Pathological lymph nodes (with the short diameter ≥10 mm while <15 mm) should be considered as unmeasurable lesions. Lymph nodes with the short diameter <10 mm should be considered non-pathological and not be recorded for follow-up.

2.1.3. Some Special Considerations for Lesion Measurability

Bone lesions, cystic lesions, and lesions that have received prior topical treatment should be noted separately:

Bone lesions:

- Bone scan, PET scan, and bone radiograph are not imaging techniques suitable for measurement of bone lesions, but they are conductive to confirm the presence or absence of bone lesions.
- Osteolytic lesions or mixed osteolytic and osteoblastic lesions with identifiable soft tissue component can be assessed using cross-sectional imaging techniques (e.g., CT or MRI), and are considered measurable if the soft tissue component meets the definition of measurable lesions as described above.
- Osteoblastic lesions are not measurable.

Cystic lesions:

- Simple cysts that meet radiographic criteria should not be considered as malignant lesions (neither measurable nor non-measurable lesions) because they are by definition simple cysts.
- Cystic metastatic “cystic lesions” are considered measurable lesions if meeting the definition of measurability mentioned above. If the same subject has a non-cystic lesion, it should be preferred as the target lesion.

Lesions that have received prior topical treatment:

- Tumor lesions located in previously irradiated areas or areas that have received other topical treatment are typically not considered as measurable lesions unless the lesion has disease progression, or is irradiated more than 6 months prior to the enrollment.

2.1.4. Measurability Description of Assessment Methods

At baseline and follow-up assessments, the assessment methods and techniques should be consistent for assessment of each clearly documented lesion. Except lesions that cannot be assessed by imaging examinations while can be assessed by clinical examination, all lesions must be assessed by imaging examinations.

CT, MRI: CT is the method currently used with optimal repeatability to measure target lesions for efficacy evaluation. The measurability of lesions for CT scan in this guideline is based on the assumption of CT slice thickness ≤5 mm. When CT slice thickness >5 mm, the minimum size of measurable lesion should be at least 2 times the slice thickness. In some cases (e.g., whole body scanning), MRI is acceptable. MRI slice thickness (to determine the measurability) refers to the distance from the top of one slice to that of the next one (including any slice interval).

If a subject is known not to use contrast medium for CT scan due to allergy or renal insufficiency prior to the enrollment, the subject should undergo chest non-contrast CT, abdominal and pelvic MRI. If a subject experiences iodine-contrast allergy during the study, it should be dealt with in the same method (chest non-contrast CT, abdominal and pelvic MRI). It should be noted that altered examination may result in the lesion unevaluable following this time point.

Clinical lesions: Clinical lesions can only be considered measurable when they are superficial and with the diameter ≥10 mm measured by caliper. For skin lesions, it is recommended to keep color photographs of lesions with a ruler or length standard on file.

Chest X-ray: CT has higher sensitivity than X-ray examination (especially to confirm new lesions), and therefore chest CT is preferred instead of chest X-ray. The chest X-ray lesion with clear boundary surrounded by pneumatic lung tissue can be regarded as a measurable lesion. However, CT is preferred than X-ray, even if non-contrast CT.

Ultrasound: Ultrasound is not used to evaluate the lesion size; therefore, it is not suitable for measurement of lesions.

3. Assessment of Tumor Response

3.1 Overall Assessment of Tumor Burden and Assessment of Measurable Lesions

It is required to assess the baseline total tumor burden as a reference for subsequent measurements to assess objective response or disease progression. This protocol only involves subjects with measurable disease at the baseline. The measurable disease is defined as the presence of at least 1 measurable tumor lesion (as detailed above).

3.1.1. Baseline Recording of Target and Non-target Lesions

The target lesion is a subset of measurable lesions. The definition of measurable lesions has been provided above. If there are 1 or more measurable lesions at the baseline, up to 5 lesions in all affected organs (up to 2 lesions in each organ) can be combined as the baseline target lesion to record and measure. It indicates that if a subject only has 1 or 2 affected organs, at most 2 (1 site) and 4 measurable lesions (2 sites) will be recorded. Other lesions in each organ are recorded as unmeasurable lesions (even though CT scanning >10 mm). The target lesion is selected according to the lesion size (the lesion with the longest diameter is preferred), and the target lesion should represent all affected organs as much as possible, and can be measured repeatedly. In a few cases, once the largest lesion cannot be measured repeatedly, it should select the submaximal lesion that can be measured repeatedly. Paired organs (lungs, kidneys, etc.) should be regarded as a single organ. All lymph nodes are also considered as a single organ.

