A single-arm, phase Ib/II study of pamiparib combined with surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARP inhibitors

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Protocol Synopsis

Protocol title	A single-arm, phase Ib/II study of pamiparib combined with surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARP inhibitors
Study objectives	**1) Phase Ib (safety run-in period)** **Primary objective:** • To determine the recommended dose (RP2D) of surufatinib in combination with pamiparib. **2) Phase II portion** **Primary objective:** • To evaluate the efficacy of the combination of pamiparib and surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARP inhibitor (PARPi). **Secondary objectives:** • To evaluate the safety and tolerability of pamiparib in combination with surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARPi. **Exploratory objectives:** • To explore biomarker asssociated with the efficacy of pamiparib in combination with surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARPi.
Study Endpoints	**1) Phase Ib (safety run-in period)** **Primary endpoint:** • To identify the RP2D of pamiparib combined with surufatinib **2) Phase II portion** **Primary endpoint:** • The 6-month progression-free survival (PFS) rate assessed by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) criteria. **Secondary endpoints:** • Objective response rate (ORR) assessed by RECIST 1.1 • Disease control rate (DCR) assessed by RECIST 1.1. • Overall survival (OS) • Safety and tolerability evaluation: Incidence and severity of

	adverse events (AEs) and serious adverse events (SAEs) during treatment as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. **Exploratory Study Endpoints:** • To assess the correlation between genetic alterations in tumor samples and efficacy by next-generation sequencing (NGS). • To assess the relationship between ctDNA levels and efficacy.
Study Design	• **Phase Ib (safety run-in period)** In the phase Ib safety run-in period, a 3+3 design will be employed to determine the RP2D of surufatinb in combination with pamiparib. Surufatinib will be administered in a dose de-escalation scheme, starting at 250 mg orally once daily and, if necessary, reduced to 200 mg once daily. Pamiparib will be given at a standard dose of 40 mg orally twice daily. The dose limiting toxicity (DLT) observation period will span the first 21 days of treatment. Once the RP2D of surufatinib is determined, this dose will be used in the subsequent phase II trial. If the initial dose of 250 mg is not tolerated, a lower dose level of surufatinib 200 mg once daily will be assessed. The RP2D-finding methods for surufatinib are outline as follows: • An initial cohort of 3 patients will receive surufatinib 250 mg once daily with pamiparib. If no DLT occur, this dose level is considered safe, and be utilized in the subsequent phase II trial. • If 1 of these 3 patients experience DLT, 3 additional patients will be entered this dose level. If no DLT is observed in this second group of 3, surufatinib 250 mg once daily is considered as RP2D. If any of the 3 newly enrolled patients experience a DLT, this dose of surufatinib will be considered the MTD, a lower dose of surufatinib 200 mg once daily will be assessed. • If 2 or more of the first 3 patients experience DLT, a lower dose of surufatinib 200 mg once daily will be assessed. • If the initial dose of 250 mg is not tolerated, the dose level of surufatinib 200 mg once daily will be assessed according to the same rule as mentioned above. If 2 or more patients among the cohort of 3 to 6 patients experience DLTs, the study will be suspended. A Safety Monitoring Committee (SMC) will assess the safety profile and determine whether a further dose reduction

	is necessary. • **Phase II portion** This study will evaluate the efficacy and safety of the combination of pamiparib and surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARPi. The phase II portion consist of three periods: screening, treatment, and follow-up. The screening process will be conducted within 28 days prior to the first dose. During the treatment period, patients will receive pamiparib 40 mg twice daily, along with surufatinib at the RP2D. A cycle was defined as three weeks of treatment. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or study termination, whichever occurs first. Tumor response will be assessed according to RECIST 1.1 every 6 weeks (± 7 days) until disease progression. After completing the treatment period, patients will enter the follow-up period.
Criteria	1. Be willing and able to provide written informed consent for the trial; 2. Histologically confirmed epithelial ovarian cancer; 3. Has platinum-resistant disease, defined as progression within 6 months from completion of most recent platinum-containing therapy. Subject may have been treated with additional regimen(s) subsequent to determination of platinum resistance; 4. Has progressed on or after prior PARP inhibitor therapy; 5. Aged 18-75 years; 6. Has measurable lesions per RECIST 1.1; 7. Eastern Cooperative Group (ECOG) score 0-1; 8. Life expectancy ≥ 3 months; 9. Has adequate organ function as defined by the following criteria: absolute neutrophil count ≥ 1.5×10^9 cells, platelets ≥ 100×10^9 cells, hemoglobin ≥ 90 g/L, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 × upper limit of normal (UNL), total bilirubin < 1.5 × UNL, serum creatinine < 1.5 × UNL; 10. Females of childbearing potential should have a negative serum or urine pregnancy test prior to receiving the first dose

	of study treatment; and should be willing to use one acceptable contraception (i.e., oral contraceptives, condoms, intrauterine devices [IUDs]) throughout the period of taking study treatment and for at least 6 months after the last dose of study drug(s).
Exclusion Criteria	A patient who meets any of the following criteria will be excluded from the study: 1. Histological diagnosis of mucinous adenocarcinoma; 2. Has received prior therapy with small molecule antiangiogenic receptor tyrosine kinase inhibitors (TKIs) within 6 months; 3. Known or suspected allergy to any of study drugs; 4. Has clinically significant cardiovascular disease within 6 months from first dose of study intervention, including New York heart association [NYHA] class > 2, unstable angina, myocardial infarction, cardiac arrhythmia associated with hemodynamic instability (including QTc interval ≥ 450 ms in men, ≥ 470 ms in female); 5. Has active ulcers, gastrointestinal perforation or obstruction; 6. Active bleeding or pathologic condition that carries a high risk of bleeding; 7. Inadequately controlled hypertension (systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 90 mmHg) with or without treatment; 8. Major surgery within 28 days of starting study treatment; 9. Urine routine showed urine protein ≥ 2 + and 24-hour total urine protein > 1.0 g; 10. Uncontrolled pericardial or pleural or peritoneal effusions; 11. Has a diagnosed and/or treated additional malignancy within the last 5 years. Exceptions include in situ cervical cancer, non-melanoma skin cancer, or superficial bladder tumors that has undergone potentially curative therapy; 12. Known Human Immunodeficiency Virus (HIV) infection; 13. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis; 14. Any medical or other condition that in the opinion of the investigator(s) would preclude the participant's participation in the study.

Treatment Discontinuation Criteria	A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons: 1. The subject requests to discontinue treatment; 2. Radiographic disease progression; 3. Completed 2 years of treatment; 4. Unacceptable toxicity; 5. Noncompliance with trial treatment or procedure requirements; 6. The subject is lost to follow-up; 7. Investigator's decision to discontinue treatment for the subject.
Treatment Regimen	**Study Drug, Dose, and Administration:** 1) Phase Ib (safety run-in period) • Pamiparil 40 mg, orally twice daily; • The starting dose of surufatinib is 250 mg once daily. If the initial dose of 250 mg is not tolerated, a lower dose level of surufatinib 200 mg once daily will be assessed. The DLT observation period will span the first 21 days of treatment. The SMC will assess the safety data from all subjects who entered the safety run-in period and completed 21-day DLT observation period, and confirmed the RP2D of surufatinib. 2) The phase II part • Pamiparib will be given at a standard dose of 40 mg orally twice daily. • Surufatinib is administered at RP2D. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or study termination, whichever occurs first.
Definition of dose limiting toxicity (DLT)	A DLT will be classified according to NCI CTCAE v5.0 and is defined as any of the following adverse events unless the event can clearly be determined to be unrelated to drugs occurring in the first cycle of treatment: 1. Hematologic toxicity: 1) Grade 4 neutropenia; 2) Grade 3 neutropenia accompanied by fever (neutrophil count $< 1.0 \times 10^9$/L; body temperature ≥ 38.5 ° C); 3) Grade 3 thrombocytopenia with a bleeding tendency or lasting more than 7 days; 2. Non-hematological toxicity: 1) ≥ Grade 3 non-hematologic toxicity lasting for more than 7

	days (with satisfactory supportive treatment), except for the following conditions: allergic reactions, only laboratory abnormalities that resolve within 7 days, symptoms caused by tumor progression; 2) Grade 4 hypertension cannot be controlled with one antihypertensive drug within 14 days of treatment; 3) Grade 3 proteinuria; 4) Recurrent Grade 2 non-hematologic toxicity requiring ≥ 2 dose interruptions or reductions. 3. Any other Grade ≥ 3 toxicity, whether hematologic or non-hematologic, that is assessed as related to surufatinib will be considered as DLT, as determined by the principal investigator.
Sample Size	i) Phase Ib (safety run-in period) A 3 + 3 dose de-escalation design will be employed. A total of 3 to 12 subjects are expected. ii) Phase 2 portion Previous studies reported a 6-month PFS rate of 25% for platinum-resistant ovarian cancer patients treated with single-agent non-platinum chemotherapy or targeted therapy. We hypothesized that the combination of surufatinib and pamiparib would achieve a 6-month PFS rate of 45%. With 80% power and a one-sided significance level of 0.05, 26 patients were required, including those treated at RP2D in phase Ib. Accounting for a 15% dropout rate, approximately 30 patients were planned for enrollment in phase II.
Statistical Methods	All statistical analyses were performed using SAS, version 9.4 or above. **Phase Ib (safety run-in period):** Descriptive statistical analysis will be performed to summarize the AEs occurred and grade the AEs according to CTCAE v5.0 based on the study results. The number of DLTs will be listed. **Phase II portion:** 1. Primary endpoint • Six-month PFS rate: defined as the percentage of patients alive without documented progression 6 months after treatment initiation. The percentage and its 95% confidence interval (CI) will be analyzed using the Kaplan-Meier method and survival curves will be plotted.

2. Secondary endpoints

• ORR: The proportion of subjects with a complete response (CR) or partial response (PR) according to RECIST 1.1 in the analysis population. ORR will be presented with a 95% CI.

