CLINICAL STUDY PROTOCOL

Protocol Title:	A multi-center, single-arm, and open-label Phase Ib/II study exploring the safety/tolerability, pharmacokinetics, and efficacy of GFH018 in combination with Toripalimab in the treatment of patients with advanced solid tumors
Protocol Number:	GFH018X0201
Study Phase:	Phase Ib/II
Brief Title:	Phase Ib/II study of GFH018 in combination with Toripalimab in the treatment of patients with advanced solid tumors
Sponsor:	Genfleet Therapeutics
Version Number:	3.0
Release Date:	18-Nov-2022

Sponsor's Signature Page

Protocol title: A multi-center, single-arm, and open-label Phase Ib/II study exploring the safety/tolerability, pharmacokinetics, and efficacy of GFH018 in combination with Toripalimab in the treatment of patients with advanced solid tumors

Protocol Number: GFH018X0201

Version Number and Date:3.0, 18-Nov-2022

This study will be conducted in accordance with the requirements of this clinical study protocol, International Council for Harmonization Good Clinical Practice Guideline (ICH-GCP), and relevant national laws and regulations.

This study will comply with the Declaration of Helsinki and take necessary measures to ensure the safety and interests of the subjects.

Sponsor: Genfleet Therapeutics

Signature of sponsor:

Name and Title (print)	Name (signature)	Date (DD /MM/YYYY)

Investigator's Signature Page

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Protocol Number: GFH018X0201

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By signing the signature page of this protocol, the investigator confirms and agrees:

I have read the protocol GFH018X0201 entitled "A multi-center, single-arm, and open-label Phase Ib/II study exploring the safety/tolerability, pharmacokinetics, and efficacy of GFH018 in combination with Toripalimab in the treatment of patients with advanced solid tumors".
I agree to conduct study and comply the ICH-GCP and applicable national or regional regulations/guidelines.
I agree to ensure that all associates, colleagues, employees assisting in this study at my site are informed about their obligations.
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Genfleet Therapeutics.

Principal investigator (print)	Principal investigator (signature)	Date (DD/MM/YYYY)

Protocol Change Summary (Nov2022)

This protocol is amended to include osteosarcoma and triple-negative breast cancer (TNBC) as two new subgroups in phase II. Specific requirements for previous immunotherapy of nasopharyngeal carcinoma subjects have been added. Tumor types with potential benefit will be expanded at the discretion of the sponsor and leading investigators. Minor changes have been made to correct some inconsistency in the protocol.

Protocol Change Summary (Apr2022)

This protocol is amended to add new strengths for GFH018 [redacted]. Hs-CRP and cysteine protease inhibitor (Cystatin C) are removed from the laboratory tests of cardiac markers due to inconvenience and limitation of clinical application. 20mg BID is removed from the recommended adjustment scheme of GFH018 considering the limited potential benefit at this dose. The dose delay for a patient to withdraw from the study treatment (from the intended day of the next scheduled dose) is adjusted from 21 days to 28 days as a cycle.

Protocol Change Summary (Mar2022)

This protocol is amended to include following changes: to add more tumor types in phase II part; to summarize updated clinical data from FIH study GFH018X1101; GFH018 7-day on/7-day off dosing regimen has been removed; study assessment schedule has been adjusted; blood sampling schema has been added and other modifications of study procedures have been made.

Summary of changes from protocol V1.2 to V 2.0:

Section #	Description of Change	Rationale(s)
3.3 & 4.1 & 7.5	Add three types of tumor (i.e. thymic carcinoma, endometrial cancer, and extranodal NK/T-cell lymphoma) in phase II part.	Based on the preclinical and clinical data, TGF-β inhibitors combined with anti-PD-(L)1 therapy might have a synergistic antitumor effect on thymic carcinoma, endometrial cancer, and extranodal NK/ T cell lymphoma
1.1 & 1.3.2	Update clinical results of GFH018 FIH study	Data of GFH018 monotherapy updated
Study Assessment Schedule & 1.2.2.1 &3.1 & 6.2.3 & 7.2.1.1	Remove 7 days on / 7 days off dosing regimen	It will be explored in a study combining with concurrent radiochemotherapy
Study Assessment Schedule	Adjust the table frame according to study phase Ib and II; study procedures were modified	Simplify study procedures and clinical operations
Blood Sampling Schema	Add blood sampling schema	Simplify study procedures and clinical operations
1.2.2.1 & 3.1	Update starting dose of GFH018	Update based on emergent data of GFH018 FIH study
2	Remove iRECIST and add Lugano 2014 Criteria for extranodal NK/T-cell lymphoma	Adjust criteria for tumor response evaluation
4.1	Tumor tissue specimen collection has been changed from mandatory to optional	For patients who meet other criteria to have access to treatment
	Add “with toxicities left from prior anti-tumor therapy not resolved to baseline or CTCAE grade 1 (neurotoxicity or alopecia ≤	For safety consideration of enrolled patients

	grade 2)”	
	For phase II part hepatocellular carcinoma patients: loosen the lower limit of platelet	Considering the characteristics of hepatocellular carcinoma patients, after evaluating the safety risks, provision on relevant indicator were loosened.
	For phase II part cervical cancer patients: loosen the lower limit of hemoglobin	Considering the characteristics of cervical cancer patients, after evaluating the safety risks, provision on relevant indicator were loosened.
4.2	Change the exclusion criteria for interstitial pneumonitis or pneumonitis	To better meet the requirements of clinical practice.
	Change washout period requirement for traditional Chinese medicine	To better meet the requirements of clinical practice.
7.3	Remove Fibronectin evaluation， and add tumor-infiltrating lymphocytes (TILs) as exploratory endpoints	TIL analysis is a potential predictive biomarker according to recent publications.
8.2.3	Time period for collecting death events has been adjusted	In accordance with SAE collection requirement
Note: Minor changes have been made throughout the protocol to address consistency pertaining to major changes made in the protocol or to clarify.		

Protocol Change Summary (Jun2021)

This protocol amendment is to address requests and feedback from the Ethics Committee and investigators. The clinical safety and pharmacokinetics information of GFH018 has been updated. The requirements for safety monitoring during and after Toripalimab administration have been specified. Eligibility criteria has been updated to remove the age upper limit and include patients with particular cured early stage cancers. Clarification for specific subtype of enrolled esophageal cancer has been made.

Changes to the Protocol:

- Section 1.1 Study Background: GFH018 clinical data have been updated to the cut-off date of 19May2021.
- Section 4.1 Inclusion Criteria #1: The age upper limit of 75 years has been removed.
- Section 4.2 Exclusion Criteria #9: Patients with cured prostate cancer or thyroid cancer will not be excluded.
- Section 5.3.2.1 Administration of Toripalimab : It has been specified that the patient should be closely monitored during and after the infusion for the first and second administration.
- Section 5.6.2.2 Prohibited Concomitant Therapies: COVID-19 vaccines have been removed from the prohibited concomitant therapies list because the subjects might benefit from the vaccine.

- 7.2 Pharmacokinetics: Changes to corresponding sections of the protocol are shown in the track changes version of the protocol. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Protocol Synopsis

Protocol number	GFH018X0201
Protocol title	A multi-center, single-arm, and open-label phase Ib/II study exploring the safety/tolerability, pharmacokinetics, and efficacy of GFH018 in combination with Toripalimab in the treatment of patients with advanced solid tumors
Brief title	Phase Ib/II study of GFH018 in combination with Toripalimab in the treatment of patients with advanced solid tumors
Sponsor	Genfleet Therapeutics
Study phase	Phase Ib/II
Study drug	Study drug 1 Code: GFH018 Dosage form: Tablet [redacted] Study drug 2 Code: Toripalimab Dosage form: Injection [redacted]
Study purpose and rationale	The purpose of the study is to evaluate the safety/tolerability, pharmacokinetics, and preliminary efficacy of GFH018 in combination with Toripalimab in patients with advanced solid tumors. Transforming growth factor beta (TGF-β), as a multifunctional cytokine, is secreted into the tumor microenvironment or peripheral circulation through a variety of cells, mainly including regulatory T cells, fibroblasts, and endothelial cells. TGF-β-bound cell membrane receptor TGF-β Receptor II(TGF-βRII), the cytokine forms the receptor dimer with TGF-βRI to activate downstream SMAD dependent and independent signal transduction pathways, thus performing various biological functions. TGF-β signaling pathway in advanced solid tumors potentiates epithelial-mesenchymal transition (EMT) and metastasis of tumor cells, induces and maintains the function of tumor stem cells, inhibits the anti-tumor immune response in the tumor microenvironment, and increases angiogenesis and tissue fibrosis in the tumor microenvironment, thereby comprehensively promoting tumor progression. TGF-β signaling pathway genes are highly expressed in blood and tumors in patients with solid tumors such as hepatocellular carcinoma, glioma, colorectal cancer, lung cancer, pancreatic cancer, and urothelial carcinoma, and the expression level is positively correlated with poorly differentiated cell, pathological malignancy and poor prognosis of patients. Moreover, numerous studies have demonstrated that the function of $CD8^+$ T cells, dendritic cells, B cells, and natural killer cells are positively correlated with the clinical response of anti-programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) antibodies, and TGF-β suppresses the function of these immune cells. Meanwhile, the function of regulatory T cells and M2 macrophages are negatively correlated with the clinical response of anti-PD-1/L1 antibodies, and TGF-β promotes the effector function of regulatory T cells and the polarization of macrophages to M2 type. Therefore, TGF-β can compromise the response of PD-1/L1 antibodies by promoting tumor fibrosis, blocking the infiltration of the cytotoxic T cells into the tumor, affecting the activity of immune cells, and suppressing the immune microenvironment. To sum up, TGF-β signaling pathway inhibitors can potentially enhance the response of the immune checkpoint inhibitors. During combined treatment, TGF-β signaling in tumor cells, stromal fibroblasts, and/or immune cells in the tumor microenvironment is suppressed, thereby enhancing the anti-tumor immunity and increasing the anti-tumor effect of the

immune checkpoint inhibitors anti-PD-1/L1 antibodies.

As a novel TGF-βRI inhibitor, GFH018 can inhibit tumor growth by inhibiting the activity of TGF-βRI kinase to block the signal transduction of TGF-βRI and modulate the tumor immune microenvironment. Toripalimab is an anti-PD-1 antibody approved for advanced melanoma and nasopharygeal carcinoma and for urothelial carcinoma in neoadjuvant and adjuvant setting by the National Medical Products Administration in China (NMPA). Pivotal studies for other indications are under development. Preclinical studies show that GFH018 in combination with PD-1 or PD-L1 monoclonal antibody can significantly inhibit tumor growth in colorectal cancer and pancreatic cancer mouse models showing synergistic effects.

Study objectives and endpoints

This is a phase Ib/II study.

The objectives and endpoints of phase Ib part (dose escalation) include:

	Objectives	Endpoints
Primary	• To evaluate the safety/tolerability of the combination therapy	• Incidence of dose-limiting toxicity (DLT) events • Incidence and severity of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), and immune-related adverse events (irAEs) • Changes in laboratory parameters, vital signs, physical examination, and electrocardiograms (ECG)
Secondary	• To evaluate the pharmacokinetic (PK) characteristics of GFH018 in the combination therapy	• Single dose plasma concentration and PK parameters of GFH018, including C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $T_{1/2}$, CL/F, and Vd/F; repeated doses plasma concentration and PK parameters of GFH018, including $C_{max,ss}$, $C_{min,ss}$, $T_{max,ss}$, AUC_{tau}, $T_{1/2,SS}$, $CL/F_{,SS}$, $Vd/F_{,SS}$, and R_{accc}
	• To evaluate the serum concentration and immunogenicity of Toripalimab in the combination therapy	• C_{trough} of Toripalimab; number and percentage of subjects who develop anti-Toripalimab-antibody
	• To explore the efficacy of the combination therapy	• Objective response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DOR), progression-free survival (PFS) evaluated per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1，and overall survival (OS)
Exploratory	• To explore the correlation between molecular characteristics and clinical efficacy	• PD-L1 expression • CD8 + cell density • Tumor-infiltrating lymphocytes (TILs) characterization

The objectives and endpoints of phase II part (indication expansion stage) include:

	Objectives	Endpoints
Primary	• To evaluate the efficacy of the combination therapy	• ORR, DCR, TTR, DOR, PFS evaluated per RECIST 1.1 or Lugano 2014 Criteria (only for extranodal NK/T-cell lymphoma), OS
Secondary	• To evaluate the safety/ tolerability of the combination therapy	• Incidence and severity of AEs, SAEs, AESIs, and irAEs
	• To evaluate the plasma concentration of GFH018 in the combination therapy	• C_{trough} of GFH018
	• To evaluate the serum concentration and immunogenicity of Toripalimab in the combination therapy	• C_{trough} of Toripalimab; number and percentage of subjects who develop anti-Toripalimab-antibody
Exploratory	• To explore the correlation between molecular characteristics and clinical efficacy	• PD-L1 expression • CD8 + cell density • Tumor-infiltrating lymphocytes (TILs) characterization

Study design

1. Phase Ib

Eligible patients with advanced solid tumors will be enrolled. GFH018 in combination with Toripalimab will be administered to evaluate the safety/tolerability. Considering a low probability of drug-drug interaction when combining the monoclonal antibody with small molecule drug, and no expected overlap of major adverse events of these two drugs, the starting dose and dosing regimen of GFH018 was derived from the safe dose and corresponding dosing regimen explored in GFH018X1101 (the dose-escalation phase I clinical study on the safety/tolerability, and pharmacokinetics of GFH018 in patients with advanced solid tumors) and have been started as 40mg BID 14 days on/14 days off. Toripalimab will be administered at the approved dose of 3 mg/kg as an intravenous infusion every 2 weeks.

The first 28 days of the treatment is the observation period of dose-limiting toxicity (DLT) for phase Ib part. The maximum tolerated dose (MTD) will be determined by Bayesian optimal interval (BOIN) design. In principle, no dose adjustment is allowed during the DLT observation period. The definition of the DLT-evaluable subject is the subject who has completed the 28-day observation period and received more than 75% of the total planned dose of GFH018, as well as the planned complete dose of Toripalimab (including the interruption allowed in the protocol), or has experienced a DLT during the DLT observation period. In the absence of DLT events, patients will receive the treatment until disease progression, intolerable toxicity, or other circumstances leading to treatment discontinuation.

The phase Ib part will employ BOIN design to find the MTD. MTD is defined as the dose level at which the incidence of DLT is closest to the target toxicity rate. The target toxicity rate for MTD is 0.3, and the planned maximum sample size is 15. Subjects will be enrolled and treated in each cohort of size 3 to 6. The BOIN design uses the following rules, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation of GFH018:

- If the observed DLT rate at current dose is ≤ 0.236, escalate the dose to

the next higher dose level;

- If the observed DLT rate at current dose is ≥ 0.359, de-escalate the dose to the next lower dose level;
- Otherwise, stay at the current dose.

Subjects in the first cohort have been assigned to receive GFH018 40 mg BID, 14 days on/14 days off. To assign a dose to next cohort of subjects, conduct dose escalation/de-escalation according to the rule displayed in the following table. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new subject at the lowest dose; if the current dose is the highest dose and the rule indicates dose escalation, treat the new subject at the highest dose. If none of actions (i.e. escalate, de-escalate, or eliminate) is triggered, stay at the current dose for treating the next cohort of subjects. Dose escalation procedure will be completed early when the suggested next dose level has had ≥ 9 evaluable subjects.

Dose escalation/de-escalation rule for BOIN design

(Target toxicity rate = 30%)

Action	Number of subjects treated at current dose								
	1	2	3	4	5	6	7	8	9
Escalate if # of DLT ≤	0	0	0	0	1	1	1	1	2
De-escalate if # of DLT ≥	1	1	2	2	2	3	3	3	4
Eliminate if # of DLT ≥	NA	NA	3	3	4	4	5	5	5

Definition of DLTs: DLT is defined as an adverse event that occurs within 28 days after the first administration, is assessed as related to GFH018 or Toripalimab, and meets the following severity. The toxicities will be assessed using the Common Terminology Criteria Adverse Events (CTCAE) version 5.0. Criteria for defining DLT are listed in the following:

1) Non-hematologic toxicity

- Grade 3 or above toxicity, except for the following circumstances:
  - i. Nausea, vomiting, diarrhea, constipation, or pain that resolves to ≤grade 2 within 3 days after starting appropriate treatment;
  - ii. Fatigue, rash, or hypertension that resolves to ≤ grade 2 within 7 days after starting appropriate treatment;
  - iii. ALT/AST ≥ grade 3 without total bilirubin ≥ grade 2, or ALT/AST ≥ grade 3 lasting for less than 14 days;
  - iv. Other laboratory abnormalities not requiring intervention at the discretion of investigator.

2) Hematologic toxicity

- Grade 4 neutropenia lasting ≥5 days; grade 3 febrile neutropenia (neutrophil count < 1.0×10^9/L with a single temperature > 38.3 °C or a sustained temperature > 38 °C for more than 1 hour);
- Grade 4 thrombocytopenia lasting ≥5 days, or grade 3 thrombocytopenia with ≥ grade 2 bleeding;
- Grade 4 anemia lasting ≥ 5 days.

