Protocol: DCC-2036-01-003

Official Title: An Open-Label, Multicenter, Phase 1b/2 Study of Rebastinib (DCC-2036) in Combination with Paclitaxel to Assess Safety, Tolerability, and Pharmacokinetics in Patients with Advanced or Metastatic Solid Tumors

NCT Number: NCT03601897

Approval Date: 07 FEBRUARY 2020

CLINICAL STUDY PROTOCOL
Protocol DCC-2036-01-003

An Open-Label, Multicenter, Phase 1b/2 Study of Rebastinib (DCC-2036) in Combination with Paclitaxel to Assess Safety, Tolerability, and Pharmacokinetics in Patients with Advanced or Metastatic Solid Tumors

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

Study Sponsor: Deciphera Pharmaceuticals, LLC

Headquarters:
200 Smith Street
Waltham, MA 02451
Phone: 785-830-2100
Fax: 781-701-8168

Research Facility:
643 Massachusetts St., Suite 200
Lawrence, KS 66044
Phone: 785-830-2100
Fax: 785-830-2150

IND Number: 128702

Document Version (Date): Version 1.0 (19 APR 2018)
Amendment 1 (30 MAY 2018)
Amendment 2 (7 SEP 2018)
Amendment 3 (08 JAN 2019)
Amendment 4 (20 JAN 2020)
Amendment 5 (07 FEB 2020)

SPONSOR SIGNATURE

PPD

PPD

Date

PPD

PPD

INVESTIGATOR STATEMENT

I understand that all documentation provided to me by Deciphera Pharmaceuticals, LLC or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator Brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board. No changes will be made to the study protocol without the prior written approval of Deciphera Pharmaceuticals, LLC and the Institutional Review Board, except where necessary to eliminate an immediate hazard to the patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Name	Investigator Signature	Date

Name of Investigational Site

CLINICAL STUDY SYNOPSIS

Protocol Title:	An Open-Label, Multicenter, Phase 1b/2 Study of Rebastinib (DCC-2036) in Combination with Paclitaxel to Assess Safety, Tolerability, and Pharmacokinetics in Patients with Advanced or Metastatic Solid Tumors
Protocol Number:	DCC-2036-01-003
Study Phase:	1b/2
Study Centers:	Part 1: Approximately 7 centers in the United States (US) Part 2: Approximately 20 centers in the US
Number of Patients Planned:	Part 1: Up to 36 evaluable patients to determine the recommended Phase 2 dose (RP2D) Part 2: Up to 165 evaluable patients in indication-specific cohorts
Objectives:	**Part 1:** **Primary Objectives:** • To evaluate the safety and tolerability of 50 mg and 100 mg rebastinib twice daily (BID) when administered in combination with paclitaxel. • To determine the recommended phase 2 dose (RP2D) of rebastinib in combination with paclitaxel. **Secondary Objectives:** • To assess the preliminary efficacy of rebastinib administered in combination with paclitaxel by evaluating the objective response rate (ORR). • To assess the pharmacokinetics (PK) of rebastinib and paclitaxel when administered in combination. • To evaluate efficacy measures, such as progression-free survival (PFS), clinical benefit rate (CBR), response duration, time to response, time to progression (TTP), and overall survival (OS) of rebastinib in combination with paclitaxel. **Part 2:** **Primary Objectives:** • To evaluate the safety and tolerability of rebastinib at the RP2D in combination with paclitaxel. • To evaluate the ORR as the primary efficacy measure of rebastinib in combination with paclitaxel. **Secondary Objectives:** • To assess the PK of rebastinib and paclitaxel when administered in combination.

- To evaluate efficacy measures, such as PFS, CBR, response duration, time to response, TTP, and OS of rebastinib in combination with paclitaxel.