The sum of diameters of all target lesions (the longest diameter of non-lymph node lesions and short axis of lymph node lesions) are reported as the baseline sum diameters. If lymph node is the target lesion, only the short axis is calculated for the sum as described above. The baseline sum diameters of target lesions will be taken as reference to assess the objective response.

All other lesions (or diseased sites), including pathological lymph nodes, should be recorded as non-target lesions at the baseline. It is not required to measure non-target lesions, but only recorded as “present” or “disappeared”, or “significantly progressed” in rare cases. Moreover, multiple non-target lesions in the same organ can be recorded as one item in the CRF (e.g., "multiple pelvic lymph node enlargement" or "multiple liver metastases").

3.2 Criteria for Tumor Response

This section provides definitions of objective tumor response determined based on target tumor lesions:

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (target and non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesion (including the baseline sum if that is the smallest on study) taking as reference the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate that an absolute increase of at least 5 mm.
- Stable Disease (SD): Neither sufficient shrinkage to quality for PR nor sufficient increase to quality for PD, taking as reference the smallest sum diameters while on study.

Special Considerations for Evaluation of Target Lesions

Lymph nodes: For lymph nodes identified as target lesions, actual short axis measurement (on the same anatomical plane as the baseline exam) should be always recorded, even if it is reduced to <10 mm while on study. It indicates that the sum of lesions may not be 0 if lymph nodes are taken as target lesions, even if the criteria for CR have been met, because the normal lymph node is defined as short axis <10 mm. Therefore, when designing the case report form or using other data collection methods, data of lymph nodes as target lesions should be collected in separate module/chapter, and requiring the short axis of all lymph nodes <10 mm if the criteria for CR have been met. For PR, SD, and PD evaluation criteria, the actual measurement of short axis of lymph nodes will be included in the sum of the diameters of target lesions.

Target lesions “too small to be measured”: All target lesions (lymph nodes or non-lymph nodes) having been recorded at the baseline should be recorded for its actual size (even if the lesion is very small, e.g., 2 mm) at each subsequent assessment. However, in some cases, lesions recorded as target lesions at the baseline (including lymph node target lesions) may be blurry in the subsequent CT scans, which makes it difficult for radiologists to determine an accurate measurement and therefore may report as "too small to measure". In such case, a value should be still recorded in the CRF. The detailed recording rules are as follows:

- If the radiologist considers that the lesion may have disappeared, the measurement should be recorded as 0 mm.
- If it considers that the lesion is still present but not clear and too small to be measured, a default of 5 mm should be recorded and marked with BML (below the measurable limit) (Note: This rule is not applicable to lymph nodes since the size of normal lymph nodes is typically determined, and retroperitoneal lymph nodes are wrapped in fat; however, if lymph nodes are considered present but not clear and too small to be measured, in such cases, it can also be recorded as a default of 5 mm and marked

with BML). The default value is derived from the CT scan slice thickness (but it does not vary with CT slice thickness). The measurement of these lesions may be non-repeatable; therefore, the default value helps to avoid tumor response or progression owing to measurement errors. It is important to reiterate that if the radiologist can give an actual measurement, even if <5 mm, it should be recorded without marking of BML (BML corresponding to <).

Treatment-induced lesion division and fusion: If a non-lymph node lesion is divided, the sum of the longest diameters of divisions should be calculated in the sum of target lesions. Similarly, if there is lesion fusion (merge) with interface remaining between lesions, the sum of the longest diameters of each lesion is calculated in the sum of target lesions. If the lesions have been fully fused, the vector of the longest diameter is taken as the largest and longest diameter of the "fused lesion".

Evaluation of Non-Target Lesions

This section provides the criteria for tumor response determined based on non-target lesions. Although some non-target lesions are in fact measurable, there is no need to measure these lesions, but to make qualitative assessments at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of at least one non-target lesion or/and maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): unequivocal progression of non-target lesions as overall assessment regardless of the status of target lesions.

Special Considerations for Evaluation of Progressive Disease of Non-Target Lesions

The definition of progressive disease of non-target lesions is supplemented as follows:

If the subject has measurable disease concomitantly: In such case, the substantial and significant deterioration of non-target lesions is required to reach the conclusion of “unequivocal progressive disease”, even if the target lesion is SD or PR, the overall tumor burden is significantly increased to require termination of treatment. The small "increase" in the size of one or more non-target lesions is normally insufficient to determine as unequivocal progressive disease. Therefore, in the case of target lesions achieving SD or PR, it is rare to make the assessment of overall progressive disease based only on changes in non-target lesions.