• DCR: The proportion of subjects with best overall response of CR, PR, or stable disease (SD) according to RECIST 1.1 in the analysis population. DCR will be reported with a corresponding 95% CI.

• OS: defined as the time from the date of treatment start date to the date of death. For subjects who are still alive at the time of follow-up, OS is calculated as censored.

• Safety analyses

Safety analyses will be conducted using data from the safety population. Descriptive statistical analysis will be used to tabulate the number of patients who experienced at least one treatment-related adverse event, severe adverse event (≥ Grade 3), serious adverse event, or withdrawal due to an adverse event during this trial.

3. Exploratory endpoints

• Biomarker measurements will be presented based on available data, with the correlation between these measurement and clinical outcomes (e.g., antitumor efficacy) depicted graphically.

Statistical Analysis Set:

• Safety analysis set: all subjects who have received at least one dose of the study drug.

• DLT analysis set: all subjects who either completed Cycle 1 of treatment in phase 1b (safety run-in period) or discontinued treatment due to a DLT in Cycle 1. This analysis set will be used to determine the RP2D.

• Full analysis set (FAS): all subjects who received at least one dose of the study drug.

• Efficacy evaluable set (EES): all subjects who have received at least one dose of the study drug and have at least one post-baseline tumor assessment. EES included eligible subjects who receive the RP2D of surufatinib in both phase Ib and phase II portion of the study.

Version No.	3.0

Trial Flow Chart

Procedure	Screening Period		Treatment Period (21-day cycles)				End of Treatment	Follow-up Period	
	- 28 to -8 days	- 7 to -1 days	Cycle 1			Cycle 2 and subsequent cycles	At the time of discontinuation	30 days post discontinuation	Survival Follow-up
			Day 1	Phase Ib only		Day 1			
				Day 8	Day 15				
Window (days)				± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures									
Written informed consent [1]	X								
Inclusion/exclusion criteria	X								
Medical history and demographics	X								
Concomitant Medications	X								
Laboratory Assessments									
Hematology		X		X	X	X	X	X	
Serum chemistries		X		X	X	X	X	X	
Urinalysis [2]		X		X	X	X	X	X	
Stool routine		X				X			
Coagulation function test [3]		X				X			
CA125		X				X			
Pregnancy testing [4]		X							
Serology testing (HBV, HCV, syphilis, HIV)	X								
Clinical assessment/examination									
Height [5], Weight		X	X	X	X	X			
Vital signs [6]		X	X	X	X	X	X	X	
ECOG score		X	X	X	X	X	X	X	

Procedure	**Screening Period**		**Treatment Period (21-day cycles)**				**End of Treatment**	**Follow-up Period**	
	- 28 to -8 days	- 7 to -1 days	Cycle 1			Cycle 2 and subsequent cycles	At the time of discontinuation	30 days post discontinuation	Survival Follow-up
			Day 1	Phase Ib only		Day 1			
				Day 8	Day 15				
Window (days)				± 3	± 3	± 3	± 7	± 7	± 7
Physical Examination [7]		X	X	X	X	X	X	X	
12-lead electrocardiogram		X				X			
Assessment of adverse events	From signing the informed consent form to 30 days after dosing								
Treatment Administration									
Pamiparib (orally twice daily)			X	X	X	X			
Surufatinib (orally once daily)			X	X	X	X			
DLT Assessment									
DLT Assessment			The DLT observation period will span the first 21 days of treatment.						
Efficacy Assessments									
Tumor imaging assessment [8]	X		Every 6 weeks (± 7 days) until disease progression, withdrawal of consent, or the end of the study.						
Follow-up after end of treatment									
Survival status [9]									Every 3 months
Biomarker exploration									
Blood sample [10]			X			Cycle 3, day 1 Cycle 7, day 1	X		
Tumor tissue [11]	X								

1. Informed consent should be obtained before initiation of the study.
2. The examination of 24-hour urinary protein quantification should be performed if proteinuria ≥ 2+.
3. Coagulation tests, including prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ration (INR), and fibrinogen (Fib) should be conducted every two cycles.
4. Females of childbearing potential should have a negative serum or urine pregnancy test prior to receiving the first dose of study treatment. For females who are not of childbearing potential, testing may be omitted at the discretion of the investigator.
5. Height will be measured at screening only.
6. Vital signs include temperature, pulse rate, respiratory rate, and blood pressure.
7. Physical examination includes examination of major body systems: head and face, dermatologic system, lymph nodes, eyes, ears, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal, neurological system, and mental status. While a complete physical examination is mandatory throughout the trial, only abnormalities need to be recorded in the CRF after the screening period.
8. Subjects will receive tumor imaging assessment every 6 weeks (± 7 days) after treatment until disease progression, withdrawal of informed consent, or the end of study.
9. Survival Follow-up: all patients will be contacted by phone every 3 months (± 7 days) for overall survival follow-up, until patient's death or loss to follow-up or withdrawal of consent.
10. Subjects are required to provide 10 ml specimens for the detection of tumor biological markers before treatment, C3D1, C7D1 and at the time of disease progression.
11. Subjects may choose to provide 10 slides of archived or fresh tumor tissue specimens for tumor biomarker detection by sequencing.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviations and Specialist Terms	Notes
ATP	Adenosine triphosphate
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
AE	Adverse events
AUC	Area under the curve
CI	Confidence interval
CA125	Cancer antigen-125
Cmax	Maximum plasma concentration
CR	Complete response
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CSF-1R	Colony-stimulating factor-1 receptor
DNA	Deoxyribonucleic acid
DCR	Disease control rate
DLT	Dose limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGFR-1	Fibroblast growth factor receptor-1
GCP	Good Clinical Practice
HR	Hazard ratio

HRD	Homologous recombination deficiency
ICH	International Conference on Harmonisation
IC50	Half-maximal inhibitory concentration
IRC	Independent review committee
KM	Kaplan Meier curves
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NET	Neuroendocrine tumor
NGS	Next-generation sequencing
NYHA	New York Core Association
ORR	Objective response rate
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PD	Progressive disease
PFS	Progression-free survival
pNETs	pancreatic neuroendocrine tumors
PR	Partial response
PROC	Platinum-resistent ovarian cancer
PSOC	Platinum-sensitive ovarian cancer
QT	QT interval (beginning of electrocardiogram Q wave to end of T wave (non-U wave))
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase II dose
SAE	Serious adverse event
SD	Stable disease
SMC	Safety Monitoring Committee
TAMs	Tumor-associated macrophages
TKI	Tyrosine kinase inhibitor
UNL	Upper limit of normal
VEGF	Vascular endothelial growth factor

CONTENTS

1. Background and Rationale

1.1 Overview of Epithelial Ovarian Cancer

Ovarian cancer is one of the most common and deadly gynecological malignancies, the highest mortality rate among cancers of the female reproductive system. According to the latest data from Globocan, there were 55,000 cases and 3.75 million deaths from ovarian cancer in China in 2020 [1]. In Europe, approximately 28,000 new cases are diagnosed annually, with around 17,000 deaths. Over 70% of patients are diagnosed at an advanced stage. For advanced ovarian cancer, standard treatment consists of cytoreductive surgery and postoperative platinum-based first-line chemotherapy. Despite improvements in surgical techniques, the clinical use of paclitaxel, platinum, and other second-line chemotherapeutic agents over the past two decades, the prognosis for advanced ovarian cancer remains poor, with a 5-year survival rate of less than 30% [2]. Even after initial treatment, the majority of patients experience recurrence, highlighting the ongoing challenge in managing this disease and the need for novel therapeutic strategies to improve survival outcomes.

Patients with recurrent ovarian cancer are classified based on their response to platinum-based chemotherapy. Patients who experience a recurrence more than 6 months after completing platinum-based chemotherapy are considered to have platinum-sensitive recurrence, while those with recurrence within 6 months are categorized as having platinum-resistant recurrence. A subset of patients may exhibit disease progression during the first-line platinum-based chemotherapy, referred to as primary resistance, which is associated with the worst prognosis.

Recurrent ovarian cancer, particularly in the platinum-resistant setting, presents a significant challenge for gynecologic oncologists. Despite the use of various chemotherapeutic agents, such as doxorubicin liposome, gemcitabine, and topotecan, the response rate for platinum-resistant ovarian cancer remain low, ranging from 10%-30% [3]. Therefore, there is an urgent need to find novel therapies to treat patients in this setting.

1.2 PARPi in Recurrent Ovarian Cancer

1.2.1 PARPi in Recurrent Ovarian Cancer with BRCA Mutations

PARP inhibitors PARPi) have shown significant efficacy in treating recurrent ovarian cancer with BRCA mutations. Olaparib was the first PARP inhibitor approved by the EMA and FDA as a monotherapy for BRCA1/2 mutant ovarian cancer. A phase II trial of olaparib (Study42) achieved an objective response rate (ORR) of 34% in the treatment of recurrent ovarian cancer with BRCA mutations, with a duration of response (DOR) of 7.9 months [4]. Based on this data, the FDA approved olaparib for the treatment of patients with BRCA1/2-mutated recurrent ovarian cancer who had failed three or more prior lines of chemotherapy in 2014. The Phase III SOLO-3 trial further confirmed the effectiveness of olaparib, demonstrating its superiority over chemotherapy in patients with BRCA-mutated, platinum-sensitive recurrent ovarian cancer who had failed two or more chemotherapy lines [5].

Similarly, the QUADRA study of niraparib, another PARP inhibitor, also demonstrated efficacy in BRCA1/2 mutant recurrent ovarian cancer [6]. This phase II clinical trial included 463 patients with ovarian cancer, of whom 63 patients had BRCA mutations. For these patients, the ORR with niraparib monotherapy was 29%, with slightly higher responses in platinum-sensitive patients (39%) compared to platinum-resistant patients (29%).

These findings solidify the role of PARP inhibitors as a critical therapeutic option for patients with BRCA-mutated recurrent ovarian cancer, especially in those with platinum-sensitive disease. However, the effectiveness in platinum-resistant cases remains a key area for further exploration.