Parts 1 and 2:

Exploratory Objectives:

- To evaluate changes in select blood and plasma biomarkers when rebastinib is administered in combination with paclitaxel.
- To evaluate changes in the tumor tissue microenvironment (e.g., changes in the composition of infiltrating mononuclear cells) when rebastinib is administered in combination with paclitaxel.
- To assess polymorphisms in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of rebastinib in combination with paclitaxel.
- Assess the effects of rebastinib administered in combination with paclitaxel using patient reported outcome (PRO) measures.

Study Design:

This is an open-label Phase 1b/2 multicenter study in patients with advanced or metastatic solid tumors where paclitaxel may be considered appropriate treatment. Rebastinib will be administered in combination with paclitaxel in repeated 28-day cycles to primarily assess the safety, tolerability and preliminary efficacy of the combination. Adverse events (AEs) will be assessed, and laboratory values, vital sign measurements, electrocardiograms (ECGs), ophthalmologic examinations, physical examinations and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) will be obtained to evaluate the safety and tolerability of rebastinib when administered in combination with paclitaxel. Pharmacokinetic (PK) and pharmacodynamic (PD) samples will be collected at pre-specified time points.

The study consists of two parts (Part 1 and Part 2). In Part 1, patients will be assigned to one of two pre-defined dose levels of rebastinib (50 or 100 mg BID) in combination with paclitaxel administered by intravenous (IV) infusion at 80 mg/m^2. Each arm is planned to enroll at least 12 evaluable patients. Additionally, if rebastinib at 100 mg BID is deemed unsafe, an additional arm dosing at 75 mg BID of rebastinib in combination with paclitaxel may be initiated. Up to 36 evaluable patients will be dosed in Part 1. Safety will be continuously monitored and any arm may be terminated early if deemed unsafe by the Sponsor.

Safety and tolerability, PK and PD, and preliminary efficacy data obtained in Part 1 will be used to determine the RP2D. Data for at least 12 evaluable patients through Cycle 1 must be available in an arm to declare the dose as the RP2D. Patients must receive ≥80% of planned doses of rebastinib and paclitaxel in Cycle 1 to be considered as evaluable. Enrollment of patients will pause for determination of the RP2D prior to initiation of Part 2. An RP2D will be chosen by the Sponsor in consultation with the Investigators.

Upon determination of the RP2D, Part 2 will be initiated to dose up to 165 evaluable patients using the RP2D across five indication-specific

	cohorts. A Simon two-stage design will be applied to Part 2 to further evaluate the safety, tolerability, and preliminary efficacy of rebastinib in combination with paclitaxel in triple-negative breast (Cohort 1), inflammatory breast (Cohort 2), ovarian (Cohort 3), endometrial (Cohort 4), and gynecological carcinosarcoma (Cohort 5) cancers. Each cohort will initially enroll up to 18 evaluable patients in the first stage. Patients must receive at least 1 dose of the combination and have 1 post-baseline assessment, or be discontinued prior to the post-baseline disease assessment due to an AE at least possibly related to rebastinib, to be considered evaluable. Tumor response will be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. The decision to enroll patients beyond the first stage will be based on response assessments obtained after the first post-dose response assessment of the last patient enrolled in the first stage of a cohort. Patients who meet criteria defined in Section 8.3 will be replaced and not be included in the responder analysis. If >4 responses (defined as partial response [PR] or complete response [CR]) are seen in a cohort, additional patients will be enrolled for a total of up to 33 patients. If ≤4 responses are seen in a cohort, the cohort will be terminated. If >4 responses are seen prior to the last evaluable patient in the first stage, expanding the cohort may be triggered earlier. Enrollment in each cohort will pause between the first and second stage of the Simon two-stage for evaluation of response.
Study Population: Inclusion Criteria	Patients must meet all of the following criteria to be eligible to enroll in the study: 1. Male or female patients ≥18 years of age at the time of informed consent. 2. Part 1, All Arms i. Histologically confirmed diagnosis of a locally advanced or metastatic solid tumor for which paclitaxel is considered appropriate treatment. ii. Patients who have progressed despite standard therapies, or for whom conventional therapy is not considered effective or tolerable, as judged appropriate by the investigator. 3. Part 2 A. Part 2, Cohort 1: Triple-Negative Breast Cancer i. Histologically confirmed metastatic triple-negative breast cancer based on the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Hammond et al, 2010). ii. Received at least one prior line but no more than three prior lines of systemic chemotherapy in the metastatic setting. iii. Has not received taxane-containing regimens within 6 months prior to the first dose of study drug.