3) Immune-related adverse events (irAEs)

- ≥ Grade 2 irAE that involves vital organs, such as immune-related myocarditis, central nervous system, ocular toxicity, and pneumonia;
- Grade 3 irAE of other organs that fails to recover to ≤ grade 2 before the planned next Toripalimab administration, except grade 3 endocrine abnormalities that can be corrected by hormone replacement therapy;
- Grade 4 irAEs

	In addition, for other significant treatment-related toxicity, the investigator and the sponsor should decide whether it is assessed as DLT after discussion; the toxicity beyond the DLT observation period but in line with the definition of DLT will be taken for consideration as an important safety signal to determine the safe dose. **2. Phase II** Eligible patients with advanced solid tumors of specific types will be enrolled into fourteen indication groups, including hepatocellular carcinoma, cholangiocarcinoma or gallbladder cancer (except carcinoma of ampulla), pancreatic cancer, colorectal cancer, urothelium carcinoma, cervical cancer, head and neck squamous cell carcinoma or esophageal squamous cell carcinoma, nasopharyngeal carcinoma, thymic carcinoma, endometrial cancer, osteosarcoma, TNBC and extranodal NK/T-cell lymphoma. Patients will be treated with the dosing regimen established in phase Ib until disease progression, intolerable toxicity, or other circumstances leading to treatment discontinuation. In phase II part, dose adjustment and/or interruption of GFH018 or Toripalimab is allowed. **3. Study Process** Both phase Ib part and phase II part of the study can be divided into three periods. 1) Screening period: Day -28 to Day -1 before the first drug administration. 2) Treatment period: Eligible patients will be treated with the combination of GFH018 and Toripalimab until disease progression confirmed by RECIST 1.1 or Lugano Response Criteria 2014 (only for NK/T cell lymphoma), intolerable toxicity, or other circumstances leading to treatment discontinuation. During the study period, subjects will receive safety monitoring regularly as planned; the imaging assessment will be performed every 8 ± 1 weeks (every 6 ± 1 weeks for hepatocellular carcinoma) in the first year and every 12 ± 1 weeks (every 8 ± 1 weeks for hepatocellular carcinoma) from the second year, and the efficacy evaluation will be performed by the investigator based on the RECIST 1.1 or Lugano 2014 Criteria for NK/T cell lymphoma . The blood samples for pharmacokinetic and immunogenic analysis will be collected as specified in the protocol. 3) Follow-up period: Patients will be discontinued from the study treatment permanently in case of disease progression, intolerable toxicity, or other circumstances leading to treatment discontinuation, and will receive the safety follow-up (which will be performed 30 days after the last administration, and SAE will be collected up to 90 days) and survival follow-up (until the subject dies, lost to follow-up, or study ends). Subjects who are discontinued from the study treatment for reasons other than disease progression and not start other anti-tumor therapies should be followed up for disease progression every 8 ± 1 weeks (every 6 ± 1 weeks for hepatocellular carcinoma) in the first year and every 12 ± 1 weeks (every 8 ± 1 weeks for hepatocellular carcinoma) from the second year. The end of study is defined as the time when all enrolled patients have been under study treatment for at least one year or have been discontinued for any reason (whichever occurs first).
Study population	• Phase Ib part: Patients with advanced solid tumors. • Phase II part: Patients with advanced solid tumors, including hepatocellular carcinoma, cholangiocarcinoma/gallbladder cancer (except carcinoma of ampulla), pancreatic cancer, colorectal cancer, urothelium carcinoma, cervical cancer, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, thymic carcinoma, endometrial cancer, osteosarcoma, TNBC and extranodal NK/T-cell lymphoma.

Inclusion criteria	**Patients eligible for inclusion in this study must meet all of the following criteria:** 1) Voluntarily participates in the study and signs the informed consent. 2) Age ≥18 years (inclusive) at the time of signing the informed consent. 3) Has histologically or cytologically confirmed diagnosis of advanced or metastatic solid tumors, progressed on at least first line therapy, or not been able to tolerate standard therapy due to toxicity or other reasons, or for whom no standard anticancer therapy exists. • For nasopharyngeal carcinoma group: patients who haven't received PD1/PDL1 inhibitor, bispecific antibody or any other checkpoint inhibitors; documented prior benefit (partial response, complete response) to checkpoint PD1/PDL1 inhibitor / bispecific antibody monotherapy or combined with chemotherapy and have an interval of > 6 months between the last dose of checkpoint inhibitor and entering the study. 4) Has sufficient organ functions, including: a. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, hemoglobin ≥ 9 g/dL, without blood transfusion or granulocyte colony-stimulating factor, thrombopoietin, erythropoietin and other therapies within 14 days prior to hematology test. b. Total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN, alkaline phosphatase (ALP) ≤ 2.5 × ULN; for subjects with tumor involvement of the liver who must have TBIL ≤ 3.0 × ULN, AST and ALT ≤ 5.0 × ULN. c. Creatinine (Cr) ≤ 1.5 × ULN, or measured/calculated creatinine clearance (CrCl) ≥ 50 mL/min (Cockcroft-Gault formula) if Cr > 1.5 × ULN; urine protein < 2+. d. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 × ULN (except for subject receiving anticoagulation treatment, as long as INR or PT is within therapeutic range of intended use of anticoagulants). 5) With toxicities from prior anti-tumor therapy resolved to baseline or CTCAE grade 1 (neurotoxicity or alopecia ≤ grade 2). 6) Eastern Cooperative Oncology Group Performance Status (ECOG P.S.) ≤ 1. Subject with tumor involvement of the liver must have the Child-Pugh score of 5-7. 7) Life expectancy ≥ 12 weeks. 8) Female or male subjects of child-bearing potential must agree to use effective contraceptive methods from the signing of the informed consent to 90 days after the last administration of the study drug. Fertile female subjects must have negative pregnancy test results within 7 days before administration. Effective contraceptive methods shown as follows: • Abstinence (avoiding heterosexual intercourse). • Use (or make their partner use) reliable and effective methods of contraception during heterosexual intercourse, such as: i. Single method of contraception (any one of the following methods is sufficient) a) Intrauterine device (IUD) b) Vasectomy in male partner of female subject c) Subcutaneous implant contraception ii. Combined condom and oral contraceptive pills. Male subjects and partners with azoospermia (caused by vasectomy or other underlying conditions) are not required to take contraception. Female subjects are considered to be infertile if the following conditions were present:

	i. Postmenopausal; ii. Documented hysterectomy, bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; iii. Congenital or acquired infertility. 9) According to the judgment of the investigator, the subject is able to communicate well with the investigator to comply with the requirement of the protocol. **In addition, eligible patients in phase II part must meet the following criteria:** 10) Histologically or cytologically confirmed diagnosis of advanced or metastatic tumors of specific types: hepatocellular carcinoma, cholangiocarcinoma/gallbladder cancer (except carcinoma of ampulla), pancreatic cancer, colorectal cancer, urothelium carcinoma, cervical cancer, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, thymic carcinoma, endometrial cancer, osteosarcoma, TNBC and extranodal NK/T-cell lymphoma. 11) At least one measurable lesion according to RECIST 1.1 or Lugano 2014 Criteria (only for extranodal NK/T-cell lymphoma). 12) For hepatocellular carcinoma patients: platelet count ≥60x10^9/L, without thrombopoietin or other therapies within 14 days prior to hematology test. 13) For cervical cancer patients: hemoglobin ≥ 8 g/dL, without blood transfusion or erythropoietin and other therapies within 14 days prior to hematology test.
Exclusion criteria	**Patients eligible for this study must not meet any of the following criteria:** 1) Impaired cardiac function or clinically significant cardiac diseases: a. Clinically significant cardiac diseases within 6 months, for example: myocardial infarction, angina, heart failure, severe arrhythmia, angioplasty, stent implantation, and coronary artery bypass grafting; b. Ascending aorta aneurysm or major artery aneurysm history, or predisposing conditions that are consistent with development of aneurysms (for example, family history of aneurysm, Marfan syndrome, evidence of damage to the large vessels of the heart documented by computerized tomography [CT] scan with contrast); c. Abnormalities at screening/baseline, which will be confirmed by the cardiologist if necessary: i. ECG: QT/QTc prolongation (QTcF > 470 ms for females or QTcF > 450 ms for males), or other clinically significant arrythmia, conduction abnormalities, morphology abnormalities; ii. Doppler echocardiography: clinically significant abnormalities, such as left ventricular ejection fraction (LVEF) < 50%, moderate or severe heart valve stenosis, and moderate or severe heart valve regurgitation; iii. Troponin > ULN in conjunction with symptoms or other abnormal testing indicating myocardial ischemia 2) With acute or chronic infections, including: a Active infections requiring intravenous treatment; b Positive human immunodeficiency virus antibody (HIV-Ab), active syphilis, active hepatitis B virus infection (positive HBsAg and positive HBV-DNA), and active hepatitis C virus infection (positive HCV-Ab and positive HCV-RNA) during the screening/baseline

period;

c Active tuberculosis.

3) With active central nervous system metastases, including symptomatic brain metastases, meningeal metastases, spinal cord compression, or requiring treatment with glucocorticoids, antiepileptic drugs, anticonvulsant drugs, or mannitol.

4) With known active autoimmune diseases or a history of autoimmune diseases within 1 year prior to enrollment, such as systemic lupus erythematosus, psoriasis, rheumatoid arthritis, inflammatory bowel disease, and Hashimoto's thyroiditis. Except for type I diabetes, hypothyroidism or hyperthyroidism that can be controlled with only hormone replacement, skin diseases requiring no systemic treatment, controlled celiac disease.

5) With clinically significant gastrointestinal diseases, such as intractable hiccup, nausea and vomiting, severe peptic ulcer, active gastrointestinal bleeding, or other conditions that interfere swallowing the tablets or significantly alter the absorption; subjects with hepatocellular carcinoma who have severe portal hypertension due to Budd-Chiari syndrome or portal vein thrombosis.

6) Uncontrollable or symptomatic ascites, pleural effusion or pericardial effusion.

7) History of non-infectious (e.g., drug-induced) ILD requiring systemic steroid treatment, or current pneumonitis.

8) With other uncontrolled systemic diseases, such as hypertension and diabetes.

9) Diagnosed with other malignant tumors within 3 years prior to starting study drug, except for cured carcinoma in situ of cervix, skin basal cell carcinoma, early stages of prostate or thyroid cancer.

10) With diseases requiring immunosuppressant therapy, or requiring prednisone > 10 mg/day or equivalent dose of similar drugs during the study period.

11) Subjects who have been treated with immunosuppressant drugs within 28 days prior to starting study drug, except for topical and inhaled cortisol and systemic cortisol of physiological dose (prednisone < 10 mg/day or equivalent dose of similar drugs).

12) Subjects who have received live vaccine, attenuated vaccine within 28 days prior to starting study drug, or plans to receive live vaccine, attenuated vaccine during treatment or within 30 days after the last administration.

13) Subjects who have been treated with radiotherapy, chemotherapy, targeted therapy, endocrine therapy, immunotherapy, and other anti-tumor therapies (except for traditional Chinese medicines), or other investigational drugs within 5 half-life periods or within 28 days (whichever is shorter) prior to starting study drug.

14) Subjects who have been treated with traditional Chinese medicine with approved antitumor indications within 2 weeks prior to starting study drug.

15) Subject who has received major surgeries (except for needle biopsy) that may affect the administration or study evaluation within 28 days prior to starting study drug.

16) Subjects who have received strong inhibitor or inducer of CYP3A4 within 5 half-life periods or within 2 weeks (whichever is shorter) prior to starting study drug.

17) Subjects who have received combined treatment of drugs targeting TGF-β and PD-(L)1, including combination of antibody and small molecule or bispecific antibody.

	18) Pregnant or lactating women. 19) With known allergies to the study drugs or components. 20) The subject is a staff member who is directly related to the investigator of the study or his/her family members, or the sponsor. 21) Other conditions judged by the investigator as inappropriate to participate in the study.
Sample size	**Phase Ib part** Subjects will be enrolled and treated in cohort size of 3-6. A minimum of 6 DLT-evaluable subjects are required for the recommended Phase II dosing level. Up to 15 subjects will be enrolled and treated in the phase Ib part. Additional subjects may be enrolled if more dose levels or alternative dosing regimens are to be explored. **Phase II part** Ten subjects will be enrolled in each tumor type. Subjects from phase Ib part who have received the phase II treatment regimen and meet the phase II part eligibility criteria will be counted. Depending on the clinical benefits of each tumor type, the sponsor will determine the enrollment of additional 10-20 subjects with the same tumor type, i.e., one tumor type can be expended to approximately a total of 20-30 subjects, tumor types with potential benefit will be expanded to maximal 60 patients at the discretion of the sponsor and leading investigators. Otherwise, if none of the ten shows response (i.e., complete response or partial response according to RECIST 1.1 or Lugano 2014 Criteria), the enrollment of subjects with the specific tumor type may be stopped.
Statistical analysis	**Analysis population** • Full Analysis Set (FAS) consists of all subjects who have received at least one dose of study treatment. • Safety Set (SS) includes all subjects from the FAS who have received at least one dose of study treatment and had at least one valid post-baseline safety assessment. • Dose Determining Set (DDS) consists of all subjects in the SS from phase Ib part who have received at least 75% of the total planned dose of GFH018 and the planned complete dose of Toripalimab (including the interruption allowed in the regimen) during the DLT observation period, are considered to have sufficient safety evaluation or developed DLT during the DLT observation period, and have no major protocol deviations that would impact the safety analyses. • Per Protocol Set (PPS) consists of all subjects in the FAS who are in compliance with the protocol from phase II part. Subjects who have major protocol deviations may be excluded from the PPS based on a study team review of all protocol deviations, which will be conducted before final database lock. • Pharmacokinetic analysis set (PKAS) consists of all subjects who take at least one dose of study treatment and have at least one blood sample providing evaluable concentration data. **Statistical Methods** The phase Ib and phase II data will be analyzed separately. The summary will be presented by dose level and regimen for phase Ib part. The summary will be presented by tumor type for phase II part, subjects who have been treated with the phase II treatment regimen in phase Ib and meet the phase II eligibility criteria will be counted. **Safety Analysis** Safety analysis will include AEs, vital signs, physical examination, ECG, and laboratory test. Treatment emergent adverse events (TEAEs), study treatment related

	AEs, SAEs, AESI, irAEs, TEAEs leading to interruption of study treatment, TEAEs leading to discontinuation of study treatment will be summarized by system organ class (SOC) and preferred term (PT). DLTs will be listed and summarized for each dose level using DDS. Laboratory parameters, vital signs, and ECGs will be listed and summarized by time point. **Efficacy Analysis** The number of subjects with the best overall response (BOR) of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) will be summarized according to the assessment results of each visit. ORR and DCR will be summarized. For phase II part, the corresponding two-sided 90% confidence interval (CI) for ORR and DCR will be estimated by the Clopper-Pearson method. For phase Ib part, DOR, TTR, PFS, and OS will be listed individually by subject. For phase II part, when the sample size of analyzed group is ten or more, the Kaplan-Meier method will be used to provide median 90% Brookmeyer-Crowley CI. **Pharmacokinetic Analysis** The drug plasma or serum concentration data will be summarized and plotted by time point for each group. PK parameters will be listed by subject and summarized descriptively. **Immunogenicity analysis** The number and percentage of subjects with positive anti-drug antibody (ADA) will be summarized.
Interim analysis	No formal interim analysis is planned.

Study Assessment Schedule

Study Assessment Schedule for phase Ib

Phase Ib	Protocol Section	Screening	Treatment (28 days for each cycle)									Safety follow-up	Survival follow-up
			Cycle 1				Cycle 2		Subsequent Cycles		EOT	30 days after the last administration	Every 90 days after safety follow-up
Days		D-28 ~ D-1	D1	D8	D15	D28	D1	D15	D1	D15	Within 7 days after discontinuation of study treatment		
Window (days)		NA	0	±2	±3	0	±3	±3	±3	±3		±3	±15
General & Safety													
Informed consent	15.3	X											
Inclusion/exclusion criteria[1]	4.1 & 4.2	X	X										
Demography	6.1	X											
Prior therapies[2]	5.6.1	X											
Medical history[3]	4.1 & 4.2	X											
Concomitant therapies	5.6.2		X（Concomitant therapies should be collected from first administration to the end of safety follow-up period）										
Subsequent disease information[4]	6.4.2										X	X	X
Survival information	6.4.2												X
Physical examination & Weight& Height[5]	7.1.1	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	7.1.1	X	X	X	X	X	X	X	X	X	X	X	
Echocardiography[6]	7.1.3	X	X			X	X		X		X	X	
ECG[6]	7.1.3	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS	7.1.1	X			X			X		X	X	X	
AE	8.1&8.5	X（AEs should be collected from informed consent form to 30 days after the last administration of the study treatment）											
SAE	8.2&8.5	X（SAEs should be collected from informed consent form to 90 days after the last administration of the study treatment）											
Laboratory assessments													
Virus serological test	7.1.2	X											
Pregnancy test[7]	7.1.2	X	X				X		X		X	X	
Hematology[8]	7.1.2	X	X	X	X	X	X	X	X	X	X	X	

Phase Ib	Protocol Section	Screening	Treatment (28 days for each cycle)									Safety follow-up	Survival follow-up
			Cycle 1				Cycle 2		Subsequent Cycles		EOT	30 days after the last administration	Every 90 days after safety follow-up
Days		D-28 ~ D-1	D1	D8	D15	D28	D1	D15	D1	D15	Within 7 days after discontinuation of study treatment		
Window (days)		NA	0	±2	±3	0	±3	±3	±3	±3		±3	±15
Urinalysis[8]	7.1.2	X	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[8]	7.1.2	X	X	X	X	X	X	X	X	X	X	X	
Coagulation[8]	7.1.2	X	X		X	X	X		X		X	X	
Thyroid function	7.1.2	X	X		X	X	X		X		X	X	
Cardiac markers	7.1.2	X	X		X	X	X		X		X	X	
Tumor markers[9]	7.1.2	X					X		X		X	X	
Efficacy assessments													
Radiological imaging and tumor assessment[10]	7.4	X											
Study Drug Administration													
GFH018 administration[11]	5.3		X										
Toripalimab administration[11]	5.3		X		X		X	X	X	X			
Sample collection													
Biomarker tissue sampling[12]		X											
PK blood sampling			X（Refer to blood sampling schema）										
ADA blood sampling													

Abbreviations: EOT, End of Treatment; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; ECG, electrocardiogram; AE, Adverse Event; SAE, Serious Adverse Event; PK, pharmacokinetics; ADA, Anti-drug Antibody.

Note: for the procedures repeated in C1D28 and C2D1, if within the 3-day window, there is no need to repeat it in C2D1.

1. Patient eligibility should be verified at Cycle1 D1.
2. Including prior anti-tumor therapies, and other therapies (within 30 days) prior to the first administration of study treatment.
3. The medical history within 30 days prior to signing of the informed consent, diagnosis and extent of cancer should be collected.
4. Including information on disease progression and subsequent anti-tumor treatment.

5. Height only measured during screening.
6. The results within 2 weeks prior to Cycle1D1 is acceptable and repeated testing at Cycle1D1 is not required.
7. The serum pregnancy test is required at Cycle1D1. For other visits, both serum test and urine test are acceptable. The results within 1 week prior to Cycle1D1 is acceptable and repeated testing at Cycle1D1 is not required.
8. The test results within 1 week prior to Cycle1D1 are acceptable and repeated testing at Cycle1D1 is not required. Unscheduled testing may be performed when necessary.
9. Specific cancer biomarkers are monitored only for patients with hepatocellular carcinoma, colorectal cancer, and pancreatic cancer.
10. The results within 4 weeks prior to first administration are acceptable for the baseline if requirements are met, and repeated assessment at baseline is not required. Every 8 ±1 weeks (every 6 ±1 weeks for hepatocellular carcinoma) in the first year and every 12 ±1 weeks (every 8 ±1 weeks for hepatocellular carcinoma) from the second year. If a patient discontinues due to reasons other than disease progression and does not start subsequent antitumor therapy, the radiological tests will be performed on the scheduled visit until disease progression, initiation of new antitumor therapy or other reasons.
11. GFH018 tablets will be received on the designated visit day and taken orally as planned. Toripalimab will be given by intravenous infusion every 2 weeks on the visit day.
12. If available, archival formalin-fixed, paraffin-embedded tumor sample shall be submitted before the first administration.