1.2.2 PARPi in Recurrent Ovarian Cancer with BRCA Wild-type

The efficacy of PARP inhibitors in recurrent ovarian cancer patients without BRCA mutations has been explored in several studies. Phase II CLIO trial (NCT02822157), compared olaparib to investigator's choice of chemotherapy in two cohorts: platinum-

sensitive recurrent ovarian cancer patients without BRCA mutation and platinum-resistant recurrent ovarian cancer patients with or without BRCA mutation [7]. The results showed that for platinum-sensitive recurrent ovarian cancer patients without BRCA mutations, olaparib demonstrated similar PFS and OS compared to standard chemotherapy, proving no-inferiority. In patients with platinum-resistant disease without BRCA mutations, olaparib showed a higher ORR compared to chemotherapy (13% vs. 6%). Additionally, the QUADRA study [6], which included 230 patients with HRD-negative tumors, showed that niraparib monotherapy had a low ORR of 3%, with a 4% ORR in platinum-sensitive patients and 3% in platinum-resistant patients. These studies suggest that while PARP inhibitors may not offer superior outcomes compared to chemotherapy in BRCA wild-type patients, they may still provide a modest benefit in platinum-resistant cases, especially in specific subgroups. However, the ORRs are generally lower than in BRCA-mutated ovarian cancer, highlighting the need for alternative therapies or combination strategies in this patient population.

1.3 PARPi Combined with Anti-angiogenic Therapy for Recurrent Ovarian Cancer

Preclinical studies have shown that anti-angiogenic agents, such as VEGF/VEGFR inhibitors, can induce a hypoxic tumor microenvironment, which reduces the expression of homologous recombination-related proteins BRCA1, BRCA2, RAD51, thus creating a HRD phenotype. This, in turn, can enhance the efficacy of PARP inhibitors. Additionally, PARP inhibitors have anti-angiogenic effects, with PARP-1 knockout mice exhibiting reduced angiogenesis compared to wild-type, suggesting a potential synergistic effect in this combination [8].

Several combination studies of PARP inhibitors and anti-angiogenic angents have demonstrated promising results. In Study 4, the combination of olaparib with the VEGFR inhibitor cediranib showed superior efficacy compared to olaparib alone in platinum-sensitive recurrent ovarian cancer [9]. The median PFS was 16.5 months for the combination therapy versus 8.2 months for Olaparib alone (HR: 0.5). The combination of olaparib and cediranib notably prolonged PFS in patients with BRCA wild-type or unknown status, from 5.7 months to 23.7 months (HR: 0.31). The

BAROCCO study further confirmed that for platinum-resistant recurrent ovarian cancer, olaparib combined with cediranib had better efficacy than paclitaxel weekly, with a PFS of 5.7 months versus 3.1 months (HR: 0.76). The PFS for BRCA non-mutated or unknown patients was prolonged from 2.1 months to 5.8 months (HR: 0.63) [10]. In the AVANOVA2 study, the combination of niraparib and bevacizumab demonstrated superior efficacy compared to niraparib alone for platinum-sensitive recurrent ovarian cancer, with a PFS of 11.9 months versus 5.5 months (HR: 0.35). The addition of bevacizumab mainly benefited BRCA wild-type patients, extending PFS from 4.2 months to 11.3 months (HR: 0.32). These studies indicate that combining PARP inhibitors with anti-angiogenic drugs holds promise for improving treatment outcomes [11].

1.4 Rationale for this Study

1.4.1 Efficacy of Pamiparib in Platinum-Resistant Ovarian Cancer

Pamiparib is a potent and selective inhibitor of PARP1 and PARP2, distinguished from other PARP inhibitors by its strong PARP trapping activity and significant ability to penetrate the blood-brain barrier.

• Chemical name: (R)-2-fluoro-10a-methyl-5,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacycloheptatrieno[def]cyclopentadieno[a]fluorene-4(7H)-one sesquihydrate.

• Molecular formula: C16H15FN4O·H2O

• Molecular weight: 325.34

1.4.1.1 Summary of Preclinical Studies of Pamiparib

Pamiparib has shown potent inhibition of the enzymatic activities of PARP1 and PARP2, with IC50 of 1.3 nM and 0.92 nM, respectively. In cell-based assays, pamiparib effectively inhibited intracellular PARP activity in HeLa cells following hydrogen peroxide treatment, with an IC50 of 0.24 nM. This compares favorably to other PARP inhibitors, such as veliparib (IC50 = 2.66 nM) and olaparib (IC50 = 0.47 nM), respectively, with pamiparib demonstrating stronger antitumor activity.

In preclinical studies, pamiparib exhibited excellent in vitro activity against tumor cell

lines deficient in the homologous recombination (HR) repair pathway. In vivo, pamiparib demonstrated robust antitumor effects in a BRCA1-mutated MDA-MB-436 breast cancer xenograft mouse model, showing tumor suppression 16 times greater than Olaparib [12-13]. These findings underscore pamiparib's potential as a promising therapeutic candidate for tumors with HR deficiencies, including in platinum-resistant ovarian cancer.

1.4.1.2 Phase I Study Results of Pamiparib

• Kinetics of BGB-290-AU-002

In the first-in-human Phase 1a study conducted in Australia, pamiparib exhibited rapid absorption and elimination after oral administration. Both maximum plasma concentration (Cmax) and area under the plasma concentration-time curve showed a dose-proportional increase from 2.5 mg to 120 mg BID, both after a single dose and at steady state. The elimination half-life was approximately 13 hours, with a range from 5.5 to 34 hours. Preliminary data from 6 patients indicated that food intake slowed the absorption rate, causing a delay in time to peak concentration (Tmax) and a reduction in Cmax, though it did not significantly affect the extent of absorption overall. The mean ratios for Cmax and AUC0-last were 0.63 (range: 0.49 to 0.85) and 0.85 (range: 0.71 to 0.95), respectively, when administered with food compared to the fasted state. ORRs were observed starting at 10 mg of pamiparib BID, maintaining up to 120 mg BID, suggesting that target inhibition occurs at doses ≤60 mg BID. Therefore, the effect of food on Cmax and AUC is not considered clinically meaningful, allowing pamiparib to be administered regardless of food intake.

• Kinetics of BGB-290-102 in China

In this Phase 1a study, pharmacokinetic (PK) data were collected from 15 enrolled patients, with samples obtained on cycle 1, day 1 and cycle 1, day 10. On cycle 1, day 1, samples were collected 1 hour prior to dosing and at 0.5, 1, 2, 4, 6, 9, 12, 24, and 48 hours post-dose. On cycle 1, day 10, samples were collected 1 hour before dosing and at 0.5, 1, 2, 4, 6, 9, and 12 hours after dosing. Preliminary PK results showed that

pamiparib plasma drug exposure increased in a nearly dose-proportional manner, with a plasma half-life of approximately 12 hours. In the 20 mg of pamiparib BID cohort, steady-state plasma Cmax and AUC 0-9 were 1450 ng/mL and 9361 ng/mL·h, respectively. In the 40 mg of pamiparib BID cohort, Cmax and AUC 0-9 were 5340 ng/mL and 33545 ng/mL·h, respectively, and in the 60 mg BID cohort, they were 6048 ng/mL and 39657 ng/mL·h, respectively. The steady-state Cmax and AUC 0-9 of pamiparib in the BGB-290-102 study (China) were approximately 35% higher compared to the BGB-290-AU-002 study (Australia). This apparent difference in plasma exposure may be attributed to the difference in patient weight, as the patients in BGB-290-102 (China) weighed 61 kg, while those in BGB-290-AU-002 (Australia) weighed 71.5 kg.

1.4.1.3 Phase II Clinical Study Results of Pamiparib

Study BGB-290-102 was a single-arm, open-label, multicenter clinical trial to evaluate the efficacy and safety of pamiparib in patients with advanced high-grade non-mucinous epithelial ovarian cancer, including fallopian tube cancer or primary peritoneal cancer, with deleterious or suspected deleterious gBRCA mutations who had received two or more prior lines of chemotherapy [14]. A total of 113 ovarian cancer patients with gBRCA mutations were enrolled, comprising 90 with platinum-sensitive ovarian cancer (PSOC) and 23 with platinum-resistant ovarian cancer (PROC). All patients received pamiparib 60 mg twice daily until disease progression, unacceptable toxicity, withdrawal of consent, or treatment discontinuation at the discretion of the investigator. The primary efficacy endpoint was the ORR assessed by an independent review committee (IRC) using RECIST 1.1 criteria. Secondary efficacy endpoints included investigator-assessed ORR, DOR, PFS, OS, and response rate based on cancer antigen 125 (CA-125) criteria.

In total, 113 patients who received at least one dose of pamiparib were included in the safety analysis set. The median age were 54 years, with 77.0% diagnosed with stage III/IV disease at initial diagnosis. Among patients with PSOC, 42.2% had received ≥3

prior lines of chemotherapy. For patients with PROC, 43.4% had received ≥4 prior lines of chemotherapy. Median follow-up times were 17.0 months in the PSOC group and 11.6 months in the PROC group. Efficacy results based on IRC assessment for PSOC and PROC patients in the efficacy evaluable analysis set are summarized in the table below.

Table 1. Efficacy in Study BGB-290-102 (Efficacy Evaluable Analysis Set)

PSOC	**IRC Assessment, N = 82**
CR, n (%)	**8 (9.8%)**
PR, n (%)	48 (58.5%)
ORR (CR + PR), n (%)	56 (68.3%) (95% CI: 57.1-78.1)
DCR (CR + PR + SD), n (%)	78 (95.1%) (95% CI: 88.0-98.7)
Median DOR (months)	13.8 (95% CI: 10.97-20.73)
PROC	**IRC Assessment, N = 19**
CR, n (%)	0 (0.0%)
PR, n (%)	6 (31.6%)
ORR (CR + PR), n (%)	6 (31.6%) (95% CI: 12.6-56.6)
DCR (CR + PR + SD), n (%)	18 (94.7%) (95% CI: 74.0-99.9)
Median DOR (months)	11.1 (95% CI: 4.21-16.59)

In 19 evaluable patients with PROC, pamiparib demonstrated an ORR of 31.6%. The DCR rate was 94.7%, indicating promising antitumor activity. Among 90 patients with PSOC, the median PFS assessed by IRC was 15.2 months (95% CI: 10.35-20.63), and median OS was not yet reached. In the 23 patients with PROC, the median PFS was 6.2 months (95% CI: 4.11-17.91), and median OS was 13.6 months (95% CI: 7.13-19.75).