B. Part 2, Cohort 2: Inflammatory Breast Cancer (IBC)
   i. Histologically or cytologically confirmed stage IV breast carcinoma with a previous clinical diagnosis of IBC based on the presence of inflammatory changes in the involved breast, such as diffuse erythema and/or edema (peau d'orange), with or without an underlying palpable mass, and involving the majority of the skin of the breast; pathological evidence of dermal lymphatic invasion should be noted but is not required for diagnosis.
   ii. Received at least one prior line of systemic chemotherapy in the metastatic setting.
   iii. Has not received taxane-containing regimens within 6 months prior to the first dose of study drug.

C. Part 2, Cohort 3: Ovarian Cancer
   i. Histologically confirmed, recurrent epithelial ovarian, peritoneal or fallopian tube carcinoma. Note: patients with low grade serous, mucinous or clear cell histology will be excluded.
      a. Progressed or relapsed within 6 months after the completion of a platinum-containing chemotherapy regimen.
      b. Patients that progressed during treatment or within 1 month after the completion of the first platinum-containing chemotherapy regimen (primary platinum refractory) are excluded.
   ii. Received no more than five prior lines of systemic anticancer therapy.
      a. Neoadjuvant and/or adjuvant is considered one regimen.
      b. Maintenance therapy, including poly (ADP-ribose) polymerase (PARP) inhibitors, is considered part of the preceding regimen.
      c. Hormonal therapy is not considered a prior systemic regimen.
   iii. Must have received prior treatment with a PARP inhibitor if patients have a BRCA1 or 2 germline or somatic mutation(s). Patients who have refused therapy with a PARP inhibitor may be considered for enrollment, following consultation with the Sponsor.

D. Part 2, Cohort 4: Endometrial Cancer
   i. Histologically confirmed adenocarcinoma of the endometrium.
   ii. Received at least one prior line of platinum-based therapy in the recurrent, metastatic, or high-risk disease setting.

a. For patients with known microsatellite instability-high (MSI-H) or mismatch repair deficiency, progressed after a regimen including an anti-PD1 agent.

E. Part 2, Cohort 5: Gynecological Carcinosarcoma

i. Histologically confirmed advanced (stage III or IV), persistent or recurrent gynecological carcinosarcoma.

a. Homologous or heterologous type carcinosarcoma (malignant mixed Müllerian tumor [MMMT]) are allowed.

ii. Must have received at least 1 prior chemotherapy regimen (including high-dose, consolidation, or extended therapy after surgical or nonsurgical assessment for gynecological carcinosarcoma).

4. At least one measurable lesion according to RECIST Version 1.1.
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2.
6. Able to provide a tumor tissue sample; if an archival tumor tissue sample is unavailable, a fresh tumor biopsy is required prior to the first dose of study drug, only if tumor biopsy is safe and accessible as judged by the Investigator.
7. Adequate organ function and bone marrow reserve as indicated by the following laboratory assessments performed within 14 days prior to the first dose of study drug:
   i. Bone marrow function: Absolute Neutrophil Count (ANC) ≥1500/µL; hemoglobin ≥9 g/dL; platelet count ≥100,000/µL.
   ii. Hepatic function: total bilirubin ≤1.5 × the upper limit of normal (ULN) or <3× ULN for Gilbert's syndrome; aspartate transaminase (AST)/alanine transaminase (ALT) ≤2.5×ULN (≤5×ULN in the presence of hepatic metastases).
   iii. Renal function: serum creatinine ≤1.5×ULN or creatinine clearance ≥30 mL/min based either on urine collection or Cockcroft Gault estimation.
   iv. Coagulation profile: prothrombin time adjusted for the international normalized ratio (PT-INR) and partial thromboplastin time (PTT) ≤1.5×ULN. Patients on a stable, maintenance regimen of anticoagulant therapy for at least 30 days prior to study drug administration may have PT-INR measurements >1.5×ULN if, in the opinion of the Investigator, the patient is suitable for the study. An adequate rationale must be provided to the Sponsor prior to enrollment.
8. If a female of childbearing potential, must have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening and agree to use two methods of contraception with, one