Study Assessment Schedule for phase II

Phase II	Protocol Section	Screening	Treatment (28 days for each cycle)					Safety follow-up	Survival follow-up
			Cycle 1		Subsequent Cycles		EOT	30 days after the last administration	Every 90 days after safety follow-up
Days		D-28 ~ D-1	D1	D15	D1	D15	Within 7 days after discontinuation of study treatment		
Window (days)		NA	0	±3	±3	±3		±3	±15
General & Safety									
Informed consent	15.3	X							
Inclusion/exclusion criteria[1]	4.1 & 4.2	X	X						
Demography	6.1	X							
Prior therapies[2]	5.6.1	X							
Medical history[3]	4.1 & 4.2	X							
Concomitant therapies	5.6.2		X（Concomitant therapies should be collected from first administration to the end of safety follow-up period）						
Subsequent disease information[4]	6.4.2						X	X	X
Survival information	6.4.2								X
Physical examination & Weight& Height[5]	7.1.1	X	X	X	X	X	X	X	
Vital signs	7.1.1	X	X	X	X	X	X	X	
Echocardiography	7.1.3	X	X (According to the clinical practice)						
ECG	7.1.3	X	X		X		X	X	
ECOG PS	7.1.1	X		X		X	X	X	
AE	8.1&8.5	X（AEs should be collected from informed consent form to 30 days after the last administration of the study treatment）							
SAE	8.2&8.5	X（SAEs should be collected from informed consent form to 90 days after the last administration of the study treatment）							
Laboratory assessments									
Virus serological test	7.1.2	X							
Pregnancy test[7]	7.1.2	X	X		X		X	X	

Phase II	Protocol Section	Screening	Treatment (28 days for each cycle)					Safety follow-up	Survival follow-up
			Cycle 1		Subsequent Cycles		EOT	30 days after the last administration	Every 90 days after safety follow-up
Days		D-28 ~ D-1	D1	D15	D1	D15	Within 7 days after discontinuation of study treatment		
Window (days)		NA	0	±3	±3	±3		±3	±15
Hematology[8]	7.1.2	X	X	X	X	X	X	X	
Urinalysis[8]	7.1.2	X	X	X	X	X	X	X	
Blood Chemistry[8]	7.1.2	X	X	X	X	X	X	X	
Coagulation[8]	7.1.2	X	X		X		X	X	
Thyroid function	7.1.2	X			X		X	X	
Cardiac markers	7.1.2	X			X		X	X	
Tumor markers[9]	7.1.2	X			X		X	X	
Efficacy assessments									
Radiological imaging and tumor assessment[10]	7.4	X							
Study Drug Administration									
GFH018 administration[11]	5.3		X						
Toripalimab administration[11]	5.3		X	X	X	X			
Sample collection									
Biomarker tissue sampling[12]		X							
PK blood sampling			X（Refer to blood sampling schema）						
ADA blood sampling									

Abbreviations: EOT, End of Treatment; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; ECG, electrocardiogram; AE, Adverse Event; SAE, Serious Adverse Event; PK, pharmacokinetics; ADA, Anti-drug Antibody.

Note:

1. Patient eligibility should be verified at Cycle1 D1.

2. Including prior anti-tumor therapies, and other therapies (within 30 days) prior to the first administration of study treatment.
3. The medical history within 30 days prior to signing of the informed consent, diagnosis and extent of cancer should be collected.
4. Including information on disease progression and subsequent anti-tumor treatment.
5. Height only measured during screening.
6. The results of ECG within 2 weeks prior to Cycle1D1 is acceptable and repeated testing at Cycle1D1 is not required.
7. The serum pregnancy test is required at Cycle1D1. For other visits, both serum test and urine test are acceptable. The results within 1 week prior to Cycle1D1 is acceptable and repeated testing at Cycle1D1 is not required.
8. The test results within 1 week prior to Cycle1D1 are acceptable and repeated testing at Cycle1D1 is not required. Unscheduled testing may be performed when necessary.
9. Specific cancer biomarkers are monitored only for patients with hepatocellular carcinoma, colorectal cancer, and pancreatic cancer.
10. The results within 4 weeks prior to first administration are acceptable for the baseline if requirements are met, and repeated assessment at baseline is not required. Every 8 ±1 weeks (every 6 ±1 weeks for hepatocellular carcinoma) in the first year and every 12 ±1 weeks (every 8 ±1 weeks for hepatocellular carcinoma) from the second year. If a patient discontinues due to reasons other than disease progression and does not start subsequent antitumor therapy, the radiological tests will be performed on the scheduled visit until disease progression, initiation of new antitumor therapy or other reasons. For subjects with extranodal NK/T cell lymphoma, the baseline imaging evaluation shall include both PET-CT and diagnostic enhanced CT/MRI of the neck, chest, abdomen, and pelvis, and enhanced MRI of the nasopharynx is necessary for nasal type. PET-CT can be used according to the local investigator interpretations in the subsequent evaluations.
11. GFH018 will be received on the designated visit day and taken orally as planned. Toripalimab will be given by intravenous infusion every 2 weeks on the visit day.
12. If available, archival formalin-fixed, paraffin-embedded tumor sample shall be submitted before the first administration.

[redacted]

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ABBREVIATIONS

Abbreviations	Full Name in English
AE	Adverse Event
AESI	Adverse Event of Special Interest
ADA	Anti-Drug Antibody
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BOIN	Bayesian Optimal Interval
BUN	Blood Urea Nitrogen
CK	Creatine Kinase
Cl^-	Blood Chlorine
Cr	Creatinine
CR	Complete Remission
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EMT	Epithelial-Mesenchymal Transition
GCP	Good Clinical Practice
GLU	Blood Glucose
Hb	Hemoglobin
HDL-C	High-Density Lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
ICH-GCP	International Council for Harmonization
irAE	Immune-Related Adverse Events
LEU	Leukocytes in Urine
K^+	Serum Potassium
KET	Urine Acetone Bodies
LDH	Lactate Dehydrogenase
LDL-C	Low-Density Lipoprotein Cholesterol
LLOQ	Lower Limit of Quantification
MTD	Maximum Tolerated Dose
Na^+	Plasma Sodium

Abbreviations	Full Name in English
NK/T	Natural killer T cell
NMPA	National Medical Products Administration
NOAEL	No-Observed-Adverse-Effect Level
ORR	Objective Response Rate
OS	Overall Survival
PD-1	Programmed Cell Death
PD-L1	Programmed Death Ligand
PFS	Progression Free Survival
PLT	Blood Platelet
PK	Pharmacokinetic
PRO	Protein in Urine
RBC	Red Blood Cell Count
RECIST	The Response Evaluation Criteria in Solid Tumors
RP2D	Recommend Phase II Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
T-BIL	Total Bilirubin
TGF	Transforming Growth Factor
TC	Total Cholesterol
TG	Triglyceride
TNBC	Triple-negative breast cancer
TTR	Time to Response
UCG	Ultrasonic Cardiogram
ULN	Upper Limits of Normal
WBC	White Blood Cell Count

1 INTRODUCTION

1.1 Study Background

Transforming growth factor-β (TGF-β) is a multifunctional cytokine, which binds transforming growth factor-β receptor II (TGF-βRII) on cell membrane, and subsequently forms a dimer with TGF-βRI to activate downstream SMAD dependent or independent signaling. This pathway plays a variety of biological functions. In advanced tumors, TGF-β signaling pathway activates and promotes epithelial mesenchymal transition (EMT) and metastasis of tumor cells, induces and maintains the function of tumor stem cells, inhibits anti-tumor immune response in tumor microenvironment, increases angiogenesis in tumor microenvironment, increases tissue fibrosis, and comprehensively promotes tumor progression[1-2]. In a variety of solid tumor patients, including hepatocellular carcinoma, glioma, colorectal cancer, lung cancer, pancreatic cancer, urothelial cancer and so on, TGF-β signaling pathway genes were found to be highly expressed in tumors, and their expression level was positively correlated with the poorly differentiated cells and tumor stages, and the poor prognosis of patients[3-6]. Therefore, targeting this signaling pathway may provide a therapeutic opportunity.

Drugs targeting PD-1/ (PD-L1) pathway have shown a substantial anti-tumor activity. Up to date, a number of monoclonal antibody products targeting PD-1 or PD-L1, including Toripalimab, have been approved for treating cancer in China and other countries. The approved indications include melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, head and neck cancer, bladder cancer (urothelial cancer), gastric cancer, liver cancer, High-level microsatellite instability (MSI-H) or Different Mismatch Repair(dMMR) colorectal cancer, cervical cancer and esophageal squamous cell carcinoma, and others as single agent or combination regimen in different settings. However, overall response rate of PD-1/PD-L1 antibodies treating cancer is still limited. Without selecting population, the response rates of treating melanoma, Merkel cell carcinoma, Hodgkin's lymphoma and microsatellite unstable tumors are relatively high, ranging from about 40% to 70%[7-10], but the response rate in most other approved tumors is only 10%-25%[11-12]. Also, patients might develop acquired drug resistance even after the initial response. The possible reasons include the different expression level of PD-L1 and heterogeneity in tumors[13-14]. Therefore, a variety of combined treatment strategies are being explored to improve the efficacy of checkpoint inhibitor. One of the directions is to improve the tumor immune microenvironment and increase the chance of immune response.

With the deepened understanding of the inhibitory effect of TGF-β in tumor immune microenvironment, the combination of TGF-β target inhibitor with PD-(L)1 inhibitor or the exploration of TGF-β/PD-L1 bispecific antibody have been promoted from preclinical to clinical study. Among them, M7824, a novel bifunctional anti-PD-L1/TGFβ Trap fusion protein from Merck has been explored among patients with cholangiocarcinoma, cervical cancer or non-small cell lung cancer. The reported clinical study data show that the combination of M7824 can bring durable response, and the safety profile is similar to PD-(L)1 and consistent with the expectations of relevant targets[15-16].

GFH018 p-toluenesulfonate (abbreviated as GFH018) is a chemically synthesized small molecule and blocks the transduction of TGF-β signaling pathway by inhibiting the activity of TGF-βRI kinase. Toripalimab is an anti- programmed cell death (PD-1) recombinant humanized antibody which belongs to the human IgG4/Kappa subtype and with increased stability by introducing point mutation. Toripalimab has been approved for melanoma, nasopharygeal carcinoma and urothelial carcinoma in China, with different setting. Detailed information on the chemistry, pharmacology, efficacy, and safety of GFH018 and Toripalimab, has been described in the Investigator's Brochure of GFH018 and Toripalimab.

GFH018 has shown anti-tumor activity as single agent in preclinical efficacy studies, and it also shows synergistic effects when combined with PD-(L)1 antibodies. The first human study of GFH018 treating patients with advanced solid tumors (GFH018X1101) is in progress.

39 patients were enrolled into the first in human (FIH) study of GFH018 received the GFH018 treatment following 14 days on/14 days off regimen as of the cutoff date (Jan 25, 2022). There were 4, 3, 4, 7, 4, 4, 6 and 7 subjects in 5mg, 10mg, 20mg, 30mg, 40mg, 50mg, 65mg and 85mg BID group respectively. The enrollment of patients in the dose escalation part has been completed. GFH018 showed a good safety profile. No DLT was observed and the maximal tolerated dose (MTD) was not reached. No GFH018-related death was reported, neither was serious adverse events (SAE) related to GFH018. No subject discontinued the study treatment due to AE. No ≥ grade 2 AESIs were reported in the study. Most TRAE were grade 1-2. Only 3 G3 treatment-related adverse events (TRAEs) per common terminology criteria for adverse events (CTCAE) were reported in 2 subjects. Two of them were reported in 1 subject and the PT terms were lymphocyte count decreased and hypocalcaemia, which were not accpomined by any clinical symptoms/signs. Another G3 TRAE was proteinuria (routine urine test) and repeated by urinary protein using 24-hour urine collection was 1.7 g/24h, grade 2 by CTCAE.

The most common TRAE summarized by PT incidence (≥ 10%) were in descending order of frequency as follows: proteinuria (28.2%), aspartate aminotransferase increased (15.4%), alanine aminotransferase increased (12.8%), anemia (12.8%), blood alkaline phosphotase increased (10.3%), blood lactate dehydrogenase increased (10.3%), and lymphocyte count decreased (10.3%).

A total of 24 subjects were evaluable for efficacy, 6 patients (1 pelvic paraganglioma, 1 small cell lung cancer, 1 breast cancer, 1 cholangiocarcinoma, 1 nasopharyngeal carcinoma and 1 thymic cancer) achieved a stable disease (SD). The subject who was diagnosed with thymic cancer and received GFH018 treatment at the dose level of 65 mg BID achieved SD with tumor shrinkage (maximum target lesion decreased by 18.4%). This subject has received the study treatment for 185 days with a sustained as an SD as of the data cutoff date. In conclusion, GFH018 shows a good safety profile from 5mg to 85 mg BID and preliminary anti-tumor efficacy in advanced solid tumors.

[redacted]

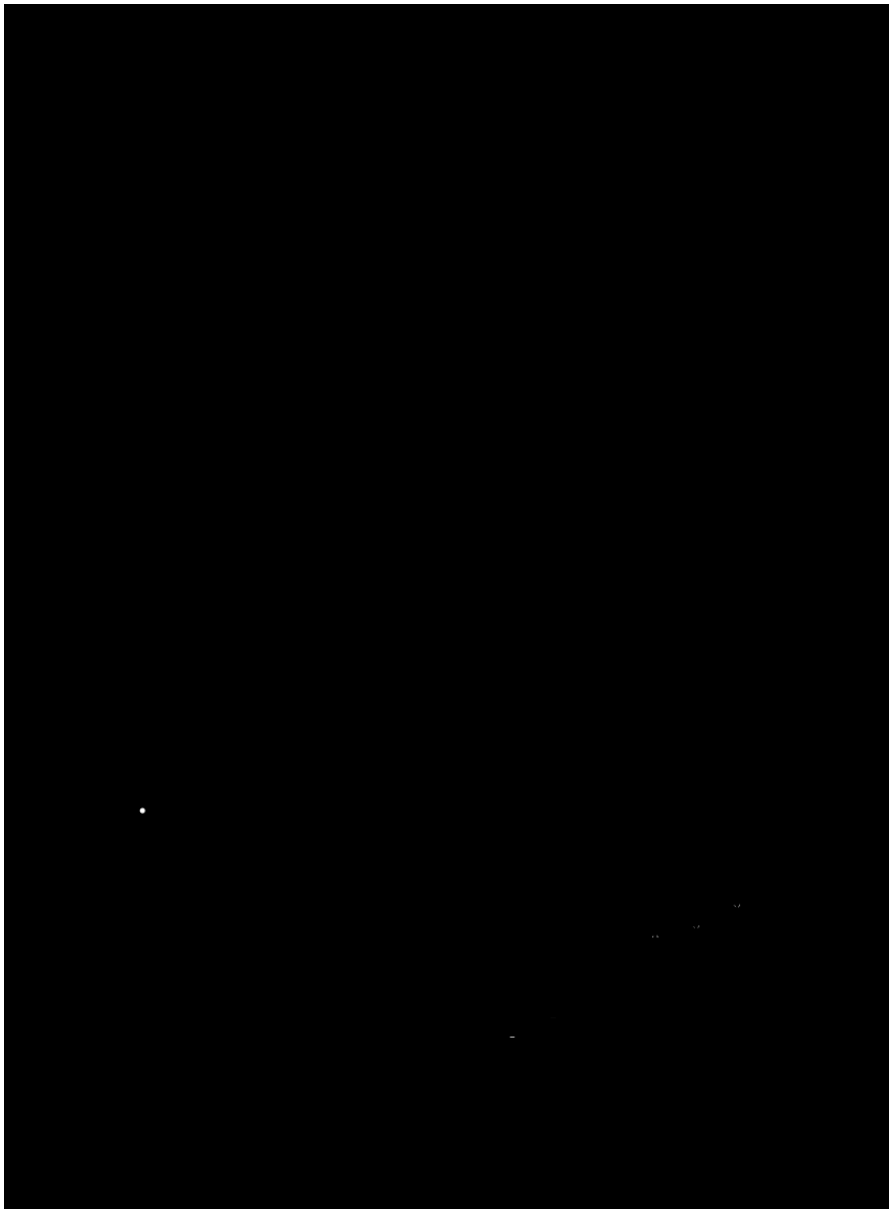
The mechanism of action combining GFH018 with PD-(L)1 and data in preclinical, as well as the favorable safety profile at completed dose levels from ongoing human study, support this study of the combination of GFH018 with Toripalimab in patients with advanced solid tumors.

1.2 Scientific Rationale

1.2.1 Research Rationale

[redacted]

[redacted]



[redacted]

1.2.2 Rational for Dose Selection

1.2.2.1 Starting Dose of GFH018

The GFH018 starting dose of dose escalation in this study was determined based on the evaluation of safety/tolerance, pharmacokinetics (PK), preliminary efficacy and pharmacodynamics data from dose escalation part of study GFH018X1101.

GFH018X1101 is an ongoing phase I study to evaluate the safety/tolerability and pharmacokinetics of GFH018 as monotherapy in patients with advanced solid tumors. The planned dose escalation levels of GFH018 in GFH018X1101 is as follow:

Groups	Dose Level	Incremental percentage
1	5 mg BID, 14 days on/14 days off	-
2	10 mg BID, 14 days on/14 days off	100%
3	20 mg BID, 14 days on/14 days off	100%
4	30 mg BID, 14 days on/14 days off	50%
5	40 mg BID, 14 days on/14days off	33%
6	50 mg BID, 14 days on/14days off	25%

Note: If the MTD is not reached at provisional maximum dose of 50mg BID, higher dose levels may be explored (such as 65mg BID, and 85mg BID).

At the present stage, the evaluation of safety/tolerance for dose level 5mg, 10mg, 20mg,30 mg, 40mg, 50mg, 65mg, and 85mg have been completed. Based on the data obtained, GFH018 is deemed safe at these eight dose levels, without dose-limiting toxicity (DLT) events observed and safety signals that need attention.

The starting dose and dosing regimen of GFH018 in study GFH018X0201 was 40mg BID 14 days on/14 days off which has been confirmed safe in GFH018X1101 before the enrollment of the first subject.

1.2.2.2 Rational for Dose Selection of Toripalimab

Toripalimab has been approved by the National Medical Products Administration (NMPA) for the treatment of melanoma, nasopharyngeal carcinoma, and urothelial carcinoma. In this study, the approved dosage will be used: 3 mg/kg intravenous infusion once every 2 weeks.