1.4.2 Introduction of Surufatinib

Surufatinib is a small molecule kinase inhibitor that primarily targets vascular endothelial growth factor receptor-1/2/(VEGFR-1/2/3), fibroblast growth factor receptor-1 (FGFR-1) and colony-stimulating factor-1 receptor (CSF-1R). It is a patented product exclusively developed by Hutchison Medi Pharma (Shanghai) Co., Ltd [15]. The chemical name is N-(2-(dimethylamino)ethyl)-1-(3-(4-(2methyl-5-

hydroxy-1H-indole)pyrimidin-2-amino)phenyl)methanesulfonamide, with a molecular formula of $C_{24}H_{28}N_6O_3S$ and a molecular weight of 480.58.

1.4.2.1 Phase I/Ib/II Clinical Study Results of Surufatinib

In the phase I dose-escalation clinical study, 18 efficacy-evaluable patients with neuroendocrine tumors (NETs) achieved a PR rate of 44.4%, including 3 of 7 efficacy-evaluable patients with pancreatic neuroendocrine tumors (PNETs), who achieved a PR rate of 42.9%. Additionally, the phase Ib/II extension study in NET patients demonstrated similar efficacy trends, supporting the preliminary efficacy of surufatinib in advanced NETs [16]. Based on the results of the phase III SANET-ep and SANET-p studies, surufatinib has been approved for the treatment of unresectable locally advanced or metastatic, non-functional, well-differentiated (G1, G2) NETs of non-pancreatic origin.

At the 2020 American Association for Cancer Research (AACR) conference, a phase I study of surufatinib (250 mg QD) combined with toripalimab included 30 patients with advanced solid tumors refractory to prior standard treatments. Among 29 evaluable patients, the DCR was 79.3%, and the ORR was 34.5%. Survival benefits were observed in patients treated with surufatinib (250 mg, 200 mg, and 300 mg) in combination with toripalimab, with respective DCRs of 100%, 50%, and 75%, and ORRs of 63.6%, 16.7%, and 16.7%, demonstrating a synergistic anti-tumor effect with good tolerability.

Following the promising phase I results, a single-arm, multicenter phase II study was conducted to further evaluate the efficacy and safety of surufatinib combined with toripalimab in advanced solid tumors. The phase I dose-escalation study demonstrated good safety and tolerability, with no maximum tolerated dose (MTD) reached. Drug exposure at the 300 mg QD dose approached saturation, and higher doses beyond 350 mg QD were not explored. Both 300 mg and 350 mg QD were effective doses, but the 300 mg QD dose group showed fewer grade ≥3 adverse events. Based on clinical safety, tolerability, efficacy, and pharmacokinetics, the RP2D of surufatinib was set at 300 mg QD for continuous oral administration.

1.4.2.2 Phase III Clinical Study Results of Surufatinib

The SANET-p study was a randomized, double-blind, placebo-controlled, multicenter phase III clinical trial evaluating the efficacy and safety of surufatinib in patients with low and moderate grade (G1 or G2) pancreatic neuroendocrine tumors (pNETs) who had progressive disease and unresectable locally advanced or distant metastases [17]. Patients were randomized in a 2:1 ratio to receive either 300 mg of surufatinib or a placebo orally once daily for 28 days per treatment cycle. The primary endpoint was PFS, with secondary endpoints including ORR, DCR, time to disease response (TTR), DOR, OS, safety, and tolerability.

As of the interim data analysis cutoff (November 11, 2019), 172 patients with advanced pNETs were enrolled—113 received surufatinib, and 59 received placebo. Baseline characteristics were balanced between the two groups, with a higher proportion of patients classified as grade 2 (G2) (87.6% in the surufatinib group and 84.7% in the placebo group). Results showed that surufatinib significantly prolonged PFS compared with placebo (10.9 months vs. 3.7 months, respectively), with a HR of 0.491 (95% CI: 0.319–0.755, P = 0.0011). Supportive analysis by the blind independent review committee (BIRC) confirmed the PFS benefit, with median PFS of 13.9 months in the surufatinib group versus 4.6 months in the placebo group (HR: 0.339, 95% CI: 0.209-0.549, P < 0.0001). Additionally, secondary endpoints favored surufatinib, with higher ORR (19.2% vs. 1.9%) and DCR (80.8% vs. 66.0%) compared to placebo.

1.4.3 Advantages of the Combination of Pamiparib and Surufatinib

A series of studies have demonstrated the effectiveness of PARP inhibitors—olaparib, rucaparib, niraparib, talazoparib, and pamiparib—in the treatment of ovarian cancer. However, resistance to these drugs often develops over time.

Macrophages in the tumor microenvironment can adopt either M2-like (tumor-promoting) or M1-like (anti-tumor) phenotypes. PARP inhibitors exacerbate the M2-like profile by increasing CSF-1R expression, which supports macrophage survival. In BRCA-deficient triple-negative breast cancer models, combining PARP inhibitors with CSF-1R inhibitors enhanced anti-tumor immunity and prolonged survival. Additionally, PARP inhibitors trigger lipid metabolic reprogramming in macrophages, promoting

tumor progression. Triple therapy involving PARP inhibitors, CSF-1R inhibitors, and SREBP1 inhibitors eradicated tumors in aggressive breast cancer models.

Combining PARP inhibitors with anti-angiogenic agents like surufatinib has shown synergistic effects. Surufatinib inhibits VEGFR, FGFR, and CSF-1R, suppressing angiogenesis and normalizing tumor blood vessels. It also reprograms tumor-associated macrophages (TAMs), improving immune responses and enhancing the efficacy of PARP inhibitors. This combination strategy offers a promising solution to overcoming resistance in cancers that are resistant to PARPi.

2. Study Objectives And Endpoints

2.1 Study Objectives

2.1.1 Phase Ib (Safety Run-In Period)

• To evaluate the safety and tolerability of pamiparib combined with surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARPi.

2.1.2 Phase II

Primary objective

• To evaluate the efficacy of pamiparib combined with surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARPi.

Secondary objectives

• To further evaluate the safety and tolerability of pamiparib combined with surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARPi.

Exploratory objectives:

• To explore the biomarkers associated with the efficacy of pamiparib combined with surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARPi.

2.2 Study Endpoints

2.2.1 Phase Ib (Safety Run-In Period)

Primary endpoint

• To determine the RP2D of surufatinib in combination with pamiparib.

2.2.2 Phase II

Primary endpoint:

• The 6-month progression-free survival (PFS) rate of pamiparib combined with surufatinib at RP2D assessed by RECIST 1.1.

Secondary endpoints:

• Objective response rate (ORR) of pamiparib combined with surufatinib at RP2D assessed by RECIST 1.1.

• Disease control rate (DCR) of pamiparib combined with surufatinib at RP2D assessed by RECIST 1.1.

• Overall survival (OS)

• Safety and tolerability evaluation: Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) during treatment as assessed by CTCAE 5.0

Exploratory Endpoints:

• To assess the correlation between genetic alterations in tumor samples and efficacy by NGS.

• To assess the relationship between ctDNA levels and efficacy.

3. Study Design

3.1 Study design

This trial was a multi-center, phase Ib/II study of pamiparib in combination with surufatinib in patients with platinum-resistant ovarian cancer who had received prior PARPi. The study included a phase Ib component, consisting a safety run-in cohort, followed by a phase II part. The phase Ib part was designed to establish the RP2D of

surufatinib plus pamiparib. The phase II study was to assess the efficacy of this combination.

3.2 Phase Ib (Safety Run-In Period)

In the phase Ib safety run-in period, a 3+3 design will be employed to determine the RP2D of surufatinb in combination with pamiparib. Surufatinib will be administered in a dose de-escalation scheme, starting at 250 mg orally once daily and, if necessary, reduced to 200 mg once daily. Pamiparib will be given at a standard dose of 40 mg orally twice daily. The dose limiting toxicity (DLT) observation period will span the first 21 days of treatment. Once the RP2D of surufatinib is determined, this dose will be used in the subsequent phase II trial. If the initial dose of 250 mg is not tolerated, a lower dose level of surufatinib 200 mg once daily will be assessed.

The RP2D-finding methods for surufatinib are outline as follows:

- An initial cohort of 3 patients will receive surufatinib 250 mg once daily with pamiparib. If no DLT occur, this dose level is considered safe, and be utilized in the subsequent phase II trial.
- If 1 of these 3 patients experience DLT, 3 additional patients will be entered this dose level. If no DLT is observed in this second group of 3, surufatinib 250 mg once daily is considered as RP2D. If any of the 3 newly enrolled patients experience a DLT, this dose of surufatinib will be considered the MTD, a lower dose of surufatinib 200 mg once daily will be assessed.
- If 2 or more of the first 3 patients experience DLT, a lower dose of surufatinib 200 mg once daily will be assessed.
- If the initial dose of 250 mg is not tolerated, the dose level of surufatinib 200 mg once daily will be assessed according to the same rule as mentioned above. If 2 or more patients among the cohort of 3 to 6 patients experience DLTs, the study will be suspended. A Safety Monitoring Committee (SMC) will assess the safety profile and determine whether a further dose reduction is necessary.

3.3 Phase II

This study will evaluate the efficacy and safety of the combination of pamiparib and surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARPi. The phase II portion consist of three periods: screening, treatment, and follow-up. The screening process will be conducted within 28 days prior to the first dose. During the treatment period, patients will receive pamiparib 40 mg twice daily, along with surufatinib at the RP2D. A cycle was defined as three weeks of treatment. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or study termination, whichever occurs first. Tumor response will be assessed according to RECIST 1.1 every 6 weeks (± 7 days) until disease progression. After completing the treatment period, patients will enter the follow-up period.