of them being highly effective, prior to the first dose of study drug and for at least 120 days following the last dose of study drug as outlined in Section 6.8.9.

9. If male, must agree to use two methods of contraception, with one of them being highly effective, and refrain from sperm donation prior to the first dose of study drug through 120 days following the last dose of study drug as outlined in Section 6.8.9.
10. Patient must provide signed consent to participate in the study and is willing to comply with study-specific procedures.

Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Received prior anticancer or other investigational therapy within 28 days or 5× the half-life (whichever is shorter) prior to the first dose of study drug. See Section 5.11.6 for further details.
2. Not recovered from all toxicities from prior therapy to Grade ≤1 (or baseline) within 1 week prior to first dose of study drug (excluding alopecia and ≤ Grade 3 clinically asymptomatic alkaline phosphatase).
3. Peripheral neuropathy of any etiology > Grade 1.
4. Patients with a prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of this clinical trial.
5. Known active central nervous system (CNS) metastases defined as:
    i. Unstable (i.e., evidence of progression by magnetic resonance imaging [MRI]) within 4 weeks prior to the first dose of study drug.
    ii. Neurologic symptoms within 2 weeks prior to the first dose of study drug and required use of enzyme-inducing antiepileptic drugs.
    iii. Patients who require steroids must be on a stable dose for 2 weeks prior to the first dose of study drug.
6. Use of systemic corticosteroids within 7 days prior to the first dose of study treatment or an existing condition that requires the concomitant use during the course of the study, unless the dose is no more than the equivalent of prednisone 15 mg/day. See Section 5.11.6 for further details.
7. Known retinal neovascularization, macular edema or macular degeneration.
8. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, history of class III or IV congestive heart failure according to New York Heart Association classification, unstable angina or poorly controlled arrhythmia as determined by the Investigator, or myocardial infarction within 6 months prior to the first dose of study drug.

9. QT interval corrected for heart rate at screening using Fridericia's formula (QTcF) >450 ms in males or >470 ms in females or history of QT interval corrected for heart rate (QTc) prolongation.
10. Left ventricular ejection fraction (LVEF) <50% at screening.
11. Arterial thrombotic or embolic events such as cerebrovascular accident (including ischemic attacks) or moderate hemoptysis within 6 months prior to the first dose of study drug.
12. Venous thrombotic event (e.g., deep vein thrombosis) within the 3 months prior to the first dose of study drug; following a venous thrombotic event of ≥3 months prior to the first dose of study drug, must be on a stable dose of anticoagulation therapy, if clinically indicated.
13. Active infection ≥ Grade 3 requiring IV anti-infective treatment within 7 days prior to the first dose of study drug.
14. Known human immunodeficiency virus or hepatitis C infection only if the patient is taking medications that are excluded per protocol, active hepatitis B, or active hepatitis C infection.
15. Use of proton pump inhibitors (PPI) within 4 days prior to the first dose of study drug or an existing condition that requires the concomitant use of a proton pump inhibitor during the course of the study.
16. If female, the patient is pregnant or lactating.
17. Major surgery 4 weeks prior to the first dose of study drug; following major surgeries >4 weeks prior to the first dose of study drug, all surgical wounds must be healed and free of infection or dehiscence.
18. Manifestation of malabsorption due to prior gastrointestinal surgery, disease or other illness which could affect oral absorption as judged by Investigator and Sponsor.
19. Known allergy or hypersensitivity to any component of rebastinib or any of its excipients.
20. Any other clinically significant comorbidities, such as uncontrolled pulmonary disease, active infection, or any other condition which, in the judgment of the Investigator, could compromise compliance with the protocol, interfere with the interpretation of study results, or predispose the patient to safety risks.