If the subject has only unmeasurable lesions: It occurs in some phase III clinical studys not requiring measurable lesions in the inclusion criteria, and the above basic viewpoints are applicable. However, in this case, there are no measurable lesions as reference to assess increased tumor burden of unmeasurable lesions. Since it is not easy to quantify the deterioration of non-target lesions (By definition: If all lesions are indeed unmeasurable), if the overall tumor burden increase assessed based on changes in unmeasurable lesions is comparable to that in size of measurable lesions assessed as PD (i.e., tumor burden increase manifested as a 73% increase in “size” (equivalent to a 20% increase in the diameter of measurable lesion)), it is considered to determine as progressive disease. Similar examples include pleural effusion from “micro” to “large amount”, lymphatic lesions from localized to disseminated or substantial disease progression requiring adjustment of treatment regimen. If "unequivocal progressive disease" is observed, overall progressive disease can be considered at the time point of assessment. Ideally, unmeasurable lesions are assessed by objective criteria, while it is hard to achieve due to the nature of such unmeasurable lesions, therefore the tumor

burden increase to reach the conclusion of progressive disease based on unmeasurable lesions must be significant and substantial increase.

New Lesions

The appearance of new malignant lesions usually indicates disease progression; therefore it is very important to identify new lesions and give proper explanation. There are no specific criteria for the imaging findings of new lesions, but it should be clear: neither varying with different scanning techniques or imaging mode, nor taking suspected non-tumor lesions (e.g., some "new" bone lesions may be just the recovery or deterioration of original lesions) as new lesions.

This is especially important when the subject's baseline lesion has PR or CR. For example, the necrosis of liver lesion may be reported as a “new cystic lesion” in CT scan, but actually it is not a new tumor lesion.

Anatomical lesions identified in the follow-up assessments while not found in the baseline exam will be considered as new lesions, suggesting progressive disease. For example, if a subject with visceral lesion at the baseline assessment is examined with metastases in brain CT or MRI on study, the brain metastases will be taken as the evidence of PD, even though the brain imaging is not performed at the baseline.

If a new lesion is hard to identify, e.g., being too small, further treatment and follow-up assessments may clarify whether it is a new lesion. If the subsequent scans confirm as a new lesion, it should be evaluated as progressive disease, and the time to progression should be the date of initial scanning.

Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

FDG-PET can serve as a supplement for CT scan to assess progressive disease (especially for suspected "new" lesions). New lesions identified by FDG-PET can be assessed according to the following rules:

- If the baseline FDG-PET finding was negative, while positive in the follow-up FDG-PET, the new lesion has a sign of PD.
- FDG-PET was not performed at the baseline, and FDG-PET indicates a positive result at the follow-up:
    - If the positive result in follow-up FDG-PET is confirmed by CT as a new lesion, PD is determined.
    - If the positive result fails be confirmed as a new lesion by CT (original lesion or it is uncertain whether there is lesion at the PET-positive site), subsequent CT scans are required to determine whether there is progressive disease at the site actually (if confirmed, the date to progression is the date of initial FDG-PET scan).
    - If the positive findings of follow-up FDG-PET are consistent with existing lesions in the prior CT scan, and there is no progression as shown in the anatomical image of the lesion, there is no PD.

3.3 Considerations for Response Evaluation

When lymph node lesions have been included in the sum of target lesions and they are reduced to the physiological size (<10 mm), measurement data are still shown in the scan results. Even if lymph nodes are normal, this measurement should be recorded to avoid exaggerating the degree of progressive disease based on lymph node enlargement. It suggests that the sum tumor

diameter recorded in the case report form (eCRF) of CR subjects may not be "0".

If the subject's overall health condition deteriorates and requires termination of treatment, but there is no objective evidence of PD at the time point, it should be reported as "symptom deterioration". Even if the treatment is terminated, its objective progression should be recorded positively. Symptom deterioration is only one reason for the discontinuation of treatment in clinical study, rather than a specific term for assessment of objective response of tumors. The objective response of such subjects should be determined through a comprehensive assessment of target lesions, non-target lesions, and new lesions in Table 1 and 2.