3.4 Dose-limiting toxicities (DLTs)

A DLT will be classified according to CTCAE 5.0 and is defined as any of the following adverse events unless the event can clearly be determined to be unrelated to drugs occurring in the first cycle of treatment:

1. Hematologic toxicity:

1) Grade 4 neutropenia;

2) Grade 3 neutropenia accompanied by fever (neutrophil count < 1.0 × 109/L; body temperature ≥ 38.5 ° C)；

3) Grade 3 thrombocytopenia with a bleeding tendency or lasting more than 7 days;

2. Non-hematologic toxicity:

1) ≥ Grade 3 non-hematologic toxicity lasting for more than 7 days (with satisfactory supportive treatment), except for the following conditions: allergic reactions, only laboratory abnormalities that resolve within 7 days, symptoms caused by tumor progression;

2) Grade 4 hypertension cannot be controlled with one antihypertensive drug within 14 days of treatment;

3) Grade 3 proteinuria;

4) Recurrent Grade 2 non-hematologic toxicity requiring ≥ 2 dose interruptions or reductions.

3. Any other Grade ≥ 3 toxicity, whether hematologic or non-hematologic, that is assessed as related to surufatinib will be considered as DLT, as determined by the principal investigator.

4. Patient Selection

4.1 Inclusion criteria

1. Be willing and able to provide written informed consent for the trial;
2. Histologically confirmed epithelial ovarian cancer;
3. Has platinum-resistant disease, defined as progression within 6 months from completion of most recent platinum-containing therapy. Subject may have been treated with additional regimen(s) subsequent to determination of platinum resistance;
4. Has progressed on or after prior PARP inhibitor therapy;
5. Aged 18-75 years;
6. Has measurable lesions per RECIST 1.1;
7. Eastern Cooperative Group (ECOG) score 0-1;
8. Life expectancy ≥ 3 months;
9. Has adequate organ function as defined by the following criteria: absolute neutrophil count ≥ 1.5×10^9 cells, platelets ≥ 100×10^9 cells, hemoglobin ≥ 90 g/L, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 × upper limit of normal (UNL), total bilirubin < 1.5 × UNL, serum creatinine < 1.5 × UNL;
10. Females of childbearing potential should have a negative serum or urine pregnancy test prior to receiving the first dose of study treatment; and should be willing to use one acceptable contraception (i.e., oral contraceptives, condoms, intrauterine devices [IUDs]) throughout the period of taking study treatment and for at least 6 months after the last dose of study drug(s).

4.2 Exclusion Criteria

1. Histological diagnosis of mucinous adenocarcinoma;
2. Has received prior therapy with small molecule antiangiogenic receptor tyrosine kinase inhibitors (TKIs) within 6 months;
3. Known or suspected allergy to any of study drugs;
4. Has clinically significant cardiovascular disease within 6 months from first dose of study intervention, including New York heart association [NYHA] class > 2, unstable angina, myocardial infarction, cardiac arrhythmia associated with hemodynamic instability (including QTc interval ≥ 450 ms in men, ≥ 470 ms in female);
5. Has active ulcers, gastrointestinal perforation or obstruction;
6. Active bleeding or pathologic condition that carries a high risk of bleeding;
7. Inadequately controlled hypertension (systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 90 mmHg) with or without treatment;
8. Major surgery within 28 days of starting study treatment;
9. Urine routine showed urine protein ≥ 2 + and 24-hour total urine protein > 1.0 g;
10. Uncontrolled pericardial or pleural or peritoneal effusions;
11. Has a diagnosed and/or treated additional malignancy within the last 5 years. Exceptions include in situ cervical cancer, non-melanoma skin cancer, or superficial bladder tumors that has undergone potentially curative therapy;
12. Known Human Immunodeficiency Virus (HIV) infection;
13. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis;
14. Any medical or other condition that in the opinion of the investigator(s) would preclude the participant's participation in the study.

4.3 Treatment Discontinuation Criteria

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

1. The subject requests to discontinue treatment;
2. Radiographic disease progression;
3. Completed 2 years of treatment;
4. Unacceptable toxicity;

5. Noncompliance with trial treatment or procedure requirements;
6. The subject is lost to follow-up;
7. Investigator's decision to discontinue treatment for the subject.

5. Trial Treatments

5.1 Investigational Product

The investigator shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol.

Table 2. Product Descriptions

Product Name	Pamiparib	Surufatinib
Source	BeiGene (Suzhou) Co., Ltd.	Hutchison Medi Pharma (Suzhou) Ltd.
Dosage Form	Capsule	Capsule
Dosage Strength	20 mg	50 mg
Usage	Oral	Oral
Storage	Stored at room temperature.	Stored below 25℃, protected from light.

5.2 Administration

5.2.1 Administration

• Pamiparib is taken orally twice daily (BID). It should be administered at least 1 hour before or at least 2 hours after meals. The recommended dosing interval is 12 hours (± 2 hours), and it is advised to take the medication at the same time each day. If a dose is missed and it has been less than 8 hours since the scheduled time, the patient should take the missed dose as soon as possible. If more than 8 hours have passed, the patient should skip the missed dose and proceed with the next scheduled dose. Do not make up for the missed or vomited dose.

• The starting dose of surufatinib in phase Ib is 250 mg, taken orally once daily (QD), at least 1 hour before or at least 2 hours after meals. For consistency, take the medication at the same time each day, if possible. If a dose is missed or vomiting occurs after

administration, the missed dose should not be made up. The phase II dose will be determined based on the results of Phase Ib.

Treatment cycles are administered every 3 weeks and may continue until one of the following occurs: unacceptable toxicity, disease progression, withdrawal of consent, loss to follow-up, death, or study termination, whichever comes first.

5.2.2 Dose Modifications

5.2.2.1 General Dose Modification Guidelines

• Dose modification and toxicity management will be conducted based on the severity of toxicities according to CTCAE v5.0, including dose interruption, dose reduction, and dose termination.

• Concurrent AEs of varying severities should be managed according to the highest observed grade.

• If the investigator determines that an AE is solely attributed to one of the study drugs, adjustments of the other drug is not required.

• Throughout the study, if a participant permanently discontinues a drug due to an unacceptable AE, treatment with the remaining drugs may continue until protocol-specified criteria for discontinuation are met, provided the investigator believes the patient can still benefit from treatment.

5.2.2.2 Dose Modification Guidelines for Pamiparib

Treatment with pamiparib should be interrupted for TRAEs of ≥ Grade 3. Once the toxicity resolves to ≤ Grade 1, the patient may resume pamiprib at the same dose or at a reduced dose level (see Table 4). If the event recurs at the same or a higher grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made if possible. If no further dose reduction is available, pamiparib should be discontinued. If the toxicity requiring dose interruption dose not resolve to ≤ Grade 1 within 12 weeks, pamiparib treatment must be permanently discontinued. Guidelines for dose modification for pamiparib are provided in Table 4.

Table 3. Dose Reduction Levels for Pamiparib

Dose level	Pamiparib dose
Starting dose	40 mg BID orally
Decrease 1 dose level	20 mg BID orally
Decrease 2 dose level	Permanent discontinuation

Table 4. Dose Modification Strategy for Pamiparib

Toxicity	Recommended Dose Modification
Anemia (hemoglobin, Hb)	
Grade 3 (Hb < 8 g/dL)	• Hold pamiparib until toxicity resolves to ≤ Grade 1 or baseline. • Maintain the current dose level if resolution occurs ≤ 14 days. • Reduce pamiparib by 1 dose level if resolution occurs > 14 days.
Grade 4	Hold pamiparib until toxicity resolves to ≤ Grade 1 or baseline, and decrease the pamiparib dose by 1 level.
Thrombocytopenia (platelet count, PLT)	
Grade 3 (PLT < 50-25 × 10^9/L)	• Hold pamiparib until toxicity resolves to ≤ Grade 1 or baseline. • Maintain the current dose level if resolution occurs ≤ 7 days. • Reduce pamiparib by 1 dose level if resolution occurs > 7 days.
Grade 4 (PLT < 25 × 10^9/L)	Hold pamiparib until toxicity resolves to ≤ Grade 1 or baseline, and decrease the pamiparib dose by 1 level.
Neutropenia (absolute neutrophil count, ANC)	
Grade 3 (ANC < 1.0-0.5 × 10^9/L)	• Hold pamiparib until toxicity resolves to ≤ Grade 1 or baseline. • Maintain the current dose level if resolution occurs ≤ 7 days. • Reduce pamiparib by 1 dose level if resolution occurs > 7 days.
Grade 4 (ANC < 0.5 × 10^9/L)	Hold pamiparib until toxicity resolves to ≤ Grade 1 or baseline, and decrease the pamiparib dose by 1 level.
Febrile Neutropenia (ANC < 1.0 × 10^9/L and a measured body temperature of ≥ 38.3 ° C or a body temperature of ≥ 38 ° C for more than 1 hour)	Hold pamiparib until toxicity resolves, then decrease the dose by 1 level.
Non-Hematologic Toxicities	
Grade 3 AEs that cannot be managed with prophylaxis or that persists despite treatment.	Hold pamiparib until toxicity resolves to ≤ Grade 1 or baseline, and decrease the pamiparib dose by 1 level.

Toxicity	Recommended Dose Modification
Grade 4	Permanently discontinue

5.2.2.3 Dose Modification Guidelines for Surufatinib

Dose interruption or reductions of surufatinib due to TRAEs may be implemented per the Investigator's judgement after cycle 1 in patients enrolled in phase Ib safety run-in period and at any time in patients enrolled in phase II. A maximum of two dose reductions are permitted for surufatinib. The dose reduction levels for surufatinib in case of toxicity are listed in Table 5.