Study Drug, Formulation, Dose and Route of Administration:	Rebastinib will be administered in combination with paclitaxel. Rebastinib will be supplied by the Sponsor as 25 mg and 75 mg formulated tablets for oral administration. Paclitaxel will be supplied by the Sponsor. Patients will each receive an oral dose of rebastinib at 50 mg or 100 mg BID in 28-day cycles. In Part 1, if rebastinib at 100 mg BID is not tolerated, an additional arm dosing at 75 mg BID may be evaluated. In Part 2, rebastinib will be administered at the RP2D in combination with paclitaxel. Paclitaxel will be administered by IV infusion at 80 mg/m^2 over approximately 60 minutes on Day 1, Day 8 and Day 15 of repeated 28-day cycles (see Section 5.2.2). All paclitaxel infusions will be administered at the study site. Rebastinib will be administered orally first, followed by paclitaxel IV infusion. Patients should be pre-medicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions per institutional practices. If the retreatment criteria as outlined in Section 5.2.2 are not met and a dose of paclitaxel is missed, a single make-up dose of paclitaxel may be administered on Day 22 of a given cycle as long as the retreatment criteria are met. Assessments required on Day 8 of the corresponding cycle must be performed. For patients that are unable to tolerate paclitaxel, rebastinib may be administered as a single agent starting in Cycle 2.
Study Endpoints:	**Parts 1 and 2 Endpoints:** **Safety:** • Overall AEs • Serious adverse events (SAEs) • Adverse events of special interest (AESIs) • Dose reduction, dose interruptions, or discontinuation of study drug due to toxicity • Physical examinations • ECOG PS • Ophthalmic examinations • Changes from baseline in laboratory parameters • Electrocardiogram (ECGs) • Echocardiograms or multigated acquisition (MUGAs) • Vital signs **Pharmacokinetics:** Pharmacokinetic (PK) endpoints when rebastinib is administered in combination with paclitaxel and as a single agent include, but are not limited to: • Time to maximum observed concentration (T_{max}: rebastinib only)

- Time to maximum observed concentration at steady state ($T_{max,ss}$: rebastinib only)
- Maximum observed concentration (C_{max})
- Maximum observed concentration at steady state ($C_{max,ss}$)
- Concentration observed at the end of the dosing interval (C_{min}, trough concentration)
- Concentration observed at the end of the dosing interval at steady state ($C_{min,ss}$)
- Area under the concentration-time curve (AUC)
- Half-life ($T_{1/2}$)
- Volume of distribution (Vd)
- Clearance (CL)

Efficacy Endpoints:

Radiographic tumor assessments (computed tomography [CT] or MRI) will be performed by RECIST Version 1.1. Patients with ovarian cancer will be assessed using both RECIST Version 1.1 and Gynecologic Cancer Intergroup [GCIG] Cancer Antigen 125 [CA-125] criteria). The endpoints for preliminary assessment of antitumor activity include:

- Objective response rate (CR + PR) of the combination therapy.
- Clinical benefit rate (CBR) (CBR = CR + PR + stable disease [SD]) at 8, 16, and 28 weeks of the combination therapy.
- Time to response (defined as time from Cycle 1 Day 1 to PR or CR).
- Progression-free-survival (PFS; defined as time from Cycle 1 Day 1 to disease progression or death due to any cause).
- Time to progression (TTP; defined as time from Cycle 1 Day 1 to the first documentation of progressive disease).
- Duration of response (DOR; time from first PR/CR to disease progression or death due to any cause).
- Overall survival (OS).