1.3 Risk/Benefit Assessment

1.3.1 Preclinical Toxicology Studies of GFH018

[redacted]

1.3.2 Clinical Data of GFH018 and Toripalimab

The study (GFH018X1101) which is the dose-escalation phase I clinical study on the safety/tolerability, and pharmacokinetics of GFH018 in patients with advanced solid tumors after single/multiple administration is still ongoing. As cut-off date of 25th Jan 2022, 39 patients had received 5mg, 10mg, 20mg, 30mg, 40mg, 50mg, 65mg and 85mg of GFH018 oral tablet twice a day, respectively, following a 14-day on/14-day off schedule. No DLT was observed and MTD was not reached. No GFH018-related death was reported, neither was SAE related to GFH018. No subject discontinued the study treatment due to AE. None of grade 2 or above AESIs were reported in the study. Most TRAE were grade 1-2. GFH018 has shown a good safety profile from 5mg to 85 mg BID, and there were no additional safety signals to be noted. Toripalimab has been approved for three indications (i.e. advanced melanoma and nasopharyngeal carcinoma and for urothelial carcinoma in neoadjuvant and adjuvant setting by NMPA) since 2018. As of 16 Dec 2020, cumulatively approximately 1,547 subjects received Toripalimab monotherapy or combination therapy in studies sponsored by Shanghai Junshi, of which 1,124 received monotherapy and 423 received combination therapy. In addition, 1225 subjects participated in partner-sponsored collaborative and investigator-initiated studies. The safety profile of Toripalimab is generally consistent with the known overall safety profile of anti-PD-1 products and no new safety signals were identified. Existing risk management measures for Toripalimab remain adequate and effective for important identified and potential risks, and the risk-benefit profiles remain good.

1.3.3 Assessment of Potential Risks and Benefits

The available data of GFH018 and Toripalimab show good safety profile. Considering the low probability of DDI between monoclonal antibody and small molecule drug, it is expected overall safety will be acceptable. Given the anti-tumor effect of GFH018 in the preclinical studies and the synergistic effect when combined with PD-(L)1 inhibitor, as well as the clinical data of Toripalimab, this study is expected to bring benefit in this patient population. Acceptable safety profile and promising outcomes are also observed in other ongoing treatment with immune checkpoint inhibitors combined with TGF-β. Therefore, the overall benefit/risk

evaluation is favorable for those patients in this study.

2 STUDY OBJECTIVES AND STUDY ENDPOINTS

The study is consisting of Phase Ib/II. The objectives and endpoints of Phase Ib and Phase II are as follows.

The objectives and endpoints of Phase Ib (Dose escalation) include:

	Objectives	Endpoints
Primary objectives	• To evaluate the safety/tolerability of the combination therapy	• Incidence of dose-limiting toxicity (DLT) events • Incidence and severity of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), and immune-related adverse events (irAEs) • Changes in laboratory parameters, vital signs, physical examination, and ECG
Secondary objectives	• To evaluate the pharmacokinetics (PK) of GFH018 in the combination therapy	• Single dose plasma concentration and PK parameters of GFH018, including: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $T_{1/2}$, CL/F, and V_d/F; repeated doses plasma concentration and PK parameters of GFH018, including: $C_{max,ss}$, $C_{min,ss}$, $T_{max,ss}$, AUC_{tau}, $T_{1/2,SS}$, $CL/F_{,SS}$, $Vd/F_{,SS}$, and R_{acc}
	• To evaluate the serum concentration and immunogenicity of Toripalimab in the combination therapy	• C_{trough} of Toripalimab; number and percentage of subjects who develop anti-Toripalimab antibody
	• To explore the efficacy of the combination therapy	• Objective response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DOR), progression-free survival (PFS) evaluated per Response Evaluation Criteria in Solid Tumors (RECIST)

		1.1， and overall survival (OS)
Exploratory objectives	• To explore the correlation between molecular characteristics and efficacy	• PD-L1 expression • CD8 + cell density • Tumor-infiltrating lymphocytes (TILs) characterization

The objectives and endpoints of Phase II part (Extension of indications phase) include:

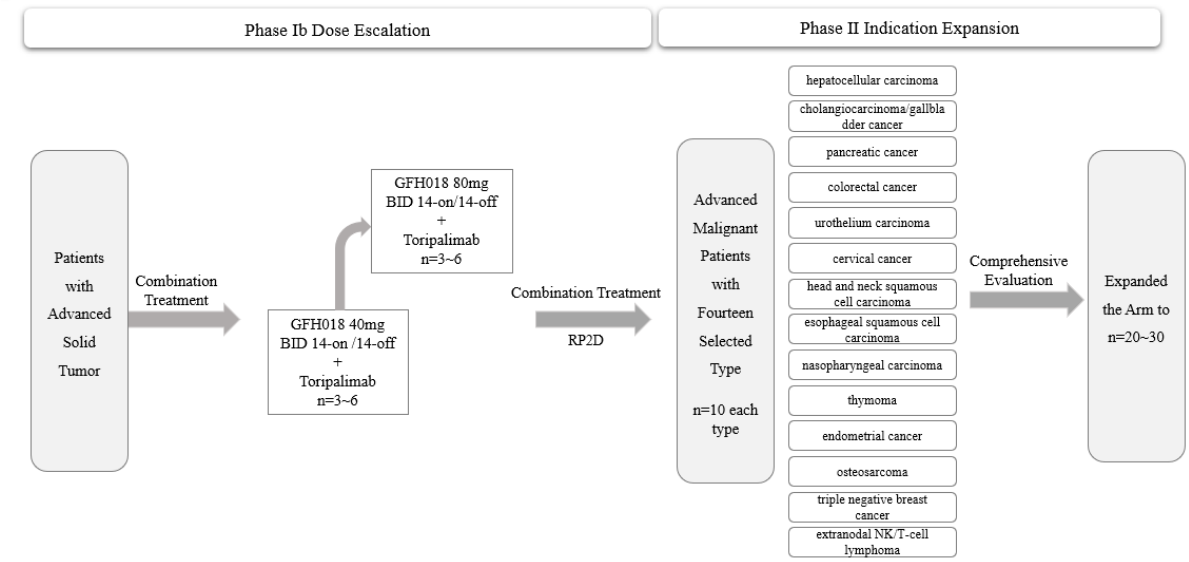
	Objectives	**Endpoints**
Primary objectives	• To evaluate the efficacy of the combination therapy	• ORR, DCR, TTR, DOR, PFS evaluated per to RECIST 1.1 and Lugano 2014 Criteria（only for extranodal NK/T-cell lymphoma）, and OS
Secondary objectives	• To evaluate the safety/tolerance of the combination therapy	• Incidence and severity of AEs, SAEs, AESIs, and irAEs
	• To evaluate the plasma concentration of GFH018 in the combination therapy	• C_{trough} of GFH018
	• To evaluate the serum concentration and immunogenicity of Toripalimab in the combination therapy	• C_{trough} of Toripalimab; number and percentage of subjects who develop anti-Toripalimab-antibody
Exploratory objectives	• To explore the correlation between molecular characteristics and efficacy	• PD-L1 expression • CD8 + cell density • Tumor-infiltrating lymphocytes (TILs) characterization

3 STUDY DESIGN

3.1 Overview of Study Design

This is a multi-center, single arm, and open-label study consisting of Phase Ib and II to explore the safety/tolerance, pharmacokinetics, and efficacy of combination of GFH018 and Toripalimab in patients with advanced solid tumors.

Figure 2. Overview of study design



Note: Carcinoma of ampulla is excluded from cholangiocarcinoma/gallbladder carcinoma; RP2D =Recommend Phase II Dose; Toripalimab:3 mg/kg, intravenous infusion once every 2 weeks. The starting dose of GFH018 in this study is 40mg BID 14 days on/14 days off.

3.2 Phase Ib

After the escalation is completed, maximum tolerated dose (MTD) will be identified (if applicable) based on isotonic regression. This computation is implemented by the Shinny app "BOIN" available at https://www.trialdesign.org/one-page-shell.html#BOIN. Specifically, MTD is the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate (0.3).

The Phase II recommended dose（RP2D）of GFH018 combining Toripalimab will be determined based on all available information including safety/tolerability, PK and preliminary efficacy data from phase Ib part, may be equal or lower than MTD.

3.2.1 Provisional Dose Levels

The provisional GFH018 dose escalation plan in this study will be consistent with the study of monotherapy (GFH018X1101). The planned dose levels are as follows:

Group	Dose level	Incremental percentage
1	20 mg BID, 14 days on/14 days off	-
2	30 mg BID, 14 days on/14 days off	50%
3	40 mg BID, 14 days on/14 days off	33%
4	50 mg BID, 14 days on/14 days off	25%

The starting dose and dosing regimen of GFH018 in study GFH018X0201 was 40mg BID 14 days on/14 days off which has been confirmed safe in GFH018X1101 before the enrollment of the first subject.

If the MTD is not reached at the provisional maximum dose level, the sponsor will comprehensively evaluate all the information obtained to determine whether to proceed with higher dose exploration. Dose escalation may be terminated at any time based on emerging safety concerns without establishing the MTD.

3.2.2 Escalation/De-escalation Rules

The first 28 days of treatment is the observation period of DLT. In principle, the patient will not be allowed to conduct dose adjustment during DLT observation period. The definition of DLT-evaluable subject is subject who have completed the 28-day-observation period and received more than 75% of the total planned dose of GFH018 and the planned completed dose of Toripalimab (including the interruption allowed per protocol), or developed a DLT event during DLT observation period. If in the absence of DLT event, patients will be treated until disease progression confirmed by RECIST 1.1 criteria, intolerable toxicity, or other conditions leading to treatment discontinuation.

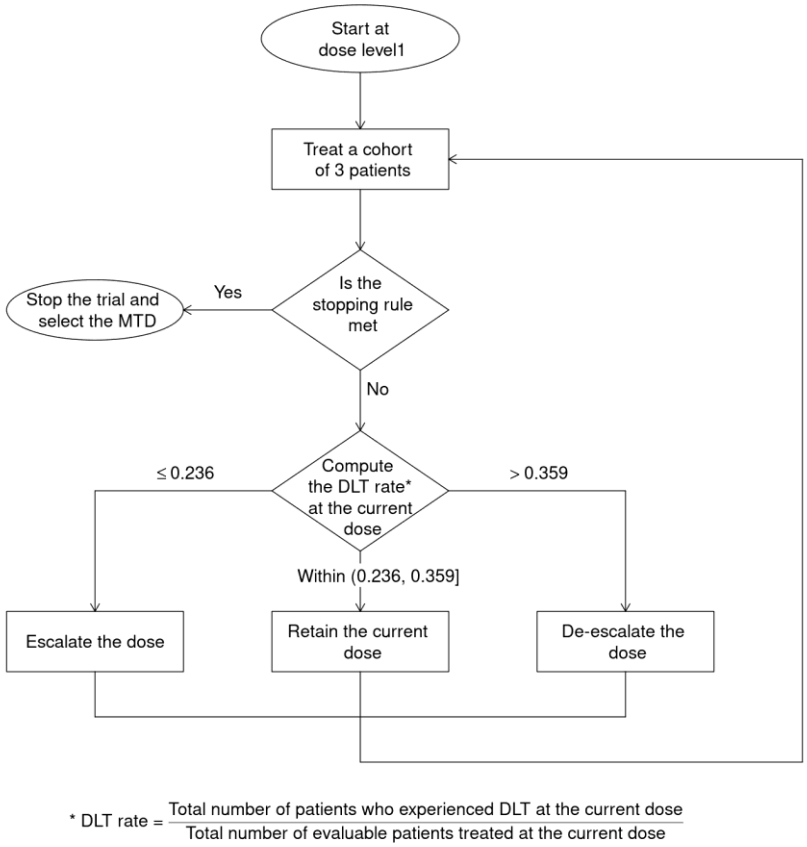
The Bayesian optimal interval (BOIN) design will be used to find the MTD. MTD is defined as the dose level at which the incidence of DLT is closest to the target toxicity rate (i.e., 0.3). The BOIN design is implemented in a simple way similar to traditional 3 + 3 design, but is

more flexible and processes superior operating characteristics that are comparable to those of the more complex model-based designs. The result of 10,000 simulations using Shinny app 'BOIN' (available at http://www.trialdesign.org) shows that the design selects the true MTD, if any, with high probability and allocates more subjects to the dose levels with DLT rate closest to the target toxicity rate of 0.3 (See Appendix 4).

The target toxicity rate is 0.3 and the planned maximum sample size is 15. Subjects are planned to be enrolled and treated in cohorts of size 3-6. As is shown in **Figure 3**, the BOIN design uses the following rule, optimized to minimum the probability of incorrect dose assignment to guide dose escalation/de-escalation of GFH018:

- If the observed DLT rate at current dose is ≤ 0.236, escalate the dose to the next higher dose level;
- If the observed DLT rate at current dose is ≥ 0.359, de-escalate the dose to the next lower dose level;
- Otherwise, stay at the current dose.

Figure 3. BOIN design flow chart



For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if Pr (p_j >0.3| data) > 0.95 and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level $j, j = 1,2,3,4$. This posterior probability is evaluated based on the beta-binomial model $y_j \mid p_j - \text{binomial}(p_j)$, with $y_j \mid p_j - \text{binomial}(p_j)$, where y_j is the number of patients experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for safety. The probability cutoff 0.95 is chosen to be consistent with the common practice that when the target DLT rate ≤ 1/6, a dose with 2/3 patients experienced DLT is eliminated.

The steps to implement the BOIN design are described as follows:

1) Subjects in the first cohort are treated at dose level 1.
2) To assign a dose to the next cohort of subjects, conduct dose escalation/de-escalation according to the rule displayed in the **Table 1**. When using the rule table, please note the following:
    a. "Eliminate" means eliminate the current dose and higher dose from the trial to prevent treating any further subjects at these doses because they are overly toxic.
    b. When a dose level is eliminated, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
    c. If none of the actions (i.e., escalate, de-escalate, or eliminate) is triggered, treat the new subject at the current dose.
    d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new subjects at lowest dose until the number of DLTs reaches the elimination boundary, at which point terminate the trail for safety.
    e. If the current dose is the highest dose and rule indicates escalation, treat the new subjects at the highest dose.
3) Repeated step 2 until is the maximum sample size of 15 is reached, or stop the enrollment if the number of subjects treated at the current reach 9 and the decision according to the table is to stay at the current dose according to the rule displayed in the **Table 1**.

Table 1 Dose escalation/de-escalation rule for target toxicity rate = 0.3

Action	Number of subjects treated at current dose								
	1	2	3	4	5	6	7	8	9

Escalate if # of DLT ≤	0	0	0	0	1	1	1	1	2
De-escalate if # of DLT ≥	1	1	2	2	2	3	3	3	4
Eliminate if # of DLT ≥	NA	NA	3	3	4	4	5	5	5

3.2.3 Definition of DLT

DLT is defined as an adverse event that occurs within 28 days after the first administration, is assessed as related to GFH018 or Toripalimab, and meets the following severity. The toxicities will be assessed using the Common Terminology Criteria Adverse Events (CTCAE) version 5.0. Criteria for defining DLT are listed in the following:

1) Non-hematologic toxicity

- Grade 3 or above toxicity, except for the following circumstances:
  i. Nausea, vomiting, diarrhea, constipation, or pain that resolves to ≤ grade 2 within 3 days after starting appropriate treatment;
  ii. Fatigue, rash, or hypertension that resolves to ≤ grade 2 within 7 days after starting appropriate treatment;
  iii. ALT/AST ≥ grade 3 without total bilirubin ≥ grade 2, or ALT/AST ≥ grade 3 lasting for less than 14 days;
  iv. Other laboratory abnormalities not requiring intervention at the discretion of investigator.

2) Hematologic toxicity

- Grade 4 neutropenia lasting ≥5 days; grade 3 febrile neutropenia (neutrophil count < 1.0×10^9/L with a single temperature > 38.3 °C or a sustained temperature > 38 °C for more than 1 hour);
- Grade 4 thrombocytopenia lasting ≥5 days, or grade 3 thrombocytopenia with ≥ grade 2 bleeding;
- Grade 4 anemia lasting ≥ 5 days.

3) Immune-related adverse events (irAEs)

- ≥ Grade 2 irAE that involves vital organs, such as immune-related myocarditis, central nervous system, ocular toxicity, and pneumonia;
- Grade 3 irAE of other organs that fails to recover to ≤ grade 2 before the planned next Toripalimab administration, except grade 3 endocrine abnormalities that can be corrected by hormone replacement therapy;

- Grade 4 irAEs

In addition, for other significant treatment-related toxicity, the investigator and the sponsor should decide whether it is assessed as DLT after discussion; the toxicity beyond the DLT observation period but in line with the definition of DLT will be taken for consideration as an important safety signal to determine the safe dose.

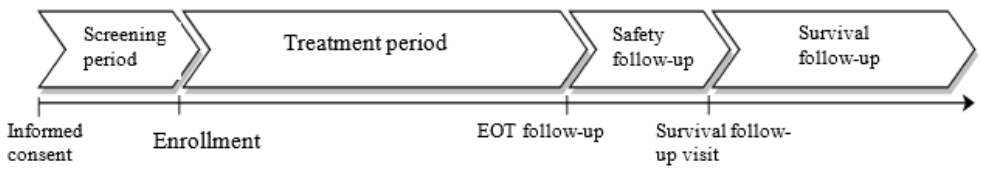
3.3 Phase II

Eligible patients with advanced solid tumors of specific types will be enrolled into fourteen indication groups, including hepatocellular carcinoma, cholangiocarcinoma or gallbladder cancer (except carcinoma of ampulla), pancreatic cancer, colorectal cancer, urothelium carcinoma, cervical cancer, head and neck squamous cell carcinoma or esophageal squamous cell carcinoma, and nasopharyngeal carcinoma, thymic carcinoma, endometrial cancer, osteosarcoma, TNBC and extranodal NK/T-cell lymphoma[29-34]. Preclinical data[35] have shown that TGF-β is highly expressed in Osteosarcoma cells and tissues and is associated with high stage, metastasis, and recurrence in vitro and in vivo. A phase I/II study[36] of Vactosertib (TGF-βR1 inhibitor) in treatment of recurrent of refractory osteosarcoma is ongoing (NCT05588648). Fibrosis with TGF-β pathway activation has been identified as an independent prognostic indicator in TNBC[37]. TGF-β-induced EMT is also shown in docetaxel-resistant and paclitaxel-resistant TNBC cancer cells[38]. Patients will be treated with the dosing regimen established in phase Ib until disease progression, intolerable toxicity, or other circumstances leading to treatment discontinuation. In phase II part, dose adjustment and/or interruption of GFH018 or Toripalimab is allowed.

3.4 Study Procedures

Studies of Phase Ib and II include three periods.

Figure 4. Schematic diagram of subject study procedures



1) Screening period: Day -28 to day -1 before the first administration.
2) Treatment period: Eligible patients will receive combination therapy of GFH018 and Toripalimab until the disease progression confirmed by RECIST 1.1 or Lugano 2014 Criteria (only for extranodal NK/T-cell lymphoma), intolerable toxicity, or other conditions leading to the treatment discontinuation. During the study period, patients will receive safety monitoring regularly as planned; imaging assessment will be performed every 8 ± 1weeks (every 6 ± 1 weeks for hepatocellular carcinoma) in the first year and every 12 ± 1 weeks (every 8 ± 1weeks for hepatocellular carcinoma) from the second year. Tumor burden assessments will be performed according to RECIST 1.1 or Lugano 2014 Criteria (only for extranodal NK/T-cell lymphoma) by investigator. The blood samples will be collected for pharmacokinetic and immunogenic analysis.
3) Follow-up period: Patients will be discontinued from the study treatment permanently in case of disease progression, intolerable toxicity, or other circumstances leading to treatment discontinuation, and will receive the safety follow-up (which will be performed 30 days after the last administration, and SAE will be collected up to 90 days) and survival follow-up (until the subject dies, lost to follow-up, or study ends). Patients who are discontinued from the study treatment for reasons other than disease progression and not start other anti-tumor therapies should be followed up for disease progression every 8 ± 1 weeks (every 6 ± 1 weeks for hepatocellular carcinoma) in the first year and every 12 ± 1 weeks (every 8 ± 1 weeks for hepatocellular carcinoma) from the second year.