Table 5. Dose Reduction Levels for Surufatinib

Dose levels	Surufatinib dose	
Starting dose	If RP2D is 250 mg QD orally	If RP2D is 200 mg QD orally
Decrease 1 dose level	200 mg QD orally	150 mg QD orally
Decrease 2 dose level	150 mg QD orally	100 mg QD orally

For hematological toxicity ≥ Grade 3 or non-hematological toxicity ≥ Grade 2, dose interruption and adjustment are required for surufatinib. Among non-hematological toxicities, controllable nausea, vomiting, and fever (below 38°C) with a confirmed cause can be managed with active symptomatic treatment without immediate dose interruption or adjustment.

During the study, the investigator may adjust the dose as appropriate based on TRAEs. Guidelines for dose modification for surufatinib are provided in Table 6. For instance, If a subject experiences multiple Grade 2 TRAEs or has poor tolerance to the study drug, the investigator may pause treatment and, once toxicity resolves, adjust the administration method of surufatinib.

Table 6. Dose Modification for Surufatinib

Toxicity	**Grade**	**Hold Surufatinib**	**Timing for Restarting Treatment**	**Dose Modification**

Hematologic Toxicity	Grade 3	Yes (except lymphocyte count decreased)	Toxicity resolves to ≤ Grade 2	First occurrence: Maintain the current dose level. Second occurrence: Decrease the dose by 1 level. Third occurrence: Decrease the dose by 1 level. If Grade 3 or higher hematological toxicity recurs after two dose reductions, permanently discontinue surufatinib.
	Grade 4	Yes	Toxicity resolves to ≤ Grade 2	First occurrence: Decrease the dose by 1 level. Second occurrence: Decrease the dose by 1 level.
Hypertension	Grade 3	Yes	Toxicity resolves to ≤ Grade 1	First occurrence: Maintain the current dose level. Second occurrence: Decrease the dose by 1 level. Third occurrence: Decrease the dose by 1 level. If Grade 3 hypertension recurs after two dose reductions, permanently discontinue surufatinib.
	Hypertensive crisis	Yes	-	Permanently discontinue surufatinib.
Proteinuria	Grade 3	Yes	Toxicity resolves to ≤ Grade 2	First occurrence: Decrease the dose by 1 level. Second occurrence: Decrease the dose by 1 level. If Grade 3 proteinuria recurs after two dose reductions, permanently discontinue surufatinib.
Hand-foot syndrome	Grade 3	Yes	Toxicity resolves to ≤ Grade 1	First occurrence: Decrease the dose by 1 level. Second occurrence: Decrease the dose by 1 level. If Grade 3 hand-foot syndrome recurs after two dose reductions, permanently discontinue surufatinib.
Hemorrhage	Grade 2 bleeding at any site	Yes	Toxicity resolves to ≤ Grade 1	Dose interruption; If toxicity resolves to ≤ Grade 1 within 4 weeks, decrease the dose by 1 level.
	≥ Grade 3	Yes	-	Permanently discontinue surufatinib.

Headache	Grade 2 headache lasting ≥ 7 days or Grade 3 headache despite symptomatic treatment	Yes	Toxicity resolves to ≤ Grade 1	First occurrence: Decrease the dose by 1 level. Second occurrence: Decrease the dose by 1 level. If Grade 3 headache recurs after two dose reductions, permanently discontinue surufatinib.
Other non-hematological toxicities *	Grade 2 (lasting for ≥ 7 days)	Yes	Toxicity resolves to ≤ Grade 1	Maintain the current dose level.
	Grade 3	Yes	Toxicity resolves to ≤ Grade 1	First occurrence: Decrease the dose by 1 level. Second occurrence: Decrease the dose by 1 level. If Grade 3 non-hematological toxicity recurs after two dose reductions, permanently discontinue surufatinib.

* Once cerebral hemorrhage, ≥ Grade 2 pulmonary hemorrhage, ≥ Grade 3 other hemorrhage, arterial thrombosis, leukoencephalopathy syndrome, gastrointestinal perforation, or nephrotic syndrome occurs during the trial, surufatinib should be permanently discontinued.

6. Trial Procedure

Adherence to the study design requirements is essential for the successful conduct of the study. The Trial Flow Chart (see Trial Flow Chart) summarizes the trial procedures to be performed at each visit. This section lists the procedures and parameters of each planned study assessment in detail. It may be necessary to perform the procedures at unscheduled time points if it is considered to be clinically necessary by investigator.

6.1 Administrative Procedures

6.1.1 Informed Consent

Written informed consent for participation must be obtained prior to all screening assessment procedures.

6.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by investigator to ensure that the patient qualifies for the trial.

6.1.3 Medical History and Demographic Data

Medical history includes all active conditions, and clinically significant condition diagnosed within the previous 5 years, cancer history, prior cancer treatments and procedures. Demographic data includes sex, age, and race/ethnicity.

6.1.4 Concomitant Medication Review

The medications taken by the patients within 28 days prior to study will be reviewed. The investigator will record all medications taken by the patients during the trial through the safety visit.

6.2 Clinical Assessment

6.2.1 Vital Signs

Vital signs will include measurements of blood pressure, heart rate, temperature, respiratory rate while the patient is in a seated position, and temperature.
Vital signs will be measured at screening, prior to each cycle, and at treatment discontinuation, as outlined in the Trial Flow Chart.

6.2.2 Eastern Cooperative Oncology Group (ECOG) performance status

The investigator will assess ECOG status at screening, prior to each cycle, and at treatment discontinuation, as outlined in the Trial Flow Chart.

6.2.3 Physical Examination

A complete physical examination include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

A complete physical examination will be performed at the screening period. Clinically significant abnormal finding should be recorded as medical history. A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate.

All patients should be monitored for symptoms of brain metastases. Symptoms suggestive of new or worsening CNS metastases should prompt a full neurological examination.

6.2.4 Cardiac Function Tests

Twelve-lead ECG is required at screening, and prior to each cycle as outlined in the Trial Flow Chart. Echocardiograms will be obtained for patients if clinical indicated.

6.2.5 Adverse Event (AE) Monitoring

The investigator will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. AEs will be graded and recorded throughout the study and during the follow-up period according to CTCAE 5.0 (see Section 7). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

6.3 Laboratory Assessment

Samples for hematology, serum chemistries, coagulation, urine routine will be analyzed specified in the Trial Flow Chart. More laboratory assessments will be performed if clinically indicated. Local laboratory assessment will include the following:

• Hematology (full blood cell count with differential including neurophils, eosinophils, lymphocytes, monocytes, basophils, and other cells, red blood cell count, hemoglobin, hematocrit, mean corpuscular hemoglobin concentration, and platelet count).

• Serum chemistries (sodium, potassium, calcium, chloride, magnesium, Carbon dioxide, ALT, AST, GGT, ALP, LDH, total bilirubin, direct bilirubin, indirect bilirubin, creatinine, blood urea nitrogen, uric acid, total protein, albumin, glucose, total cholesterol, high density cholesterol, low density cholesterol, creatine kinase, Creatine kinase isoenzyme, and C-reactive protein)

• Coagulation (PT, APTT, INR, TT, FIB, FDP, D-Dimer, AT-III).

• Urine routine (blood, glucose, ketones, protein, specific gravity, microscopic exam)

• Stool routine test

• Thyroid function test (T3, free T3, T4, free T4, thyroid stimulating hormone)

• HBV serology (HBsAg, HBsAb, HBeAg, HBeAb, HBcAb). HBV DNA test is required for patients who have positive serology for anti-HBC.

• HCV serology (anti-HCV). HCV RNA test is required for patients who have positive serology for anti-HCV.

6.4 Tumor Assessment

Tumor assessment include computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Bone scans and CT scan of the neck will also be performed if clinically indicated. Initial tumor imaging must be performed within 28 days prior to the treatment.

For subsequent tumor assessments, the same radiographic procedure used to assess disease sites at screening period should be used throughout the study when possible. At the investigator's discretion, CT scans should be repeated at any time if progressive disease is suspected. Response will be assessed by the investigators with radiologists using RECIST 1.1. Scans will be performed every 6 weeks (± 7 days) until disease

progression. Per RECIST 1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented.

At the investigator's discretion, CT scans or MRI should be repeated at any time if progressive disease is suspected.

At the investigator's discretion, disease progression may be confirmed at least 4 weeks after the first scan indicating progressive disease in clinically stable subjects. Patients who have unconfirmed disease progression may continue on treatment until progression is confirmed.

6.5 Blood Sample and Tumor Tissue Collection

Instructions for providing blood samples and tumor tissues for biomarker detection.

1. Blood samples for ctDNA detection

Participants are required to provide blood samples (~10 mL each) at the following time points:

• Screening

• Cycle 3, day 1 (C3D1)

• Cycle 7, day 1 (C7D1)

• At progressive disease (PD).

The collected samples will be used for ctDNA detection to analyze the relationship between ctDNA levels and treatment efficacy.

2. Tumor tissue for biomarker analysis

Participants are encouraged to provide previously archived tumor specimens, if available. A total of 10 unstained histopathological sections will be required for biomarker analysis. Genetic alterations identified in the tumor samples will be analyzed using NGS to evaluate their correlation with treatment efficacy.

6.6 End of Treatment/Withdrawal Assessments

If a patient meets any of the discontinuation criteria (see 4.3 for details), the patient should be withdrawn from study treatment. The following examinations will be performed at the end of the study:

- Adverse event assessment and concomitant medication review;
- ECOG score;
- Physical examination;
- Hematology, serum chemistries and urinalysis;

6.7 Post-Treatment Visits

6.7.1 Safety Follow-up Visit

The safety follow-up visit should be conducted approximately 30 days after the last dose of trial treatment. All AEs that occur prior to the safety follow-up visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

6.7.2 Survival Follow-up Visit

After completing the safety follow-up visit, patients will move into survival follow-up. For the subjects who discontinue trial treatment for a reason other than disease progression, every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, or death. Subjects who experience disease progression and enter the survival follow-up phase should be contacted by telephone approximately every 3 months to assess their survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7. Safety Assessment

7.1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product and which dose not necessary have to have a causal relationship with the treatment.

The term AE is used to include both serious and non-serious AEs. An AE includes but is not limited the following:

• An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to that medicinal product.

• Pre-existing medical conditions that have worsened in severity or frequency or change in character during the protocol-specified AE reporting period is an AE.