Pharmacogenomics:

The pharmacogenomics endpoints of the study include, but are not limited to:

- Assessment of polymorphic variations in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of rebastinib
- Assessment of polymorphisms in genes that may be associated with clinical response and/or study drug-related toxicity.

Pharmacodynamics:

The pharmacodynamic endpoints of the study include, but are not limited to:

- Assess changes of plasma chemokines/cytokines upon treatment.
- Assess changes in monocyte population in peripheral blood.
- Evaluate changes in tumor microenvironment, including but not limited to tumor associated macrophage, tumor infiltrating lymphocytes using immunohistochemical (IHC), *in situ* hybridization (ISH) or other fit-for-purpose assays.

Patient Reported Outcomes:

- Assess the safety profile of rebastinib in combination with paclitaxel using the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (NCI-PRO-CTCAE), a "treatment-bother" question (GP5) from Functional Assessment of Chronic Illness Therapy's (FACIT), Functional Assessment of Cancer Therapy - General (FACT-G), as well as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC-QLQ-C30).

Statistical Considerations:

General

Descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) will be used to describe continuous variables. Categorical variables will be summarized using frequency distributions and percentages. Data may be displayed by each of the Part 1 arms and Part 2 indication-specific cohorts.

This is a Phase 1b/2 study. Time-to-event data will be summarized via Kaplan-Meier (KM) using medians with associated 2-sided 90% confidence intervals (CIs). Proportions, when appropriate, will be reported with exact 2-sided 90% confidence intervals.

Analysis Populations

Safety Population: All patients who are exposed to any amount of either study drug. This population will be used for analysis of safety data.

Modified Intent-to-Treat Population (mITT): All patients who had at least one full dose of the combined study drugs, had measurable disease at baseline, and had at least one post-baseline assessment unless the patient discontinued prior to the post-baseline disease assessment due to an AE at least possibly related to rebastinib or due to clinical progression. This population will be used for analysis of efficacy data.

PK Population: The PK population will include all patients who received at least one dose of either study drug and had at least one measurable

concentration in plasma for either study drug. Additionally, this population will be used for analysis of PD data, if post-dose PD data is available.

Analysis of Efficacy Endpoints

The point estimate and 2-sided 90% exact CIs will be presented for all the response endpoints and by the arm or indication-specific cohort. For time-to-event endpoints, Kaplan-Meier method will be used. Point estimates and 90% CIs will be presented.

ORR (defined as CR+PR) is the primary efficacy endpoint of Part 2 and a secondary endpoint of Part 1. The secondary endpoints of both parts include CBR, time to response, PFS, TTP, DOR, and OS. All response endpoints will be defined based on RECIST Version 1.1.