The end of study is defined as the time when all enrolled patients have been under study treatment for at least one yeah or have been discontinued for any reason (whichever occurs first).

This study will explore and evaluate the safety and preliminary efficacy of the combination of GFH018 and Toripalimab. The biomarkers may contribute to further understand mechanisms of drug action and drug resistance. It is expected that this combination will exert synergistic anti-tumor effects through dual inhibition of TGF-β and immune checkpoint, and enhance immunotherapy by modulating the immune micro-environment providing the basis for further clinical development.

The dose, dosing regimen, study procedures, time points of sample collection may be revised based on obtained safety and PK data from the study.

4 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1 Inclusion Criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1) Voluntarily participates in the study and signs the informed consent.
2) Age ≥18 years (inclusive) at the time of signing the informed consent.
3) Has histologically or cytologically confirmed diagnosis of advanced or metastatic solid tumors, progressed on at least first line therapy, or not been able to tolerate standard therapy due to toxicity or other reasons, or for whom no standard anticancer therapy exists.
   - For nasopharyngeal carcinoma group: patients who haven't received PD1/PDL1 inhibitor, bispecific antibody or any other checkpoint inhibitors; documented prior benefit (partial response, complete response) to checkpoint PD1/PDL1 inhibitor / bispecific antibody monotherapy or combined with chemotherapy and have an interval of > 6 months between the last dose of checkpoint inhibitor and entering the study.
4) Has sufficient organ functions, including:
   a. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, hemoglobin ≥ 9 g/dL, without blood transfusion or granulocyte colony-stimulating factor, thrombopoietin, erythropoietin and other therapies within 14 days prior to hematology test.
   b. Total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN, alkaline phosphatase (ALP) ≤ 2.5 × ULN; for subjects with tumor involvement of the liver who must have TBIL ≤ 3.0 × ULN, AST and ALT ≤ 5.0 × ULN.
   c. Creatinine (Cr) ≤ 1.5 × ULN, or measured/calculated creatinine clearance (CrCl) ≥ 50 mL/min (Cockcroft-Gault formula) if Cr > 1.5 × ULN; urine protein < 2+.
   d. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 × ULN (except for subject receiving anticoagulation treatment, as long as INR or PT is within therapeutic range of intended use of anticoagulants).

5) With toxicities from prior anti-tumor therapy resolved to baseline or CTCAE grade 1 (neurotoxicity or alopecia ≤ grade 2).
6) Eastern Cooperative Oncology Group Performance Status (ECOG P.S.) ≤ 1. Subject with tumor involvement of the liver must have the Child-Pugh score of 5-7.
7) Life expectancy ≥ 12 weeks.
8) Female or male subjects of child-bearing potential must agree to use effective contraceptive methods from the signing of the informed consent to 90 days after the last administration of the study drug. Fertile female subjects must have negative pregnancy test results within 7 days before administration.

   Effective contraceptive methods shown as follows:

   - Abstinence (avoiding heterosexual intercourse).
   - Use (or make their partner use) reliable and effective methods of contraception during heterosexual intercourse, such as:
     i. Single method of contraception (any one of the following methods is sufficient)
        a. Intrauterine device (IUD)
        b. Vasectomy in male partner of female subject
        c. Subcutaneous implant contraception
     ii. Combined condom and oral contraceptive pills.

   Male subjects and partners with azoospermia (caused by vasectomy or other underlying conditions) are not required to take contraception. Female subjects are considered to be infertile if the following conditions were present:

   i. Postmenopausal;
   ii. Documented hysterectomy, bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion at least 6 weeks prior to screening;
   iii. Congenital or acquired infertility.
9) According to the judgment of the investigator, the subject is able to communicate well with the investigator to comply with the requirement of the protocol.

In addition, eligible patients for phase II part must meet the following criteria:

10) Histologically or cytologically confirmed diagnosis of advanced or metastatic tumors of specific types, including hepatocellular carcinoma, cholangiocarcinoma/

gallbladder cancer (except carcinoma of ampulla), pancreatic cancer, colorectal cancer, urothelium carcinoma, cervical cancer, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, thymic carcinoma, endometrial cancer, osteosarcoma，TNBC and extranodal NK/T-cell lymphoma.

11) At least one measurable lesion according to RECIST 1.1 or Lugano 2014 Criteria (only for extranodal NK/T-cell lymphoma).

12) For hepatocellular carcinoma patients:
platelet count ≥60x10^9/L, without thrombopoietin or other therapies within 14 days prior to hematology test.

13) For cervical cancer patients:
hemoglobin ≥ 8 g/dL, without blood transfusion or erythropoietin and other therapies within 14 days prior to hematology test.

4.2 Exclusion Criteria

Patients eligible for this study must not meet **any** of the following criteria:

1) Impaired cardiac function or clinically significant cardiac diseases:

   a. Clinically significant cardiac diseases within 6 months, for example: myocardial infarction, angina, heart failure, severe arrhythmia, angioplasty, stent implantation, and coronary artery bypass grafting;

   b. Ascending aorta aneurysm or major artery aneurysm history, or predisposing conditions that are consistent with development of aneurysms (for example, family history of aneurysm, Marfan syndrome, evidence of damage to the large vessels of the heart documented by computerized tomography [CT] scan with contrast);

   c. Abnormalities at screening/baseline, which will be confirmed by the cardiologist if necessary:

      i. ECG: QT/QTc prolongation (QTcF > 470 ms for females or QTcF > 450 ms for males), or other clinically significant arrythmia, conduction abnormalities, morphology abnormalities;

      ii. Doppler echocardiography: clinically significant abnormalities, such as left ventricular ejection fraction (LVEF) < 50%, moderate or severe heart valve stenosis, and moderate or severe heart valve regurgitation;

iii. Troponin > ULN in conjunction with symptoms or other abnormal testing indicating myocardial ischemia

2) With acute or chronic infections, including:

a. Active infections requiring intravenous treatment'

b. Positive human immunodeficiency virus antibody (HIV-Ab), active syphilis, active hepatitis B virus infection (positive HBsAg and positive HBV-DNA), and active hepatitis C virus infection (positive HCV-Ab and positive HCV-RNA) during the screening/baseline period;

c. Active tuberculosis.

3) With active central nervous system metastases, including symptomatic brain metastases, meningeal metastases, spinal cord compression, or requiring treatment with glucocorticoids, antiepileptic drugs, anticonvulsant drugs, or mannitol.

4) With known active autoimmune diseases or a history of autoimmune diseases within 1 year prior to enrollment, such as systemic lupus erythematosus, psoriasis, rheumatoid arthritis, inflammatory bowel disease, and Hashimoto's thyroiditis. Except for type I diabetes, hypothyroidism or hyperthyroidism that can be controlled with only hormone replacement, skin diseases requiring no systemic treatment, controlled celiac disease.

5) With clinically significant gastrointestinal diseases, such as intractable hiccup, nausea and vomiting, severe peptic ulcer, active gastrointestinal bleeding, or other conditions that interfere swallowing the tablets or significantly alter the absorption; subjects with hepatocellular carcinoma who have severe portal hypertension due to Budd-Chiari syndrome or portal vein thrombosis.

6) Uncontrollable or symptomatic ascites, pleural effusion or pericardial effusion.

7) History of non-infectious (e.g., drug-induced) ILD requiring systemic steroid treatment, or current pneumonitis.

8) With other uncontrolled systemic diseases, such as hypertension and diabetes.

9) Diagnosed with other malignant tumors within 3 years prior to starting study drug, except for cured carcinoma in situ of cervix, skin basal cell carcinoma, early stages of prostate or thyroid cancer.

10) With diseases requiring immunosuppressant therapy, or requiring prednisone > 10

mg/day or equivalent dose of similar drugs during the study period.

11) Subjects who have been treated with immunosuppressant drugs within 28 days prior to starting study drug, except for topical and inhaled cortisol and systemic cortisol of physiological dose (prednisone < 10 mg/day or equivalent dose of similar drugs).

12) Subjects who have received live vaccine, attenuated vaccine within 28 days prior to starting study drug, or plans to receive live vaccine, attenuated vaccine during treatment or within 30 days after the last administration.

13) Subjects who have been treated with radiotherapy, chemotherapy, targeted therapy, endocrine therapy, immunotherapy, and other anti-tumor therapies (except for traditional Chinese medicines), or other investigational drugs within 5 half-life periods or within 28 days (whichever is shorter) prior to starting study drug.

14) Subjects who have been treated with traditional Chinese medicine with approved antitumor indications within 2 weeks prior to starting study drug.

15) Subject who has received major surgeries (except for needle biopsy) that may affect the administration or study evaluation within 28 days prior to starting study drug.

16) Subjects who have received strong inhibitor or inducer of CYP3A4 within 5 half-life periods or within 2 weeks (whichever is shorter) prior to starting study drug.

17) Subjects who have received combined treatment of drugs targeting TGF-β and PD-(L)1, including combination of antibody and small molecule or bispecific antibody.

18) Pregnant or lactating women.

19) With known allergies to the study drugs or components.

20) The subject is a staff member who is directly related to the investigator of the study or his/her family members, or the sponsor.

21) Other conditions judged by the investigator as inappropriate to participate in the study.

5 STUDY TREATMENT

5.1 Study Treatment Assignment

Each patient is uniquely identified in the study by an identification number, that is assigned when the patient is firstly enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the study.

This is an open-label study with no blinding or randomization. All enrolled patients will receive a combination therapy of GFH018 and Toripalimab. All dose changes during the study must be recorded on the source document.

5.2 Supply of Study Drugs

5.2.1 Strength and Packages of Study Drugs

Study Drugs	**GFH018 tablet**	**Toripalimab injection**
Active ingredients	GFH018	Toripalimab
Type	Chemical drugs	Biological product
Dosage form	Tablet	Injection
Administration route	Oral administration	Intravenous infusion
Storage requirements	Stored below 25 ℃, sealed and protected from light	Stored at 2–8 ℃ away from light, do not freeze
Source	GenFleet Therapeutics (Zhejiang) Co., Ltd.	Shanghai Junshi Biosciences Co., Ltd.

5.2.2 Preparation and Dispensing of Study Drugs

The investigator or his/her designee must ensure that all drugs or related items used for study treatment are maintained in appropriate temperature conditions during transport. If deviations occur, they are to be reported and resolved before proceeding with the study treatment.

Only patients enrolled in the study may receive the study treatment, and only authorized study center staff can provide or administer the study treatment products. All study intervention drugs

or related items must be stored in a secure and environmentally controlled area that can be monitored (manual or automated) in accordance with the storage conditions indicated on the label and it is ensured that only the investigator and authorized study center staff have relevant access to the study treatment products.

5.3 Dose and Administration

5.3.1 Dose and Administration of GFH018

5.3.1.1 Administration of GFH018

GFH018 will be administered orally as a continuous twice daily (BID) dosing for 14 days in a 28 days cycle during the treatment period of the escalation phase and during the entire expansion phase.

GFH018 will be administered orally served with approximately 200 mL warm water. Subjects need to be informed of the condition that the tablets must be swallowed in whole and not chewed or broken apart. When taking the medication twice daily, the interval is about 12 hours, e.g. schedule it around 8:00 am and 20:00 pm, it is recommended to keep the daily medication time be consistent. Subjects will be fasted at least 2 hours before administration of drug and remain fasted one hour post-dose. If a PK blood sample is collected in the morning, the drug will be taken after sampling.

If a missed dose occurs, the dose can be made up within 4 hours after the scheduled time, the actual dosing time will be recorded, and the subsequent dosing time will remain on schedule. If it has been more than 4 hours since the missed dose, the dose should be skipped and the subject should continue treatment at the scheduled time. All actual dosing times are recorded in the subject diary or recorded as "missed doses". If vomiting occurs after administration of the drug, no re-dosing of the patient is allowed before the next scheduled dose.

5.3.1.2 Dose Adjustment of GFH018

During the study period, dose adjustment or interruption of GFH018 within the DLT observation period is not allowed in principle; if at discretion of the investigator, adjustments are deemed necessary in the best interest of the patient, they should be discussed and agreed upon with the sponsor; otherwise, the treatment of subject will be discontinued, and the subject should be transferred to the follow-up period.

After observation period of DLT in Phase Ib and during the Phase II study, in the event of an adverse event related to GFH018 that meets the definition of DLT in Section 3.2.3 of the protocol, the recommended adjustment scheme is:

1) Temporary interruption of GFH018 is allowed. If recovery to ≤ grade 1 or baseline within 1 week, stay at the current dose; if recovery to ≤ grade 1 or baseline within 2 weeks, de-escalate the dose to the next lower dose level; if there is no tendency to recover within 2 weeks, discontinuation should be considered.

2) Discontinuation should be considered if a recovering adverse event turns worse after administration at a de-escalate dose level, or if a recovered adverse event recurs.

3) The recommended adjustment scheme of GFH018 is 80mg BID, 60mg BID, and 40mg BID.

Intra-patient dose escalation of GFH018 is not permitted during the first 4 cycles of treatment. After the 4th cycle is completed, individual patients may be considered for treatment at a dose of GFH018 higher than the dose to which they were initially assigned. For a patient to be treated at a higher dose of GFH018, he or she must have received the lower dose for at least four cycles of therapy without a toxicity ≥ CTCAE grade 2 that is at least possibly related to the study treatment. Moreover, the higher dose with which the patient is to be treated must be the dose that has completed evaluation in a dose-escalation meeting given all available data. When Phase II study begins, for subjects who are still receiving treatment in Phase Ib, it will be judged by the investigator whether to adjust their treatment regimen to RP2D in the best interest of the patient.

If a patient requires a dose delay of > 28 days from the intended day of the next scheduled dose of GFH018 or Toripalimab for other reasons, the patient must be discontinued from the study treatment. All dose adjustments must be documented in the source data and recorded in the CRF as required.

5.3.2 Dose and Administration of Toripalimab Injection

5.3.2.1 Administration of Toripalimab

The duration of the first intravenous infusion of Toripalimab should be at least 60 min. The patient should be closely monitored with vital signs every 30±5 minutes during infusion and within one hour after the infusion completion. If the patient is well tolerated with the first

infusion, the time for the second infusion can be reduced to no less than 30 min following with one hour observation period. If the patient has good tolerance during the infusion of 30 min, all subsequential infusion can be completed within 30 min. Administration by the intravenous bolus or a one-time rapid intravenous injection is not allowed.

Dilution method for Toripalimab injection before administration is as follows:

Dilution of this drug should be prepared within 24 h after it is taken from the refrigerator.

Visually inspect the drug for particles and color change before dispensing. The drug should be colorless or light-yellow clear liquid, slight opalescence is acceptable. If visible particles or abnormal color is observed, the drug should be discarded.

The drug does not contain preservative. Under the aseptic condition, the required volume of the drug is taken and slowly injected into an infusion bag containing 100 ml of normal saline (0.9% sodium chloride). It is diluted to a final concentration of 1-3 mg/ml, and the bag is then gently turned over and mixed well before intravenous infusion. The infusion tube utilized during infusion must be equipped with a sterile core filter without pyrogen and low protein binding (with pore size of 0.2 or 0.22 μm).

The dilution prepared under the aseptic condition can not be stored more than 8h at room temperature, including the storage time after dilution and the time for infusion. It can not be stored more than 24h at 2-8℃ either. If it needs to be refrigerated, please allow the diluent return to room temperature before administration. It can not be frozen for storage either.

It cannot be mixed or diluted with other drugs.

The residual drug in the vial cannot be re-used.

5.3.2.2 Dose Adjustment of Toripalimab

The dose of Toripalimab is 3 mg/kg. Intravenous infusion is given once every two weeks.

The study treatment should be given as far as possible in accordance with the planned dose and time. The dose of Toripalimab should not be adjusted within DLT observation period. In the sequential cycles, Toripalimab may be interrupted or discontinued permanently based on safety and tolerance of individual subjects. The dose adjustment should be conducted based on the observed worst toxicity to proceed if many adverse events occurred at one time. It is not recommended to increase or decrease dose.

For details, recommended to refer to latest "Drug Instruction" or "Investigator's Brochure". The following information was extracted from the "Toripalimab Instruction" of the version revised on May. 27, 2022.

Table 2 Recommended treatment adjustment scheme of Toripalimab

Immune-related adverse reactions	Severity *	Treatment modification regimen
Pneumonia	Grade 2	Withhold until improved to Grade 0-1
	Grade 3-4 or recurrent Grade 2	Permanent discontinuation
Diarrhea or colitis	Grade 2-3	Withhold until improved to Grade 0-1
	Grade 4	Permanent discontinuation
Hepatitis	Grade 2, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 3-5 times upper limit of normal (ULN) or total bilirubin 1.5-3 times ULN	Withhold until improved to Grade 0-1
	Grade 3-4, AST or ALT > 5 times ULN, or total bilirubin > 3 times ULN	Permanent discontinuation
Nephritis	Grade 2-3 blood creatinine increased	Withhold until improved to Grade 0-1
	Grade 4 blood creatinine increased	Permanent discontinuation
Endocrine disorders	Symptomatic Grade 2-3 hypothyroidism, Grade 2-3 hyperthyroidism, Grade 2-3 hypophysitis, Grade 2 adrenal insufficiency Grade 3 hyperglycemia or type I diabetes	Withhold until improved to Grade 0-1
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3-4 adrenal insufficiency Grade 4 hyperglycemia or type I diabetes	Permanent discontinuation
Cutaneous adverse reactions	Grade 3 rash	Withhold until improved to Grade 0-1
	Grade 4 rash, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanent discontinuation
Thrombocytopenia	Grade 3	Withhold until improved to Grade 0-1
	Grade 4	Permanent discontinuation
Other	Grade 2-3 blood amylase increased or lipase increased Grade 2pancreatitis Grade 2 myocarditis [a] Grade 2-3 other initial immune-related adverse	Withhold until improved to Grade 0-1

	reactions	
	Grade 4 blood amylase increased or lipase increased Grade 3-4 pancreatitis Grade 3-4 myocarditis Grade 3-4 Encephalitis Grade 4 other initial immune-related adverse reaction	Permanent discontinuation
Recurrent or persistent adverse reactions	Recurrent Grade 3-4 adverse reactions (except endocrine diseases); Grade 2-3 adverse reactions not improved to Grade 0-1 within 12 weeks after last dosing (except endocrine diseases) Corticosteroids not reduced to ≤ 10 mg/day prednisone equivalent within 12 weeks after the last dosing	Permanent discontinuation
Infusion reaction	Grade 2	Reduce the dripping speed or suspend the administration, and consider resuming the administration and closely observing the patient when the symptoms are relieved
	Grade 3-4	Immediately and permanently discontinue the transfusion and treat symptomatically

* Graded according to NCI-CTCAE v5.0
** The safety of restarting Toripalimab after myocarditis is improved to grade 0-1 through treatment is unclear.