• An abnormal laboratory finding that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

7.2 Definition of Serious Adverse Event (SAE)

A serious adverse event is defined as any of the following adverse events occurring at any dose of the investigational product, or during any period of the observation:

• Results in death;

• Is immediately life-threatening;

• Requires hospitalization or prolongation of existing hospitalization;

• Results in persistent or significant disability/incapacity or significant impairment of normal life functions;

• Results in a congenital anomaly or birth defect;

• Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

7.3 Evaluating Adverse Events

Adverse events will be recorded using a recognized medical term or diagnosis that accurately reflects the event. All Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE.

Each AE reported during the study should be assessed and graded based on the NCI CTCAE, version 5.0.

The investigator is required to assess the possible causal relationship between study treatment and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. The causality will be assessed according to the following terms:

- **Definitely Related**: Investigational product administration and onset of the AE are related in time and a direct association can be demonstrated.
- **Probably Related**: Investigational product administration and onset of the AE are reasonably related in time and the investigational product provides a more likely explanation of the AE than other causes.
- **Possibly Related**: Investigational product administration and onset of the AE are reasonably related in time and causes other than the investigational product could equally well provide an explanation for the AE.
- **Probably not Related**: A potential relationship between the investigational product and the AE could exist, i.e., the possibility cannot be excluded, however causes other than the investigational product provide a more likely explanation for the AE.
- **Not Related**: The AE is clearly explained by another cause not related to the investigational product.

7.4 Serious Adverse Event Reporting

All SAEs occurring to any patient on this study, regardless of attribution, should be reported to IRB and regulatory authority within 24 hours of the investigator's knowledge of the events. The report of SAE should be consistent with standard SAE

reporting guidelines.

8. Statistical Analysis

8.1 Sample Size

8.1.1 Phase Ib (Safety run-in phase)

A 3 + 3 dose de-escalation design will be employed. A total of 3 to 12 subjects are expected.

8.1.2 Phase II

Previous studies reported a 6-month PFS rate of 25% for platinum-resistant ovarian cancer patients treated with single-agent non-platinum chemotherapy or targeted therapy. We hypothesized that the combination of surufatinib and pamiparib would achieve a 6-month PFS rate of 45%. With 80% power and a one-sided significance level of 0.05, 26 patients were required, including those treated at RP2D in phase Ib. Accounting for a 15% dropout rate, approximately 30 patients were planned for enrollment in phase II.

8.2 Statistical Analysis Set

- Safety analysis set: all subjects who have received at least one dose of the study drug.
- DLT analysis set: all subjects who either completed Cycle 1 of treatment in phase 1b (safety run-in period) or discontinued treatment due to a DLT in Cycle 1. This analysis set will be used to determine the RP2D.
- Full analysis set (FAS): all subjects who received at least one dose of the study drug.
- Efficacy evaluable set (EES): all subjects who have received at least one dose of the study drug and have at least one post-baseline tumor assessment. EES included eligible subjects who receive the RP2D of surufatinib in both phase Ib and phase II portion of the study.

8.3 Statistical Analysis Methods

Statistical analysis will be performed using SAS software version 9.2 or higher. Descriptive statistical analysis and graphical presentations of the trial results will be organized by dose level. For quantitative variables, the mean, standard deviation, median, maximum, and minimum will be reported. For qualitative variables, the number and percentage will be provided. Time-to-event data will be summarized and presented using the Kaplan-Meier method.

8.3.1 Phase 1b

The analysis will be based on the DLT analysis set. Descriptive statistical analysis will be performed to summarize the AEs occurred and grade the AEs according to CTCAE v5.0 based on the study results. The number of DLTs will be listed.

8.3.2 Phase II

8.3.2.1 Primary endpoint

• Six-month PFS rate: defined as the percentage of patients alive without documented progression 6 months after treatment initiation. The percentage and its 95% confidence interval (CI) will be analyzed using the Kaplan-Meier method and survival curves will be plotted.

Table 7. Censoring Rules for Progression-free survival

Situation	Date for progression or censoring	Outcome
No post baseline tumor assessment and no death	Treatment start date	Censored
No PD and no death; new anticancer treatment is not initiated	Date of the last tumor assessment with no documented progression	Censored
No PD and no death; new anticancer treatment is initiated	Date of the last tumor assessment before new anticancer treatment	Censored
PD or death documented after ≤ 1 missed tumor assessment	Date of documented PD or death	Progressed
PD or death documented after ≥ 2 missed tumor assessment	Date of last tumor assessment prior to the ≥ 2 missed tumor assessment	Censored

8.3.2.2 Secondary Endpoints

• ORR is defined as the proportion of subjects with complete response (CR) or partial response (PR) according to RECIST 1.1 in the analysis population (formula below). A 95% confidence interval (CI) will be provided for the ORR.

$$\text{ORR}= \frac{\text{Number of subjects who have CR or PR}}{\text{Total number of subjects in the study}} *100\%$$

• Disease control rate (DCR) will be calculated as the proportion of subjects with CR, PR, and SD according to RECIST 1.1 in the analysis population (formula below). A 95% CI will be provided for DCR.

$$\text{DCR}= \frac{\text{Number of subjects with CR, PR, or SD}}{\text{Total number of subjects in the study}} *100\%$$

• Overall survival (OS) is defined as the time from the date of the first dose to the date of death from any cause. For subjects still alive at the time of follow-up, OS will be censored at the last known date of contact. If a subject is lost to follow-up, OS will be censored at the last confirmed survival date.

OS will be analyzed using the Kaplan-Meier method. A survival curve will be plotted to present the results.

• Safety analyses

Safety analyses will be conducted using data from the safety population. Descriptive statistical analysis will be used to tabulate the number of patients who experienced at least one treatment-related adverse event, severe adverse event (≥ Grade 3), serious adverse event, or withdrawal due to an adverse event during this trial.

8.3.2.3 Exploratory endpoints

• Biomarker measurements will be presented based on available data, with the correlation between these measurement and clinical outcomes (e.g., antitumor efficacy) depicted graphically.

9. Data collection and management

9.1 Case Report Forms (CRF)

Case Report Form (CRF) is used to document clinical data in a clinical trial. The data documented in the CRF must be consistent with the corresponding source documents. CRFs must be filled out completely and legibly, using black or blue ink to meet legal documentation requirements. To protect subject privacy, subject name should be coded in the CRF. All amendments and corrections must be made and confirmed by the investigator, with the date of the change clearly noted. Errors should retain visible, and correction must not obscure the original entry (e.g., correction fluid cannot be used). Missing notes in the medical records and blank in the CRF should be crossed out to prevent unnecessary follow-up. As regulatory documents, CRFs must be suitable for submission to hospital authorities.

9.2 Data Management

In accordance with ICH/GCP guidelines, the investigator or institution will maintain CRFs, source documents for each subject, and all essential study documents required by regulatory standards. Measures must be implemented to prevent accidental or premature destruction of these documents. Key documents must be retained for at least 10 years after the formal discontinuation of the clinical trial.

10. Regulatory Ethics Compliance

10.1 Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is conducted in accordance with the study protocol, ethical principles of the Declaration of Helsinki, and Good Clinical Practice (GCP) guidelines. In addition, the investigator must make any necessary adjustments to accommodate China's national conditions. These requirements should be clearly outlined in the informed consent form, which must specify the fundamental prerequisites for including subjects in the clinical study.

10.2 Institutional Review Board (IRB)

Before the start of the study, the investigator will provide the IRB with current and complete copies of the documents, which include, but are not limited to, final protocol, informed consent, investigators' curriculum vitae, information regarding funding, and other potential conflicts of interest. The study will be undertaken only after the IRB has given full approval of all the documents. All the protocol amendments must be submitted to the IRB for review and approval before implementation of the changes.

10.3 Informed Consent

The informed consent document must be signed by the subject or the subject's legally authorized representative before her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

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12. Appendix I: Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)

1. measurability of the tumor at baseline

1.1 Definition

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows: 1.1.1 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:

• CT scan 10 mm (CT scan slice thickness no greater than 5 mm)

• Clinical routine examination instrument 10 mm (tumor lesions that cannot be accurately measured with a caliper instrument should be recorded as non-measurable)

• Chest X-ray 20 mm

• Malignant lymph nodes: Pathologically enlarged and measurable, a single lymph node must be ≥ 15 mm in short axis on CT scan (CT scan slice thickness recommended not to exceed 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

1.1.2 Non-measurable lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis) and non-measurable lesions. Lesions considered truly non-measurable include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis carcinomatosa of the skin/lung, abdominal involvement not confirmed and followed by imaging, and cystic lesions.

1.1.3 Special considerations regarding lesion measurement

Bone lesions, lesions and lesions previously treated with local therapy should be particularly noted:

Bone lesions:

• Bone scans, PET scans or photographs are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;

• Lytic lesions or mixed lytic/osteoblastic 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;

• Osteoblastic lesions are non-measurable.

Focus:

• Lesions that meet the criteria for radiographically defined simple cysts are considered malignant lesions by definition and are neither measurable nor non-measurable;

• Metastatic lesions that meet the definition of measurability described above may be considered measurable. However, if non-target lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local therapy:

• Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. The study protocol should detail the conditions under which such lesions would be considered measurable.

1.2 Description of measurement method

1.2.1 Lesion Measurements

For clinical evaluation, all tumor measurements were recorded in metric notation. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Evaluation method

The same technique and method should be used for baseline assessment and subsequent measurement of lesions. All lesions should be evaluated by imaging, except those that cannot be imaged but can only be evaluated by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For patients with skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. When lesions are evaluated by both imaging and clinical examination, imaging evaluation should be used whenever possible because imaging is more objective and can be reviewed repeatedly at the end of the study.

Chest X-ray: When tumor progression is an important endpoint, chest CT is preferred because CT is more sensitive than X-ray, especially for new lesions. Chest X-ray is only applicable when the measured lesion has clear boundary and good pulmonary ventilation.