In some cases, it is difficult to distinguish between residual lesions and normal tissue. When the assessment of complete response depends on this determination, it is recommended to assess residual lesions (fine needle aspiration/biopsy) prior to classifying them to complete response.

For the findings undetermined as progressive disease (e.g., very small and undetermined new lesion, cystic changes or necrosis of the lesion, etc.), the treatment can be continued until the next scheduled evaluation. If progressive disease is confirmed in the following scheduled evaluation, the date to progression should be the date on which the disease progression has been previously suspected.

3.4 Determination of Missing Evaluation and Non-evaluable

If lesion imaging/measurement cannot be done at a particular time point, the subject is not evaluable at that time point. If only partial lesion can be measured in an evaluation, it is typically considered unevaluable at that time point unless there is convincing evidence that the missing lesion does not affect the overall response at that time point. Such cases happen mostly in the progressive disease.

For example, the sum of 3 measurable lesions in one subject was 50 mm at baseline, but only 2 lesions were evaluable at the follow-up, with a sum of 80 mm, regardless of impact of the missing lesion, the subject still experiences progressive disease. If one or more target lesions cannot be evaluated due to absent scanning or poor image quality affecting observation for evaluation, the subject is unevaluable, and therefore the response of target lesion is “not evaluated”. Similarly, if one or more non-target lesions are “not evaluated”, the overall response of non-target lesions should be “not evaluated” (except unequivocal progression). If the response of target or non-target lesions is “not evaluated”, the overall response is “not evaluated” (except there is clear evidence for progressive disease) as it is equivalent to unevaluable at that time point.

3.5 Response Evaluation at Specific Time Points

The tumor response should be assessed at each time point specified in the protocol. Appendix A-Table 1 provides the summary of overall response at each time point for subjects with measurable disease at baseline.

If the subject has only unmeasurable lesions (non-target), Appendix A-Table 2 is used for evaluation.

Appendix A-Table 1. Response of subjects with Target (+/- Non-target) Lesions at Specific Time Points:

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/not evaluated	No	PR
SD	Non-PD/not evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = no evaluated.

Appendix A-Table 2. Response of Subjects with Only Non-target Lesions at Specific Time Points:

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = no evaluated.

a "Non-CR/Non-PD" is preferred over "stable disease" for non-target diseases since SD is increasingly used as an endpoint for assessment of efficacy.

References:

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Appendix B. Immune-Related RECIST Guidelines

The immune-related RECIST (irRECIST) are adapted from Wolchok 2009.

All patients will be required to have at least 1 measurable lesion to be considered as having measureable disease at baseline for the determination of eligibility for this study. Measureable lesions are defined below.

1 Measurability of Tumor at Baseline

1.1 DEFINITIONS

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

1.1.1 Measurable

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

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

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

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with $\geqslant$ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measureable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

1.1.3 Special considerations regarding lesion measurability

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

Bone lesions:

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

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measureable 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 loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion prior to study enrollment.

1.2 Specifications by methods of measurements

1.2.1 Measurement of lesions

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

1.2.2 Method of assessment

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

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

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 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.

Tumor markers: Tumor markers will not be used to assess objective tumor response.

2 Tumor Response Evaluation

2.1 Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above).

2.2 Baseline documentation of 'target' and 'non-target' lesions

Where more than one measurable lesion is present at baseline all lesions up to a maximum of

five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. For example, in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesions which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted previously, pathological nodes which are defined as measurable and may be identified as target lesions must meet criterion of a short axis of $\geqslant$ 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 two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x30 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 $\geqslant$ 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.

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

2.3 Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions by immune-related response criteria (i.e., irRECIST).

2.3.1 Evaluation of target lesions

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

Immune-Related Partial Response (irPR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Immune-related Progressive Disease (irPD): 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.

Unlike conventional RECIST criteria, the appearance of new measurable lesions does not automatically denote disease progression under immune-related response criteria. Rather the dimensions of new measurable lesions are added to overall sum of tumor diameters for determination of objective response status. Patients will not be considered as having progression unless the new overall sum of diameters has increased by > 20% from the smallest sum of tumor diameters achieved while on study.

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

2.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 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 complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In order to qualify for irCR, each node must achieve a short axis < 10 mm. For irPR, irSD and irPD, 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 nonnodal) 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 case report form. 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. 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 lesions. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of non-target lesions

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

Immune-Related Complete Response (irCR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesions(s)

Immune-Related Progressive Disease (irPD): Unlike conventional RECIST 1.1, new measurable lesions or increases in the size of non-target lesions do not define PD in isolation in the immunerelated response criteria. Rather, immune-related PD is established if the sum of diameters is > 20% of the nadir of the sum of diameters for a given patient.