5.3.3 Subject Compliance

GFH018 is taken and recorded by the subject after received on the designated visit day. Subject will be required to return all unused GFH018 tablets from the previous cycle on the designated visit day and return the completed subject diary. The number of tablets returned by the subject will be counted, recorded, and archived.

Toripalimab injection will be infused at the study center on the designated visit day. The study center will complete drug preparation and record infusion information according to the drug instruction. The documentation system of the clinical study center should include all information related to the preparation and administration of the drugs.

5.4 Drug Storage

The investigator or other authorized staff of study center, such as pharmacist, will ensure that all study drugs are stored in a secure and access-controlled area that meets the storage conditions described in Section 5.2.1 and that their storage meets applicable regulatory requirements. The subject should follow the guide of investigators or authorized staff to store correctly after receiving GFH018 tablet. If non-conforming storage conditions are identified, the investigator should contact the sponsor for guidance.

5.5 Records of Administration and Destruction

The study center must maintain records of the supply of research drugs, including receipt, distribution, use, recovery, loss or other whereabouts. The subject should follow the guide of investigator to return all unused GFH018 tablets and packages to the investigator at the designated follow-up date and return the finished *Subject diary card*. Toripalimab will be administrated in visit time and it will be recorded by the authorized investigators.

The unused study drug and packages will be recycled and destroyed by sponsor after making an inventory or destroyed by authorized study center. The sponsor or the personnel authorized by it will provide the guide about destroying the unused study drug to the study center. If it is authorized to destroy at the study center, the investigator should ensure that all recovery and destruction is conducted and documented in accordance with the appropriate regulatory guidelines and regulations.

5.6 Prior and Concomitant Therapies

5.6.1 Prior Therapies

Please refer to Section 4.2 for prohibited therapies before the enrollment of the study.

After signing of the informed consent, the prior anti-cancer therapies will be recorded, including setting, regimen, start date, stop date, best response, reason for discontinuation.

All other prior therapies that were being taken 30 days before the first administration will be documented.

5.6.2 Concomitant Therapies

All concomitant medications and treatments are to be collected from the enrollment through the end of safety follow-up period.

In general, the use of concomitant medication, procedures and non-drug therapies deemed necessary for the care of the patient are permitted during the study. Using of medications that may significantly affect the evaluation of the study results, such as safety and tolerance, should be avoided. In case of serious adverse reactions or serious adverse events or deterioration of the original condition or other serious diseases, the investigator should promptly administrate corresponding medication as clinically indicated. The subject should withdraw from the study if he/she meets the withdrawal criteria.

5.6.2.1 Permitted/Caution Concomitant Therapies

The investigators should follow the underly principles and cautiously use concomitant therapies, to ensure the safety of the subjects.

1) Corresponding treatment is permitted in the study period, depending on the investigator's judgment and relevant guidelines (e.g., *American Society of Clinical Oncology (ASCO) Guidelines*). For example, palliative local radiotherapy for symptomatic relief is permitted for painful bone lesions, these lesions should be present at the time of enrollment and are not the only target lesion. Investigator should make judgement and record whether the use of radiotherapy is associated with disease progression before radiotherapy.

2) Allow to use topical steroid and inhaled corticosteroid. Allow to use systemic corticosteroids (i.e., prednisone ≤ 10 mg/day) at a physiologically alternative dose. Allow to use corticosteroids in short period to prevent (e.g., contrast agent irritability) or treat non-autoimmunity diseases (e.g., the delayed anaphylaxis due to contact allergens), or to address the adverse reaction of study drugs.

If the investigator cannot determine whether the concomitant therapy affects the subject safety, or whether it affects the judgment for the safety and tolerance of the subjects after administration, or whether it affects the eligibility of the subjects to participate in the study after administration, the investigator should consult the sponsor before therapy initiation.

5.6.2.2 Prohibited Concomitant Therapies

During the course of the study, the subject should not receive following therapies:

1) Any other anti-tumor therapies (chemotherapy, immunotherapy, biologic products, extensive radiotherapy, hormone therapy, targeted therapy, surgery, and traditional Chinese medicine with approved antitumor indications), including research-based therapies. Taking antagonism GnRH to treat PC (prostatic cancer), orally contraceptive and hormone replacement therapy are allowed.

2) Any immunosuppressant or systemic corticosteroids for immunosuppressive effects except using for adverse events during the study.

3) Use the drug of G-CSF (granulocyte colony-stimulating factor) as the prophylactic. Such drugs can be only used for treatment of adverse events under the judge of the investigator.

4) Live vaccine or attenuated vaccine (COVID19 vaccine will be allowed if there is no interference to the study in the discretion of investigator).

5) Any other drugs under clinical investigation other than the treatment in this study.

6) Based on preclinical study, GFH018 is mainly metabolized by CYP3A. To avoid drug-drug interactions, the strong inducers and inhibitors of CYP3A4/5 are forbidden. In addition, the moderate inhibitor or inducer of CYP3A4/5 should be used with caution. Some typical drugs are listed as follows:

Table 3 Inducers and inhibitors of CYP3A4/5 (partial)

Interaction mechanism	Drug name
Strong inducer	Carbamazepine, phenytoin, rifampicin, and St. John's wort
Strong inhibitor	Clarithromycin, ritonavir, indinavir, ketoconazole, and itraconazole
Moderate inducer	Bosentan, Modafinil, Nafcillin, and Thioridazine Hydrochloride
Moderate inhibitor	Cimetidine, Ciprofloxacin, Grapefruit, Verapamil, and Imatinib

1) Other lifestyle requirements: Grapefruit-based fruits and beverages (e.g., citrus, grapefruit, or grapefruit juice) are prohibited from at least 7 days prior to the first dose until the end of study treatment; products containing caffeine or xanthines (e.g., coffee, tea, cola drinks, and chocolate) will not be permitted for 6 hours prior to each dose until

final pharmacokinetic (PK) samples have been collected. Alcohol will not be permitted for 24 hours prior to each dose until final PK samples have been collected.

6 STUDY PROCEDURES

An institutional review board/independent ethics committee (IRB/IEC) approved informed consent form (ICF) must be dated and signed prior to any screening procedures.

All procedures of the study should be conducted within the time window specified in the assessment schedule. If procedures of the study cannot be completed on time or as required under special cases, the investigator will take all necessary measures to ensure the safety and benefits of subjects, and record the reasons and interventions. In addition, the investigator needs to notify the study team of unexpected situations in time.

6.1 Screening Period

The screening period starts once a patient has provided written informed consent to participate in the study and ends on the day of study entry. Screening assessments must be performed within 28 days prior to starting study treatment:

- The ICF must be dated and signed prior to any screening procedures
- Demographic data including date of birth, sex, and race will be collected
- Medical history within 30 days prior to signing of the informed consent, and diagnosis and extent of cancer (including histopathology, cytological diagnosis, and clinical staging, tumor-related symptoms, and imaging findings)
- Height and Weight
- Prior therapies: prior anti-cancer therapies will be recorded, including setting, regimen, start date, stop date, best response, reason for discontinuation. All other prior therapies that were being taken 30 days before the first administration will be documented.
- Physician examination
- Vital signs (blood pressure, respiratory rate, pulse, and temperature)
- ECOG PS
- ECG
- Echocardiography
- Laboratory tests (See Table 4 in Section 7.1.2)

- If done, they will be assessed by the investigator as normal or abnormal and details about abnormality will be entered in the CRF
- Radiological imaging and tumor assessment as necessary
- AE/SAE reporting
- Biomarker sampling or collection
- Determine patient eligibility based on the inclusion/exclusion criteria

This study allows one-time re-screening of subjects. Subjects should be re-consented when re-screening. A new identification number will be assigned to the re-screened subject. Once the subject is re-screened, a new 28-day screening window will begin. All screening assessments are allowed to be repeated once during a screening process. For subjects who have failed screening, detailed information at least including demographics, diagnosis of disease, reasons for screening failure, and SAEs should be documented.

6.2 Treatment Period

Patients will be treated with GFH018 and Toripalimab. A treatment cycle is defined as 28 days. Tumor assessment based on RECIST 1.1 and Lugano 2014 Criteria (only for extranodal NK/T-cell lymphoma) will be performed every 8 ± 1 weeks (every 6 ± 1 weeks for hepatocellular carcinoma) in the first year and every 12 ± 1 weeks (every 8 ± 1 weeks for hepatocellular carcinoma) from the second year.

6.2.1 Cycle 1

Day 1

- Reassess inclusion/exclusion criteria before starting study treatment
- Physical examination and weight
- Vital signs
- Laboratory tests (See Table 4 in Section 7.1.2)
- ECG Echocardiogram (for phase II period, conducted as clinically indicated), no need to repeat tests them within the allowed time window
- AE/SAE reporting
- Concomitant therapies
- GFH018 PK blood sampling
- Toripalimab PK and ADAblood sampling

- GFH018 and Toripalimab administration

Day 8(±2) (only for phase Ib)

- Physical examinations and weight
- Vital signs
- Laboratory tests (See Table 4 in Section 7.1.2)
- ECG
- AE/SAE reporting
- Concomitant therapies
- GFH018 PK blood sampling
- GFH018 administration

Day 15(±3)

- Physical examinations and weight
- Vital signs
- ECOG PS
- Laboratory tests (See Table 4 in Section 7.1.2)
- ECG (only for phase Ib)
- AE/SAE reporting
- Concomitant therapies
- GFH018 PK blood sampling (phase II part only)
- Toripalimab PK and ADA blood sampling
- Toripalimab administration

Day 28 (only for phase Ib)

- Physical examination and weight
- Vital signs
- Laboratory tests (See Table 4 in Section 7.1.2)
- ECG
- Echocardiogram
- AE/SAE recording
- Concomitant therapies.

6.2.2 Subsequent Cycles

The following procedures will be performed on Day 1 and Day 15 of the subsequent cycles:

Day 1(±3)

- Physical examination and weight
- Vital signs
- Laboratory tests (See Table 4 in Section 7.1.2)
- ECG
- Echocardiogram (for phase II period, conducted as clinically indicated)
- AE/SAE recording
- Concomitant therapies
- GFH018 and Toripalimab administration.

Day 15(±3)

- Physical examination and weight
- Vital signs
- ECOG PS
- Laboratory tests (See Table 4 in Section 7.1.2)
- ECG (only for phase Ib)
- AE/SAE recording
- Concomitant therapies
- GFH018 PK blood sampling (Cycle 2-4)
- Toripalimab PK and ADA blood sampling (Cycle 2-4)
- Toripalimab administration

6.3 End-of-Treatment (EOT) Visit

For patient who has confirmed disease progression based on the RECIST 1.1 or Lugano 2014 Criteria (only for extranodal NK/T-cell lymphoma), or meets any of the criteria described in Section 6.5.1, the EOT visit should occur as soon as possible (within 7 days) after making the decision of discontinuation. Radiological test within 6-8 weeks will not require additional image test. Monitoring tests for AE will be at the discretion of investigator. If a patient discontinues due to reasons other than disease progression and does not start subsequent anticancer therapy, the radiological tests will be performed on the scheduled visit (i.e., every 8 ± 1 weeks or every 6 ± 1 weeks in the first year; every 12 ± 1 weeks or every 8 ± 1 weeks since the second year) until disease progression, start of new anticancer therapy or other reasons.

The following procedures should be performed at the EOT visit:

- Vital signs
- Physical examination and weight
- ECOG PS
- ECG
- Echocardiogram (for phase II period, conducted as clinically indicated)
- Laboratory tests (See Table 4 in Section 7.1.2)
- AE/SAE reporting
- Concomitant therapies
- Collection of subsequent disease information and subsequent anti-tumor treatment

If the EOT visit is conducted within the time window of the safety follow-up, it shall be carried out according to the safety follow-up visit, and the same examination items do not need to be repeated.

6.4 Follow-up Period

6.4.1 Safety Follow-up

After the EOT visit, the subject starts the follow-up period. Tumor assessment performed within 6 weeks (for hepatocellular carcinoma) or 8 weeks is acceptable and repeated assessment is not required. But AE related assessment could be performed according to the investigator' judgment. The safety follow-up visit should occur 30 (± 3) days after the last administration, subjects will return to the study center for a safety follow-up visit. The following procedures will be performed:

- Vital signs
- Physical examination
- ECOG PS
- Laboratory tests (See Table 4 in Section 7.1.2)
- ECG
- Echocardiogram (for phase II period, conducted as clinically indicated)
- AE/SAE reporting
- Concomitant therapies
- Collection of subsequent disease information and subsequent anti-tumor treatment

After the safety follow-up visit, AEs will not be collected actively, but all treatment-related AEs must be followed up to resolve, recover to baseline, or the investigator judges it a stable and irreversible condition.

6.4.2 Survival Follow-up

Following the safety follow-up period, there will be a survival follow-up. Subjects will be followed up every 90 (±15) days until death, lost to follow-up, or the study ends (whichever occurs first). Investigator may inquire subjects, their family members, or local physicians through email or telephone to obtain survival information (including date and cause of death), disease status, and subsequent anti-cancer treatment. The follow-up information needs to be recorded in the source data.

6.4.3 Disease Progression Follow-up

If a patient discontinues due to reasons other than disease progression and does not start subsequent anticancer therapy, the radiological tests will be performed on the scheduled visit (i.e., every 8 ± 1 weeks or every 6 ± 1 weeks in the first year; every 12 ± 1 weeks or every 8 ± 1 weeks since the second year) until disease progression, start of new anticancer therapy or other reasons.

All subjects will be permitted to continue treatment beyond initial RECIST 1.1-defined or Lugano 2014 (only for extranodal NK/T-cell lymphoma) progression if the investigator judged that the subject is beneficial to treatment without safety concern.

6.4.4 Unscheduled Follow-up

If it is necessary judged by investigator for safety concerns, AEs follow-up, or clinical symptoms suggesting disease progression, the investigator may arrange unscheduled follow-up for further examination and evaluation.

6.5 Discontinue/Withdraw from Treatment or Study

6.5.1 Discontinuation of Study Treatment

Patients may voluntarily withdraw from the study treatment or be dropped from it at the discretion of the investigator at any time. If withdrawal occurs, the investigator must determine

the primary reason for a patient's premature withdrawal from the study treatment. Patients may be withdrawn from the study treatment prematurely for one of the following reasons:

- Disease progression
- Adverse event(s)
- Start other anti-cancer treatment
- Non-compliance
- Pregnancy
- Subject request
- Lost to follow-up
- Death
- Withdrawal of consent
- Investigator decision
- Study terminated by sponsor

Patients who discontinue study treatment should be scheduled for an EOT visit within 7 days after making the decision of discontinuation. If a patient discontinues due to reasons other than disease progression and does not start subsequent anticancer therapy, the radiological tests will be performed on the scheduled visit (i.e., every 8 ± 1 weeks or every 6 ± 1 weeks in the first year; every 12 ± 1 weeks or every 8 ± 1 weeks since the second year) until disease progression, start of new anticancer therapy or other reasons.

Investigators may provide suggestions or alternative treatment for subjects based on their actual conditions.

6.5.2 Withdraw from the Study

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Reasons for removal of a subject from the study are：

- Withdrawal of consent
- Death
- Lost to follow-up
- Study terminated by sponsor

If the subject fails to return to the study center for follow-up visit as scheduled, the investigator should make efforts to contact them in time and reschedule the missed visit as soon as possible. The investigator should ask about the reason for dropping out and ask the subject to return to the center as much as possible to complete the visit and follow up the unresolved AEs. If possible, every effort should be made to record the outcome of the subject in any case.

If the subject refuses to come back to the research center for further visit, the investigator should continue to track and collect information of their disease and survival, unless the subject withdraws informed consent. In this case, no more study evaluations will be performed, and no more information should be collected.

All attempts to make contact should be recorded on the source document.

6.6 Study Completion and Early Study Termination

The end of study is defined as the time when all enrolled subjects have been under study treatment for at least one yeah or have been discontinued for any reason (whichever occurs first).

This study may also be discontinued early or interrupted. This may be due to decision of the authority, opinion of the Ethics Committee, suggestion from SMC, or decision of the sponsor. Additionally, the sponsor reserves the right to stop the research and development of GFH018.

Reasons for early termination and interruption of the study may include but not limited:

- Determined unexpected, significant, or unacceptable risks to the subject.
- The results of the efficacy support early termination of the study.
- Non-compliance to the study.

The party that decides to discontinue/interrupt the study will give a written notice to record the reasons for the discontinuation or interruption to the investigator, sponsor, and regulator. If the study is early discontinued or interrupted, the investigator should immediately notify the Ethics Committee.

Once the above-mentioned drug safety and protocol compliance issues that caused the discontinuation have been resolved and approved by the sponsor, Ethics Committee or regulatory agency, the study will be reinitiated.

6.7 Continue to Use the Study Drug after the Study Ends

If the investigator judges that the subject will get benefit continuing the treatment after study completion, the subject may be allowed to continue to be treated with GFH018 and/or Toripalimab after fully informed and reconsent until the treatment discontinuation criteria are met (see Section 6.5.1). Study drugs will be provided through other extended studies or other programs provided by the sponsor.

7 EVALUATION

The procedures required by the protocol should be performed as planned to ensure that the examination results can be evaluated in a timely manner. If it cannot be completed on time as required under special cases, the investigator will take all necessary measures to ensure the safety and benefits of subjects. The investigator should record the reasons and remedial measures and notify the study team in time.

7.1 Safety Evaluation

Safety evaluation includes vital signs, physical examination, laboratory assessments, ECG, echocardiogram, AEs, SAEs, and concomitant therapies.

7.1.1 Physical Examination

The physical examination may be performed by a physician, physician’s assistant, or nurse practitioner licensed to perform assessment. The subject's vital signs (respiration, pulse, blood pressure, and body temperature) will be recorded. The physical examinations include examination of general appearance, weight and examinations of disease-related systems if indicated based on medical history and/or symptoms, and ECOG PS will be recorded based on the examination results.

If necessary, a complete physical examination will be performed, including general appearance, skin and lymph nodes, head and neck, chest, abdomen, spine and limbs, nervous system, genitals, anus and rectum examination and weight.

7.1.2 Laboratory Assessment

Hematology, urinalysis, blood chemistry, coagulation, thyroid function, cardiac markers, tumor markers, and pregnancy test will be performed based on the schedule of study procedures. The

laboratory testing will be completed in the local laboratory. In the screening/baseline period, test of viral serology will be required to assess the eligibility for enrollment. Tumor markers other than which are listed in the Table 4 may be collected if available.