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

Ultrasound: Ultrasound should not be used as a method of measurement to measure lesion size. Ultrasonography, because of its operational dependency, is not reproducible after the end of a measurement and does not guarantee the identity of techniques and measurements between different measurements. If new lesions are identified by ultrasound in the course of the trial, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT.

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. However, if markers are present at baseline above the upper limit of normal, they must normalize for a patient to be considered in complete response. Because tumor markers vary from disease to disease, this should be taken into account when writing measurement criteria into protocols. Specific criteria for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytological/histological techniques: These techniques can be used to differentiate between PR and CR in certain situations defined by the protocol (e.g. residual benign tumor tissue in lesions of germ cell tumors). 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 assessment

2.1 Assessment of overall tumor burden and measurable disease

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

2.2 Baseline documentation of target and non-target lesions

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

five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions must be selected on the basis of their size (longest diameter), be representative of all involved organs, and be measured with good reproducibility. Sometimes when the largest lesion cannot be measured repeatedly, a new largest lesion which can be measured repeatedly can be selected.

Lymph nodes require special attention because of normal tissue and imaging detection even without tumor metastasis. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. The baseline is only required to test the short diameter. The short axis of a node is the diameter normally used by radiologists to judge whether a node has metastatic disease. Nodule size is generally expressed by two dimensions of image detection data (for CT, use the axial plane; for MRI, select a plane from the axial plane, sagittal plane or coronal plane). The smallest value is the short diameter. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm is the measurement of the nodule. Nodules ≥ 10 mm but < 15 mm in diameter should not be considered target lesions. Nodules < 10 mm are not considered pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, only the short axis will be included as noted above. The baseline sum diameters will be used as reference for baseline disease. All remaining lesions including pathological lymph nodes should be identified as non-target lesions and should be recorded at baseline. If present, absent or in rare cases unequivocal progression is recorded. The presence of widespread target lesions can be noted with the documentation of the target organ (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3 Response Criteria

2.3.1 Target Lesion Assessment

Complete response (CR): Disappearance of all target lesions. All pathological lymph nodes (including target and non-target nodules) 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.

2.3.2 Special notes on assessment of target lesions:

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that if lymph nodes are included as target lesions, the nodes must not have completely disappeared, even if complete response criteria are met, since the short axis of a normal lymph node is defined as < 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 are too small to measure: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded

as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important to record a value on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should also be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). The default value of 5 mm is derived from the cut thickness of the CT scan (this value does not change with different cut thickness values for C). Since there is little chance of repeated occurrences of the same measurement, providing this default value will reduce the risk of false evaluation. To reiterate, however, if the radiologist is able to provide an exact measure of lesion size, the actual measure must be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions' fragment ', the longest diameters of the fragmented portions should be added together to calculate the lesion sum. Similarly, when lesions appear coalescent, the plane between them may be maintained to distinguish them, and the maximal diameter will be calculated. However, if the union is inseparable, the longest diameter should be the longest diameter of the fusion lesion as a whole.

2.3.3 Assessment of Non-Target Lesions

This section defines the criteria for tumor response in non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and only qualitatively assessed 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: Unequivocal progression of existing non-target lesions. Note: The appearance of one or more new lesions is also considered progression.

2.3.4 Special notes on assessment of progression of non-target lesions

The definition of progression of non-target disease requires additional explanation as follows: When the patient also has measurable disease, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for progression; therefore, it may be rare for changes in non-target lesions alone to define overall tumor progression in the face of SD or PR of target lesions. When patients have non-measurable non-target disease: This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The overall assessment also refers to the above criteria, but there are no measurable lesions in this case. 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 in the diameter of 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 '. Examples include pleural effusions ranging from trace to large, lymphatic involvement spreading from the primary site to distant, or may be described in the protocol as' necessitating a change in therapy '. If unequivocal progression is observed, the patient should be considered to have had overall PD at that time point. While it is preferable to have objective criteria to be applied in

the assessment of non-measurable disease, increased criteria must be reliable.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on 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 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 at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

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

A negative FDG-PET at baseline and a positive FDG-PET at follow-up is a sign of PD. 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 for confirmation (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 imaging, there is no PD.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the trial until the end of the trial, taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. The patient's best response assignment will depend on the findings of both target and non-target disease and will also take into account the appearance of new lesions. It is also dependent on the nature of the trial, protocol requirements, and measurement of results. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the best overall response.

2.4.1 Time Point Response

It is assumed that at each protocol-specified time point a response occurs. Table 1 provides a summary of overall response at each time point for the patient population with measurable disease at baseline. If patients have non-measurable disease (no target disease), Table 2 is to be used.

2.4.2 Missing Assessments and Non-evaluable Designation

If 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 is 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 is likely to occur in the setting of disease progression. For example, if a patient had three lesions with a sum of 50 mm at baseline and at follow-up only two lesions were evaluable with a sum of 80 mm, the patient will be evaluated as PD, regardless of the contribution of the missing lesion.

2.4.3 Best overall response: all time points

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

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

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

2.4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions, and the nodes decrease to 'normal' size (< 10 mm), they will still have a measurement reported on scans. To avoid situations where assessment is based on increased nodule size, measurements will be recorded even if the nodule is normal. As mentioned earlier, this means that subjects with CR will not have a total sum of 'zero' on the CRF.

If confirmation of response is required during the course of the trial, repeated 'non-measurable' time points will complicate best response assessment. 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, a subject's response of PR-NE-PR can be considered confirmed.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression should be reported as symptomatic progression. Every effort should be made to assess objective progression even after treatment discontinuation. Symptomatic deterioration is not a descriptor of an objective response: it is the reason for stopping treatment. The objective response status of such subjects will be determined by evaluation of target and non-target disease as shown in Tables 1 – 3.

Conditions that define early progression, early death and unevaluability are study specific and should be clearly described in each protocol (depending on treatment interval and treatment cycle).

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

Table 1. Time point response: subjects with target lesions (including or excluding non-target lesions)

Target Lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	Non	CR
CR	Non-CR/Non-PD	Non	PR
CR	Not evaluable	Non	PR
PR	Non-progressive or not fully evaluable	Non	PR
SD	Non-progressive or not fully evaluable	Non	SD
Not all evaluated	Non-progression	Non	NE

PD	Any condition	Yes or No	PD
Any condition	PD	Yes or No	PD
Any condition	Any condition	Yes	PD
CR = complete response	PR = partial response	SD stable disease	PD = progressive disease NE = not evaluable

Table 2. Time Point Response - Subjects with Non-Target Lesions Only

Non-target lesions	**New lesions**	**Overall response**
CR	Non	CR
Non-CR or Non-PD	Non	Non-CR or Non-PD
Not all evaluated	Non	Not evaluable
Unequivocal PD	Yes or No	PD
Any condition	Yes	PD

Note: 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease. Since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised. For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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

Overall Response First Time Point	**Overall response at later time points**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD or PRa
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable. 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). The best response depends on whether SD occurs at the shortest treatment interval. 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. In this case, the original CR should be changed to PR and the best response is PR.

2.5. Frequency of Tumor Re-evaluation

The frequency of tumor re-evaluation during treatment depends on the treatment regimen and should be consistent with the type and schedule of treatment. However, in phase II trials where the beneficial effect of treatment is unclear, follow-up every 6 to 8 weeks (timed to coincide with the end of a cycle) is reasonable, and the length of the time interval may be adjusted in special regimens or situations. The protocol should specify which tissue sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, target and non-target lesions are evaluated at each assessment. In selected circumstances, certain non-target lesions may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

After the end of treatment, re-evaluation of tumors depends on whether the response rate or the time to an event (progression/death) is used as the clinical trial endpoint. If time to an event (e.g. TTP/DFS/PFS) requires routine repeat evaluation as specified in the protocol. In particular, the scheduled evaluations in randomized comparative trials should be listed within the schedule (e.g., 6 to 8 weeks on treatment, or 3 to 4 months after treatment) and should not be affected by other factors, such as treatment delays, dosing intervals, and any other events that may lead to imbalances in the treatment arm in the timing of disease evaluation.

2.6. Confirmation of response assessment/duration of response

2.6.1. Confirmation

In non-randomized clinical studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This also allows for a sound interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may make central review to prevent bias even more important, especially in non-blind experimental studies.

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 to 8 weeks) that is defined in the protocol.

2.6.2 Overall Response Period

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

2.6.3. 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 between 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 minimum time interval required between two measurements for determination of SD.

Note: The duration of response and stable disease as well as PFS are influenced by the frequency of follow-up after baseline evaluation. It is not within the scope of this guideline to define a standard follow-up frequency. The frequency of follow-up should take into account many factors, such as disease type and stage, treatment cycle and standard practice. However, these limitations in the accuracy of the measured endpoints should be taken into account if comparisons between trials

are needed.

4.7. PFS/TTP

4.7.1. Phase II clinical trial

This guideline focuses on the use of objective response endpoints for phase II trials. In some cases, response rate may not be optimal for evaluating the potential anticancer activity of new drugs/regimens. In these cases, PFS/PPF (Proportion progress-free) at demarcation time points can be considered as an appropriate surrogate to provide the original signal of biological activity of a new drug. However, it is clear that in an uncontrolled trial, these assessments can be called into question because an apparently valuable observation may be related to biological factors such as patient screening rather than the effect of the drug intervention. Therefore, phase II clinical trials with these as study endpoints are best designed with randomized control. However, since certain tumours behave consistently (and often consistently do not perform well), non-randomised trials are justified. However, in these cases, due to the lack of an active control, careful attention should be paid to document evidence of efficacy when assessing expected PFS or PPF.

13. Appendix II: ECOG Performance Status Scoring Criteria

Score	Activity level
0	Fully active, able to perform all normal activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities and confined to bed for no 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	Death.

14. Appendix III: New York Heart Association (NYHA) Functional Classification

Grade Symptoms of physical activity (fatigue, palpitation, asthma or angina) at rest
I Not limited Asymptomatic Not caused by general physical activity
II Mild limitation Asymptomatic daily physical activity can cause
III Significantly limited symptoms caused by lower than daily physical activity
IV Loss of Symptoms Any physical activity is increased