2.3.4 New Lesions

The appearance of new malignant lesions alone does not denote disease progression. Instead, the diameter of new lesions is added to the sum of diameters for target and non-target lesions.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease.

2.4.1 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. For

patients experiencing irCR or irPR, a confirmatory scan obtained no less than 4 weeks after the original scan is required to confirm the objective response. For patients experiencing

irPD, but who demonstrate acceptable tolerability of treatment as evaluated by the Investigator, a

confirmatory scan obtained no less than 4 weeks after the original scan is required for the confirmation of irPD.

Immune-related response determination per irRECIST

Target Lesions	Non-Target Lesions	%Change Tumor Burden	Immune-Related Response Status
CR	CR	-100%	irCR
PR	Any	≤-30%	irPR
PR	Any	≥-30% to <+20%	irSD
PR	Any	≥+20%	irPD
SD	Any	≥-30% to <+20%	irSD
SD	Any	≥+20%	irPD
PD	Any	≥+20%	irPD

No new lesions allowed to achieve irCR status. Otherwise, presence or absence of new measurable or new non-measurable lesions does not affect response status in isolation. New measurable lesions added to cumulative tumor burden to calculate % change tumor burden for the determination of immune-related response status.

Immune-Related Complete Response (irCR): Complete disappearance of all target and nontarget lesions and no new lesions. The short axis of all lymph nodes must be ≤ 10 mm.

Immune-Related Partial Response (irPR): The sum of diameters has decreased ⩾ 30% from the baseline, but does not meet the criteria for irCR.

Immune-Related Stable Disease (irSD): The patient does not meet criteria for irCR, irPR, or irPD.

Immune-Related Progressive Disease (irPD): The sum of diameters for target lesions and new measureable lesions has increased by ⩾ 20% from the nadir sum of diameters.

2.4.2 Missing assessments and inevaluable designation

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

2.4.3 Best overall response: all time points

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

Complete or partial responses may be claimed only if the objective response is confirmed on a follow-up scan obtained no less than 4 weeks after the initial scan demonstrating an objective response. Absent this subsequent radiographic confirmation, irCR or irPR designations will be considered as unconfirmed responses.

2.4.4 Special notes on response assessment

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table.

2.5 Confirmation/Duration of response

2.5.1 Confirmation

Objective responses should be confirmed by CT and/or MRI scans obtained no less than 4 weeks after the original scan.

2.5.2 Duration of overall response

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

2.5.3 Duration of stable disease

Stable disease is measured from the start of the treatment 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 irPD).

Reference: Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al., Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin. Cancer Res, 2009. 15(23): p. 7412-7420.

Appendix C. Barcelona Clinic Liver Cancer (BCLC)

Stage	PST	Tumor	Liver function
Stage A			
A1	0	Single tumor	No portal hypertension, bilirubin normal
A2	0	Single tumor	Portal hypertension, bilirubin normal
A3	0	Single tumor	Portal hypertension, bilirubin abnormal
A4	0	1 - 3 tumors, <3 cm	Child-Pugh A-B
Stage B	0	Large multinodular tumors	Child-Pugh A-B
Stage C	1-2	Vascular invasion or extrahepatic spread	Child-Pugh A-B
Stage D	3-4	Any stage	Child-Pugh C

Appendix D. Child-Pugh Classification

Compensated and decompensated liver cirrhosis are a rough estimate for liver function of subjects with liver cirrhosis. It is difficult to divide the boundary of the two stages, and the severity of subjects at decompensated stage also varies greatly. Child (1964) divided the five indexes, including serum bilirubin, ascites, serum albumin level, prothrombin time and general condition into three grades (1, 2, 3) for scoring. The lowest score of 5 indicators is 5, and the highest score is 15, classifying as grade A, B, and C according to the score.

Child-Pugh Scoring and Scale on Severity of Liver Disease

Measure	Score		
	1	2	3
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4
Ascites	None	Mild	Moderate and over
PT prolongation or INR	1-3 sec <1.7	4-6 sec 1.7-2.3	>6 sec >2.3
Total serum bilirubin (μmol/L)	<34	34-51	>51
Serum albumin (g/L)	>35	28-35	<28

Note: Class A 5-6; class B 7-9; class C 10-15;

Class A and better class B (i.e., score 7) can be enrolled.