Table 4 Laboratory test items

Test item	Observation index
Hematology	Count of red blood cell (RBC), concentration of hemoglobin (HGB), hematocrit (HCT), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), count of white blood cell (WBC), count of platelet (PLT), Absolute neutrophil count (ANC), lymphocyte (LY) count, monocyte (MO) count, eosinophil (EO) count, basophil (BA) count, percentage of neutrophils, percentage of lymphocytes, percentage of monocytes, percentage of eosinophils, and percentage of basophils
Urinalysis	White urine cells (LEU), urine nitrite (NIT), pH of urine, urine specific gravity (SG), urine protein (PRO), urine glucose (GLU), urine ketone body (KET), urobilinogen (UBG), urinary bile red pigment (BIL), urine occult blood (BLD), and 24-hour urine protein (if necessary)
Coagulation	Prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR)
Blood chemistry	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), glutamyl transpeptidase (GGT), urea (UREA)/urea nitrogen, blood creatinine (CREA), total protein (TP), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), creatine kinase (CK), amylase/pancreatic amylase (AMY/p-AMY),lipase, blood glucose, total cholesterol (TCHO), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), phosphate, calcium, sodium, chlorine, and potassium
Virus serology test	Hepatitis B surface antigen (HBsAg), anti-hepatitis C virus antibody (anti-HCV), HIV antibody, Treponema pallidum antibody; If HBsAg positive, then add test of HBVDNA; If anti-HCV positive, then add test of HCVRNA.
Thyroid function	Free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH)
Cardiac markers	Troponin, brain natriuretic peptide (BNP) or NT-proBNP
Tumor markers	AFP (hepatocellular carcinoma only), CEA (colorectal cancer only), CA199 (pancreatic cancer only)
Pregnancy test	Female subjects in child-bearing period undergo serum β-HCG pregnancy test at baseline, and both serum test and urine test are acceptable at other visits

7.1.3 Electrocardiogram and Echocardiogram

A standard 12-lead electrocardiogram (ECG) and echocardiogram will be completed according to the date and time requirements specified in the schedule of the study.

Standard 12-lead ECGs should be taken in supine, after at least 10 minutes rest. Recording of specific ECG parameters, include but are not limited to heart rate, QT, QTcF, and PR. Single ECGs will be performed at all timepoints. Triplicate 12-lead ECG will be performed when 1) QTcF 450≥ msec at screening; 2) in case of a post-screening QTcF interval ≥450 msec or an increase of ≥30 msec from baseline. These ECGs should be at least 10 min interval to ensure the accuracy of the examinations, and the average of the triplicate measurements will be recorded and used for evaluation.

Echocardiography should include at least the condition of the heart valve, aortic valve, and systolic and diastolic function in the heart. During the study period, the consistency of test items should be ensured as much as possible.

7.1.4 Adverse events and Concomitant Therapies

The evaluation of adverse events includes term of event, severity (grading based on NCI CTCAE version 5.0), starting and ending time, whether it is an immune-related adverse event, whether it is a serious adverse event, relevance to study treatment (GFH018 or/and Toripalimab), the adjustment of study treatment and outcomes.

After signing of the informed consent until the completion of the safety follow-up visit, the AEs that occurred during the period will be recorded in the original medical records and collected in the CRF. Comedication/treatments received by the subject during the study treatment period will be recorded in the original medical records and collected in the CRF.

7.2 Pharmacokinetics

7.2.1 GFH018 PK Samples Collection

7.2.1.1 For the 14 days on/ 14 days off Dosing Regimen

1. Phase Ib

As shown in the table of PK blood sampling schedule (see Table 5 Schedule of pharmacokinetic blood sample collection (14/14)), blood samples will be collected on Cycle 1 Day 1 and Day 8, and Cycle 2, Cycle 3, and Cycle 4 Day 15 for PK analysis.

[redacted]

2. Phase II

Blood samples will be collected pre-dose in the morning of Cycle 1 Day 1 and Day 15, and Cycle 2, Cycle 3, and Cycle 4 Day 15.

7.2.1.2 Unscheduled Sampling

In addition to the samples in the schedule, it may be necessary to collect GFH018 additional blood samples for subjects with unexpected AE and/or SAE related to the study treatment. In this case, it is necessary to record the sampling date and specific time points, as well as the details for the last administration.

Every effort should be made to collect PK samples according to the date and time points specified in the protocol. The collection of PK samples with exact dates and clock times of drug administration and sample collection will be recorded on the appropriate blood collection CRF. If the blood sample cannot be obtained within the planned time, the investigator should contact the sponsor at the first time to discuss possible remedial measures.

For details of sample preparation and processing, please refer to the laboratory manual.

7.2.2 Toripalimab PK and ADA Samples Collection

Pre-dose PK and ADA blood samples of Toripalimab will be collected on the Cycle 1 Day 1 and Day 15, and Cycle 2, Cycle3 and Cycle 4 Day 15. For details, please refer to "Laboratory Manual".

7.2.3 Sample Analysis Methods

The PK samples of the GFH018 will be analyzed with a validated liquid chromatography-tandem mass spectrometry method, with the lower limit of qualification (LLOQ) of 20 ng/ml or less.

The PK sample of Toripalimab will be analyzed by the validated electrochemiluminescence method, with LLOQ of 2.56 ng/ml or less. ADA will be detected by another chemiluminescence method.

For details of processing method of biological samples, please refer to the "Laboratory Manual".

7.2.4 Calculation of Pharmacokinetic Parameters

The non-compartmental model will be used to calculate the PK parameters of GFH018 after single and multiple doses. The PK parameters include C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $T_{1/2}$, CL/F and Vd/F for single dose, while $C_{max,ss}$, $C_{min,ss}$, $T_{max,ss}$, AUC_{tau}, $T_{1/2,ss}$, $CL/F_{,ss}$, $Vd/F_{,ss}$ and R_{acc} for repeated doses.

The drug concentration data below LLOQ before T_{max} will be marked as 0 when calculating PK parameters, and BQL after T_{max} will not be included in the calculation of PK parameters. The linear trapezoidal method will be used to calculate AUC. During the calculation of $T_{1/2}$, the data of at least 3 time points after T_{max} should be used. $T_{1/2}$ will not be reported if the adjusted R^2 value of the regression analysis is <0.75.

7.3 Evaluation of Biomarkers

During the study, the formalin-fixed, paraffin-embedded specimens of tumor tissue from patients will be collected before starting study treatment evaluation. The PD-L1 expression, CD8 + cell density and TILs in tumor tissue will be analyzed to explore potential predictive biomarkers.

For details of sample preparation and processing, please refer to the "Laboratory Manual".

7.4 Evaluation of Tumor Response

The evaluation of tumor response will include all known or suspected sites by radiologic techniques. Imaging includes computed tomography (CT) or magnetic resonance imaging (MRI) scanning of chest, abdomen or pelvic cavity; brain CT or MRI is used for the known or suspected brain metastasis of the subjects; bone scanning and/or bone X-ray are/is used for the known or suspected bone metastasis of the subjects. For subjects with extranodal NK/T cell lymphoma, the baseline imaging evaluation shall include both PET-CT and diagnostic enhanced CT/MRI of the neck, chest, abdomen, and pelvis, and MRI of the nasopharynx is necessary for nasal type. PET-CT can be used according to the local investigator interpretations in the subsequent evaluations.

An imaging examination and tumor evaluation will be performed every 8 ± 1weeks (every 6 ± 1 weeks for hepatocellular carcinoma) in the first year and every 12 ± 1 weeks (every 8 ± 1weeks for hepatocellular carcinoma) from the second year. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow up. The evaluation of anti-tumor activity will be conducted in the screening period and treatment process through radiology, according to the study flow chart; it shall be also evaluated when the disease progression (such as symptom deterioration) is suspected or the subject withdraw (if the subject receives the imaging examination within 4 weeks, it will not be necessary to repeat the examination).

The tumor response will be assessed based on the RECIST 1.1 (Appendix 1) and Lugano 2014 Criteria (Appendix 4) by investigator. Radiographic imaging examination of all subjects must meet the RECIST 1.1 or Lugano 2014 Criteria (only for extranodal NK/T cell lymphoma). All data shall be properly preserved and can be verified by source and peer review.

8 REPORT OF ADVERSE EVENTS

8.1 Adverse Events (AE)

8.1.1 Definition of AE

The time period for collecting AEs for each subject begins from the time that the subject provides written informed consent, until the end of safety follow-up (30 calendar days after the last administration of investigational products) (see Section 8.5 for details). An AE for the purposes of this protocol is defined as the appearance of undesirable sign(s), symptom(s), or

medical condition(s), whether or not considered related to the investigational product. Whenever possible, a diagnosis should be reported instead of underlying signs and symptoms. Examples of AEs include, but are not limited to:

- Aggravation of existing (prior to enrollment of study) medical conditions/ diseases (including exacerbation of symptoms, signs, laboratory abnormalities);
- Any new occurrence of AEs: any adverse medical conditions that newly occur (including symptoms, signs, newly diagnosed diseases);
- Abnormal laboratory test findings of clinical significance.

8.1.2 Immune-Related Adverse Events (irAE)

Based on the mechanism of Toripalimab, immune-related adverse events may occur during the study. When adverse events occur, investigators need to make a comprehensive judgment according to the symptoms, signs and laboratory examination results of the subjects. In the absence of alternative causes (such as infection or disease progression), all inflammation-related events such as myocarditis, enteritis, pneumonia, dermatitis, hepatitis, and endocrine diseases require consideration of immune-related possibilities. Early recognition and timely treatment are needed to avoid potential major complications. For irAE and other management guidelines and principles of special adverse events that may be related to Toripalimab, please refer to "Investigator's Brochure".

8.1.3 Adverse Events of Special Interest (AESI)

The AESI of this study is cardiotoxicity ≥ Grade 2, such as increased cardiac markers, and abnormal electrocardiogram or echocardiography with clinical significance.

8.1.4 Severity Assessment

For severity of each AE, refer to the 5-grade scale developed from CTCAE v5.0. For AEs not included in CTCAE v5.0, the severity of each AE will be graded based on the general guidelines in **Table 6**.

Table 6 General guideline on the severity of adverse events

Grade	Clinical description of severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living. Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event.

8.1.5 Causality Assessment

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that investigational products caused or contributed to an AE, such as whether the occurrence of AE follows a reasonable time sequence to administration of investigational product, the properties of investigational products toxicological and pharmacological effects of investigational products, the use of concomitant medications, underlying diseases, medical history, family history, dechallenge and rechallenge reactions, etc. Generally, the facts (evidence) or arguments to suggest a causality should be provided.

The causality of AE with GFH018 and Toripalimab administration will be assessed as "related" and "unrelated". If the investigator considers that the AE is related to Toripalimab, this AE should be determined whether it is immune related adverse event.

8.2 Serious Adverse Event (SAE)

8.2.1 Definition of SAE

An SAE is any untoward medical occurrence during the study as one of the followings:

- Death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Constitutes a congenital anomaly/birth defect;

- Is considered to be medically significant

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples 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.

8.2.2 Hospitalisation

Hospitalisation is defined as any initial admission (even less than 24 h) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission.

Hospitalisation does not include the following:

- Rehabilitation facilities;
- Nursing homes;
- General emergency admission (less than 24h);
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for workup of a persistent pretreatment laboratory abnormality);
- Administrative admission (e.g., for yearly physical examination);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins

during the reporting period should be reported if the AE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.2.3 Disease Progression and Death

Clinical symptoms of progression of malignancies may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study. If it is clearly consistent with the suspected progression of the underlying cancer, it will not be reported as adverse events. Progression of malignancy itself will be not reported as an AE.

Clinical symptoms of progression of malignancies that meet SAE criteria may be reported as SAEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study. An event which meets serious criteria of SAE (except death event) due sole to the progression of underlying malignancy should not be reported as a SAE.

Any death event occurred in clinical trials from the subject's signing the informed consent until 90 days after the last administration must be reported as SAE, regardless of whether the investigator evaluates a possible association with progression of malignancies. The term ‘death’ should not be reported as an SAE term, but rather as an outcome of an event. The cause of death, medical conditions/disease (including exacerbation of symptoms, signs) should be used to be recorded in the eCRF and reported as SAEs; if the cause of death is unknown at the time of report, it should be recorded as “unknown cause of death”.

8.2.4 SAE Reporting Requirements

All SAEs should be reported to Genfleet/designated CRO drug safety department by the investigator on the report form (signed and dated) within 24 h of investigator awareness, regardless of whether this is an initial report or a follow-up report. The investigator should also report the SAEs to relevant organizations in a timely manner as required by local regulations. In countries or regions outside China, SAEs should be reported in accordance with the most stringent standards in accordance with local regulations.

SAEs occurring in a subject after the active collection period has ended are reported to Genfleet/designated CRO drug safety department if the investigator becomes aware of them; at

a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational products must be reported. The detailed record content of SAE should include symptoms, severity, causality with investigational products, time of onset, time of treatment, action taken with investigational products, follow-up time and way as well as outcome. If the investigator considers that a SAE is not related to investigational products while potentially related to the study conditions (e.g., termination of the original treatment or complications during the study), the relationship should be described in detail in the narrative section of SAE report form.

The sponsor's email to receive safety reports (for SAEs or exposure during pregnancy) in this study:

[redacted]

8.3 Pregnancy

If a female subject becomes pregnant during the clinical study, the subject must discontinue study treatment and be removed from the study; if a male subject's partner becomes pregnant during the clinical study, the subject may continue the clinical study. The investigator shall report to the sponsor within 24 hours of being informed of the pregnancy event by completing the report form.

The investigator should follow up on the pregnancy outcome (e.g., any early termination of pregnancy, or a live birth) until 1 month after delivery, and notify the sponsor the pregnancy outcome. If the pregnancy outcome meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs.

If a subject experiences an SAE during pregnancy, the SAE should be reported following the procedures for reporting SAEs.

8.4 Hy's law

Increased values in AST and/or ALT concurrent with abnormal elevations of TBIL that meet all of the following 3 criteria in the absence of other etiologies should be reported as SAEs. Needs to be reported following by SAE report process.

Table 7 Criteria for Liver Function Test Abnormalities

Conditions of satisfaction	Criteria
Abnormal ALT or AST	Baseline within normal range: ALT or AST in treatment stage > 3 × ULN; Baseline within abnormal range: ALT or AST in treatment stage > 3 × baseline level.
Abnormal TBIL	Baseline within normal range: treatment stage TBIL in treatment stage > 2 × ULN; Baseline within abnormal range: treatment stage TBIL in treatment stage > 2 × baseline level.
Alkaline phosphatase < 2 ×ULN (or no other information available)	

Subjects who present with abnormal values in AST and/or ALT concurrent with abnormal elevations of TBIL during the treatment or follow-up period should return to the investigational site and be evaluated as soon as possible. This evaluation should include laboratory tests, detailed history, physical assessment and information of concomitant treatments. In addition, the condition of tumor affecting the liver shall be considered.

8.5 Collection and Follow-Up of AE/SAE/AESI/Pregnancy Events

AE collection starts from the time that the subject signs the informed consent to participate in the study and continues until the end of safety follow-up (30 calendar days after the last administration of the investigational product).

At each study visit period, the investigator shall assess whether the subject has experienced an adverse event. All adverse events should be followed until they are resolved, or returned to baseline, or be stable, or judged by the investigator to be irreversible, or be reasonably explained (e.g., lost to follow-up, death), or until the event is conclusively confirmed to be unrelated to the study treatment or study procedure at the end of the safety follow-up period. Every effort

should be made to ensure that subjects achieve optimal outcomes and receive a clear evaluation of causal relationship.

All AEs should be documented in detail on the AE page of the CRF, including term of event, severity (grading according to CTCAE version 5.0), starting and ending time, whether it is an irAE or AESI, whether it is a serious adverse event, and causality of investigational products (GFH018 or/and Toripalimab), the action taken of investigational product, and outcomes.

Table 8 Collection of AE/SAE/AESI/pregnancy events

Period	Requirements of collection
From the subject's signing the informed consent until the end of the safety follow-up period	All AE/SAE/AESI/pregnancy events Pregnancies: collection starts from the first administration of the investigational product.
From the end of the safety follow-up period to 90 days after the last administration	All SAE/AESI/pregnancy events.
After the above period	SAEs/AESIs which are considered related to the investigational product.

Abbreviations: AE = adverse events, SAE = serious adverse events, AESI = adverse events of special interest.

9 CLINICAL MONITORING

In order to ensure that the rights and interests of patients are protected, the data obtained in the study is accurate, complete and reliable, and the study is in compliance with the approved protocol/revised protocol, ICH-GCP, and applicable regulatory requirements, the study site will be monitored by the sponsor or its authorized agent. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The detailed planning and the implementation of clinical monitoring will be recorded in this study monitoring plan (SMP).

10 STATISTICAL ANALYSIS

The phase Ib and phase II data will be analyzed separately. The summary will be presented by dose level and regimen for phase Ib part. The summary will be presented by tumor type for phase II part, subjects who have received the phase II treatment regimen in phase Ib and meet the phase II eligibility criteria will be counted.

The detailed methods for the summary and statistical analysis of the data collected by this study will be included in the Statistical Analysis Plan (SAP).

10.1 Analysis Sets

- Full Analysis Set (FAS) consists of all subjects who have received at least one dose of study treatment.
- Safety Set (SS) includes all subjects from the FAS who have received at least one dose of study treatment and had at least one valid post-baseline safety assessment.
- Dose Determining Set (DDS) consists of all subjects in the SS in phase Ib part who have received at least 75% of the total planned dose of GFH018 and the planned complete dose of Toripalimab (including the interruption allowed in the regimen) during the DLT observation period, are considered to have sufficient safety evaluation or developed DLT during the DLT observation period, and have no major protocol deviations that would impact the safety analyses.
- Per Protocol Set (PPS) consists of all subjects in the FAS who are in compliance with the protocol in phase II part. Subjects who have major protocol deviations may be excluded from the PPS based on a study team review of all protocol deviations, which will be conducted before final database lock.
- Pharmacokinetic analysis set (PKAS) consists of all subjects who take at least one dose of study treatment and have at least one blood sample providing evaluable concentration data.

10.2 Distribution of Subjects

Summary the distribution of subjects who participated in the screening. Summarize and list the conditions of participating in screening, receiving study treatment, reason for discontinuation of study treatment, reason for end of study, inclusion in each analysis set.

10.3 Protocol Deviations

Compliance with the protocol will be assessed by the number and proportion of patients with major protocol deviations. Protocol deviations will be identified prior to database lock and will be listed and summarized.

10.4 Demographic and Baseline Characteristics

Demographic and other baseline characteristics including age, gender, height, weight, medical conditions, etc. will be listed individually by patient, and summarized by treatment assigned using descriptive statistics (continuous data) or contingency tables (categorical data) for the FAS.

10.5 Treatment Exposure

The actual dose and duration of study treatment as well as the dose intensity and the relative dose intensity will be listed and summarized. Categories for relative dose intensity will be specified. The number and proportion of patients within each category will be presented.

10.6 Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD). A summary of concomitant medications by anatomical therapeutic chemical (ATC) and preferred term (PT) will be provided.

10.7 Efficacy Analysis

The efficacy endpoints include objective response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), progression-free survival (PFS), and overall survival (OS). The efficacy endpoints are defined as follows:

- ORR: The proportion of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR).
- DCR: The proportion of subjects with a BOR of CR, PR or stable disease (SD).
- DOR: Time from first evidence of CR or PR to disease progression or death from any cause, whichever occurs first.
- TTR: Time from start of study treatment until the first evidence of CR or PR.
- PFS: Time from start of study treatment until disease progression or death from any cause, whichever occurs first.
- OS: Time from start of study treatment until death due to any cause.

For Phase Ib part, the efficacy analysis will be based on FAS. The number of subjects with the BOR of CR, PR, SD, progressive disease (PD) will be summarized according to the assessment results of each visit. ORR and DCR of each group will be also calculated. A by-subject list of DOR, TTR, PFS, and OS will be provided.

For Phase II part, the efficacy will be analyzed based on FAS and PPS. FAS will be used for primary analysis, sensitivity analysis will be performed based on PPS. The number of subjects with the BOR of CR, PR, SD, PD will be summarized according to the assessment results of each visit. ORR and DCR will be calculated, the corresponding two-sided 90% confidence intervals (CI) will be estimated by the Clopper-Pearson method. When the sample size of analyzed group is ten or more, the Kaplan-Meier method will be used to provide median 90% Brookmeyer-Crowley CI for DOR, TTR, PFS, and OS.

10.8 Safety Analysis

All safety analysis will be based on SS except for DLTs which based on DDS.

Adverse events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of treatment-emergent adverse events (TEAEs), study treatment related adverse events, serious adverse events (SAEs), adverse events of special interest (AESIs), immune-related adverse events (irAEs), TEAEs leading to study treatment interruption and study treatment discontinuation will be summarized by the system organ class (SOC) and preferred term (PT). The list of AEs will be provided. DLTs will be listed and summarized for each dose level using DDS.

Laboratory tests

All laboratory parameters and change from baseline will be summarized by time point. Shift table by baseline and worst post-baseline will be provided.

Vital signs

Vital sign parameters and change from baseline will be summarized by time point. A by-subject listing of vital sign will be provided.

ECG

ECG parameters and change from baseline will be summarized by time point. A by-subject listing of ECG parameters will be provided.

10.9 Immunogenicity analysis

The number and percentage of subjects with positive anti-body antibody (ADA) will be summarized.

10.10 Pharmacokinetic Analysis

The drug plasma or serum concentration data will be summarized and plotted by time point for each group. PK parameters will be listed and summarized descriptively.

10.11 Pharmacodynamic Analysis

If necessary, the correlation between the PD parameters and efficacy may be explored.

10.12 Sample Size

Phase Ib

Subjects will be enrolled and treated in cohort of size 3-6. A minimum of 6 DLT-evaluable subjects should be included in the selected treatment regimen for Phase II. Up to 15 subjects will be enrolled and treated for Phase Ib. Additional subjects may be enrolled if more dose levels or alternative dosing regimens are to be explored.

Phase II

Ten subjects will be enrolled in each tumor type. Subjects who have received the phase II treatment regimen in the phase Ib part and meet the phase II part eligibility criteria will be counted. Depending on the clinical benefits of each tumor type, the sponsor will determine the enrollment of additional 10-20 subjects with the same tumor type, i.e., a tumor type can be expended to approximately a total of 20-30 subjects, tumor types with potential benefit will be expanded to maximal 60 patients at the discretion of the sponsor and leading investigators. If none of the ten shows response (i.e., complete response or partial response according to RECIST 1.1 or Lugano 2014 Criteria), the enrollment of subjects with the specific tumor type may be stopped.

10.13 Interim Analysis

No formal interim analysis is planned for this study.

11 SAFETY MONITORING

The sponsor team and the investigators will review drug safety data on an ongoing basis from the first visit for the first subject until the end of the study, and make decision of dose escalation for the phase Ib part.

If it is assessed that the safety of the subject cannot be ensured or that the limits of his or her tolerance have been reached, administration of this study will be hold immediately until the subject's risk-benefit ratio has changed and that continued study treatment is beneficial to the subject.

12 DATA COLLECTION AND MANAGEMENT

The sponsor is responsible for the clinical study data management of this study and Electronic Data Capture (EDC) will be used for data collection and management.

12.1 Data Collection

This study will use Electronic Data Capture (EDC) for data collection. The investigator or the designated staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). Site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

PK and PD samples drawn during the course of the study will be collected from the study sites and analyzed by a Sponsor contracted laboratory. Designated investigational site staff will enter the information required by the protocol into the appropriate eCRFs. The monitor will review the eCRFs for accuracy and completeness and instruct site personnel to make any required corrections or additions.

12.2 Data Management

Sponsor or designated CRO staff will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the

investigational site via the EDC system. Designated study site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHODD, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the MedDRA terminology.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data.

13 SOURCE DATA AND ORIGINAL FILE

In accordance with ICH E6, relevant regulations and the requirements of the study institution for the protection of subjects' personal information, each study center is required to keep records related to this study properly. As part of Genfleet's sponsoring or participating in the study, each study center shall allow Genfleet's authorized representatives and regulatory agencies to inspect (and, if permitted by law, copy) clinical records for quality review, audit, evaluation of safety, study progress, and data validity.

Source data is all the information necessary to reconstruct and evaluate a clinical study and is the original record of clinical findings, observations or other activities. Examples of these original documents and data records include, but are not limited to: hospital records, laboratory records, memoranda, subject diary cards, pharmacy dispensing records, recordings of consultation sessions, recorded data from automated instruments, photocopied or transcribed records verified as accurate and complete, microfilm, photographic negatives, microfilm or diskettes, x-rays, and documents and records of subjects maintained in participating pharmacies, laboratories, and medical and technical departments.

14 QUALITY ASSURANCE AND QUALITY CONTROL

To ensure the quality of the study, the clinical study plan will be discussed and developed by the sponsor and the investigator before the study officially starts. And to confirm that the relevant study staff participating in the study have undergone appropriate GCP training.

Each study center must manage study drugs in accordance with SOPs, including receipt, storage, dispensing, recycling, and destruction process.

According to the GCP guidelines, the necessary steps should be taken during the design and implementation phases of the study to ensure that the data collected are accurate, consistent, complete, and credible. All observed results and abnormal findings in clinical studies shall be verified and recorded in a timely manner to ensure the reliability of the data. The instruments, equipment, reagents, standards, etc. used for various tests in clinical study shall follow strict quality standards and ensure that they are in proper working condition.

The investigator enters the information required by the protocol into the CRF, and the supervisor verifies that it is completed completely and accurately and directs the study center staff to make any necessary revisions and additions.

Drug regulatory authorities, Ethics Committees, sponsors' monitors and/or auditors may conduct systematic inspections of clinical study-related activities and documents to evaluate whether the study is conducted in accordance with the study protocol, SOPs, and relevant regulatory requirements, and whether study data are recorded in a timely, truthful, accurate, and complete manner. The audit shall be performed by staff who are not directly involved in the clinical study.

15 ETHICAL CONSIDERATIONS

15.1 Ethical Compliance

This clinical study must follow the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, 2002), the current ICH-GCP, the Declaration of Helsinki, and applicable regulations. The study protocol, protocol revisions, “Informed Consent Form” and other relevant documents such as enrollment advertisements shall be provided to the Ethics Committee before the study. Prior approval must be obtained from the relevant regulatory authorities and the hospital ethics committee before this study can be initiated.

Neither party may unilaterally modify this study protocol without the consent of both the sponsor and the investigator. The modified protocol can only be implemented after approval by the Ethics Committee. If the investigator has to enter the protocol deviation process in order to eliminate obvious and immediate harm to the subject, the Ethics Committee and the sponsor

must be notified in writing immediately after the deviation process is implemented, along with an explanation and documentation of any protocol deviation made.

Any changes made to this study protocol during the clinical study shall be submitted to the Ethics Committee and, if necessary, other study documents should also be revised accordingly and submitted and/or approved in accordance with the requirements of the Ethics Committee. It is the responsibility of the investigator to submit regular interim reports in accordance with the relevant requirements of the Ethics Committee and to inform the Ethics Committee that the study has been completed after the end of the study.

15.2 Independent Ethics Committee

The protocol, "Informed Consent Form", enrollment materials and all patients materials will be submitted to the Ethics Committee for review and approval. Patients are enrolled only after the protocol and "Informed Consent Form" are approved. Any revision of the protocol must be reviewed and approved by the Ethics Committee before implementation. All revisions to the "Informed Consent Form" must also be approved by the Ethics Committee, and the Ethics Committee will decide whether patients who have signed the previous, older version of the informed consent form are required to sign the new version again.

15.3 Informed Consent

15.3.1 Informed Consent Form

Informed Consent Form described the research process in detail and fully explained to the subjects the risks of the study. Informed consent form must be obtained before conducting any study procedures.

15.3.2 Informed Consent Procedures

Informed consent process begins before a patient agrees to participate in a clinical study and continues throughout the course of the clinical study. The investigator or the authorized staff should inform the patient that "Informed Consent Form " has been approved by the EC/IRB and that it is the responsibility of the investigator to provide the patients with a complete and comprehensive description of the purpose of the project, how the study will be conducted, the effects of the drug, the risks and possible benefits of participation in the study, and that the patient should be promptly informed of any new information regarding information about the study drug. Patients should be informed that they can withdraw unconditionally at any time

during the experiment. Patients should be informed that the investigator and sponsor have the right to read, preserve, and statistically process the subject's trial data in accordance with legal requirements. Patients should have adequate time for consultation and consideration before signing informed consent. Subjects could only participate in the study after signing an “Informed Consent Form”. Patients may withdraw consent at any time during the entire course of the clinical study. If the patient cannot read the “Informed Consent Form”, an informed explanation needs to be completed in the presence of a neutral third-party witness and verbal consent obtained from the patient, and both the investigator and the witness completing the explanation need to sign the name and date on the “Informed Consent Form”. An original copy of the “Informed Consent Form” will be retained by the patients. Even if the enlisted patients decline to participate in this study, their rights will be fully protected and the quality of their medical care will not be affected in any way.

15.4 Confidentiality of Patients' Information

Procedures for the confidentiality of Patients' information are strictly enforced by the investigator, other staff in the study, the sponsor, and their agents. Confidential information covers patients' clinical information and biological samples. Therefore, study protocols, documents, data, and all other study information will be taken to preserve confidentiality. All relevant study information should not be disclosed to any third party without sponsor’s authorization.

Authorized representative of the sponsor, EC, and regulatory authorities may perform audits or inspections documents and records that is required to maintain by the investigator, which include, but are not limited to: medical records and subjects' IP records. The site should allow access to these records.

It is the responsibility of the investigator to maintain the subject's anonymity. Subjects may be identified on case report forms or other documents only by capital letters, numbers, and/or codes, not by the subject's name. The investigator must maintain Identification code Form that records the subject's code, name and home address. The investigator must prevent data being linked to the identity of the patient.

15.5 Future Use of Preserved Specimens

Not applicable.

16 PUBLICATION OF STUDY RESULTS

The investigator should keep information and data related to this study confidential and should not cite or publish relevant study results or information without the consent of the sponsor. If the investigator plans to publish any study-related data and information, the original, abstract or full text of all planned publications (posters, invited presentations or guest lectures) must be agreed to by the sponsor and provided to the sponsor at least 30 days prior to submission of the document for publication or other release.

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Appendix 1 Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

39. (E.A. Eisenhauer, P. Therasse, J. Bogaerts, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1),European Journal of Cancer,2009;228-247.)

1. Measurability of tumor at baseline

1.1 Definition

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

Measurable lesions

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter 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; see Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be P15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed (see Schwartz et al. in this Special Issue15). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable lesions

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal dis- ease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung,

abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurement

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. How- ever, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

- A lesion located at a site that has been radiated or otherwise treated regionally is generally treated as a non-measurable lesion unless the lesion shows definite progression. The study protocol shall describe in detail the conditions under which these lesions are measurable.

1.2 Specifications by methods of measurements

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.

Method of assessment

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical 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. See Appendix II for more details.

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. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in Appendix II.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed the same technique and measurements will be taken from one assessment to the next

(described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is ad- vised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published.16–18 In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.19

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

2. Tumor response evaluation

2.1 Evaluation of target lesions

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

<10 mm.

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

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

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

2.2 Special notes on the assessment of target lesions

Lymph nodes: 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. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each sub-sequent evaluation, even when very small (e.g.,2 mm). How- ever, 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 de- fault value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The

measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

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

2.3 Evaluation of non-target lesions

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

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

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

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

2.4 Special notes on assessment of progression of non- target disease

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

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or

more non-tar- get lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circum- stance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable dis- ease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.5 New Lesions

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

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

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

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

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

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

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

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

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

2.6 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-

up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.7 Special notes on response assessment

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

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in **Tables 1–3**.

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

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

must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

Table 1 – Time point response: patients with target (+/-non-target) disease

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

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

Table 2 – Time point response: patients with non-target disease only

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

CR = complete response, PD = progressive disease, and NE = inevaluable.

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

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

Overall response	Overall response	BEST overall response

First time point	Subsequent time point	
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

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

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

2.8 Confirmatory measurement/duration of response

Confirmation

In non-randomized trials where response is the primary end- point, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. However, in all other circumstances, i.e., in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Duration of overall response

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

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

Duration of stable disease

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

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard

practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

2.9 PFS/TTP

PFS or TTP is the main endpoint in many studies of advanced cancer. If the protocol requires all patients to have measurable lesions, the evaluation of progression is relatively simple. More and more studies allow patients with measurable lesions and non- measurable lesions to enter the study. In this situation, the clinical findings of disease progression in patients without measurable lesions must be described in detail. Because the progression date often has definite deviation, the observation time arrangement of each study group shall be the same.

40.

Appendix 2 ECOG Performance Status

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

Appendix 3 Operating Characteristics of the BOIN Design

Table A-1 shows the operating characteristics of the trial design based on 10,000 simulations of the trial with the following trial and design specifications using Shinny app "BOIN" available at http://www.trialdesign.org. The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more patients to the dose level with the DLT rate closest to the target toxicity rate of 0.3.

Parameters	Value
Number of doses	4
Starting dose	1
Max sample size	15
Cohort size	3
Stop trial if # patients assigned to single dose reaches	9
Use accelerated titration	False
Target toxicity probability	0.3
Use the default alternatives to minimize decision errors	True
Alternative (unacceptable high toxicity) for optimization	Default
Alternative (unacceptable low toxicity) for optimization	Default
Eliminate dose threshold (pE)	0.95
Number of repetitions per scenario	10000
Random number generator seed	2021

Table A-1. Operating characteristics of the BOIN design

	Dose 1	Dose 2	Dose 3	Dose 4	Number of Patients	% Early discontinuation
Scenario 1						
True DLT Rate	0.3	0.47	0.55	0.64	11.8	12.72
Selection%	65.94	17.13	3.92	0.29		
% Pts Treated	65.8	29.5	4.5	0.3		
Scenario 2						
True DLT Rate	0.11	0.3	0.45	0.67	14.4	0.38
Selection%	23.77	49.54	24.37	1.94		
% Pts Treated	38.3	42.7	17	2		
Scenario 3						
True DLT Rate	0.02	0.13	0.3	0.47	14.9	0
Selection%	1.03	25.87	52.74	20.36		
% Pts Treated	23.1	34.8	32	10.1		
Scenario 4						
True DLT Rate	0.05	0.1	0.15	0.3	14.9	
Selection%	1.22	8.67	38.64	51.43		
% Pts Treated	24.3	28.3	28	19.4		

Note: "% Early discontinuation" refers to early stopping due to excessive DLT.

Appendix 4 Lugano Response Criteria 2014 for Non-Hodgkin Lymphoma

PET should be performed with contrast enhanced diagnostic CT and can be performed simultaneously or as separate procedures.

Response	Site	PET-CT (Metabolic response)	CT (Radiologic response)[d]
Complete response	Lymph nodes and extralymphatic sites	Score 1, 2, 3[a] with or without a residual mass on 5-point scale (5-PS)[b,c]	All of the following: Target nodes/nodal masses must regress to ≤1.5 cm in longest transverse diameter of a lesion (LDi) No extralymphatic sites of disease
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate and flow cytometry IHC negative
Partial response	Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline. No new progressive lesions. At interim these findings suggest responding disease. At end of treatment these findings may indicate residual disease.	All of the following: ≥50% decrease in SPD of up to 6 target measureable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value. When no longer visible, 0x0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New lesions	None	None

Response	Site	PET-CT (Metabolic response)	CT (Radiologic response)[d]
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the content of a nodal response, consider further evaluation with biopsy, or an interval scan.	Not applicable
No response or stable disease	Target nodes/nodal masses, extranodal lesions	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment. No new or progressive lesions.	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Non-measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease	Individual target nodes/nodal masses, extranodal lesions	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment [e]	Requires at least one of the following PPD progression: An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly

Response	Site	PET-CT (Metabolic response)	CT (Radiologic response)[d]
	Non-measured lesion	None	New or clear progression of preexisting nonmeasured lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered [e]	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Footnotes
[a]Score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider score 3 as an inadequate response (to avoid under-treatment).
[b]See PET Five-Point Scale (5-PS).
[c]It is recognized that in Waldeyer's ring or extranodal sites with high physiological uptake or with activation within spleen or marrow, e.g. with chemotherapy or myeloid colony stimulating factors, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake.
[d]FDG-avid lymphomas should have response assessed by PET-CT. Diseases that can typically be followed with CT alone include CLL/SLL and marginal zone lymphomas.
[e]False-positive PET scans may be observed related to infectious or inflammatory conditions. Biopsy of affected sites remains the gold standard for confirming new or persistent disease at end of therapy.

PET 5-Point Scale (5-PS)

1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately > liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

- SPD – Sum of the product of the perpendicular diameters for multiple lesions
- LDi – Longest transverse diameter of a lesion
- SDi – Shortest axis perpendicular to the LDi
- PPD – Cross product of the LDi and perpendicular diameter

Measured dominant lesions – Up to 6 of the largest dominant nodes, nodal masses and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body, and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs, e.g., liver, spleen, kidneys, lungs, etc, gastrointestinal involvement, cutaneous lesions of those noted on palpation.

Non-measured lesions – Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected

as dominant, measurable or which do not meet the requirements for measurability, but are still considered abnormal. As well as truly assessable disease which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses and other lesions that cannot be confirmed and followed by imaging.