Sample Size Justification

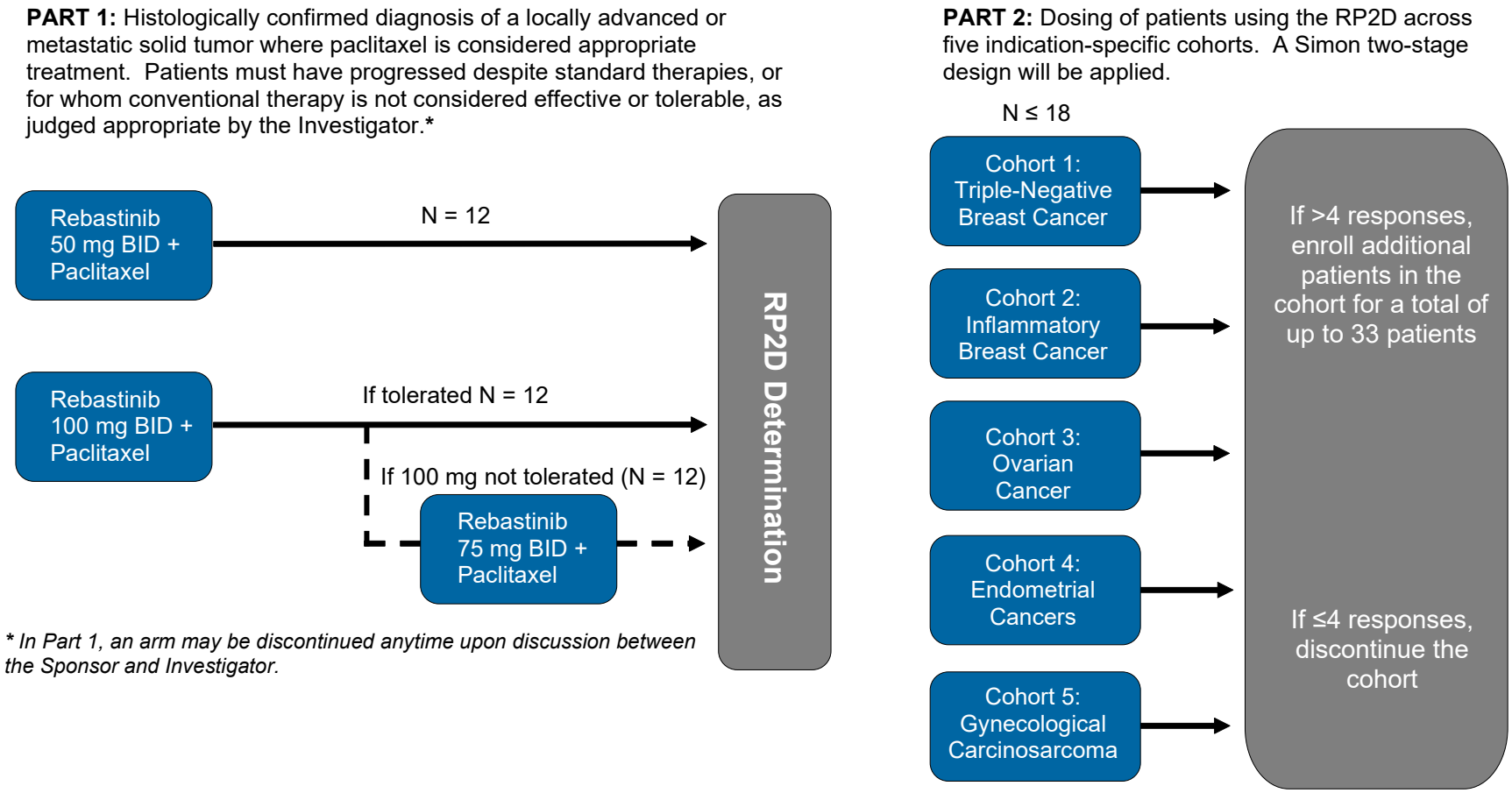
Part 1: Part 1 will primarily be used to evaluate the safety and tolerability of the combination. At least 12 evaluable patients will be enrolled in each arm, which is considered appropriate for analysis of safety and tolerability to determine the RP2D.

Part 2: A Simon two-stage design will apply to Part 2 of the study. The number of patients required for each cohort was calculated to demonstrate 20% improvement in ORR (from 20% historical ORR in the setting to 40% for the combination) under 80% power and one-sided alpha of 0.05. In the initial stage, up to 18 patients will be evaluated. Greater than 4 responses will be required to enroll additional patients in order to demonstrate the target efficacy of >10 responses in a total of 33 patients. Thus, this part of study may enroll up to 165 (33 patients per indication-specific cohort) evaluable patients. If a non-evaluable rate of 10% is considered, approximately 183 patients may be enrolled.

Duration of Study: Patients will receive study treatment until they develop progressive disease, experience unacceptable toxicity, or withdraw consent.

Patients will be eligible to receive study treatment for as long as the Investigator and the Sponsor agree that the patient is showing clinical benefit and for as long as rebastinib is being developed to support the indication and continuation of treatment does not conflict with the Sponsor's right to terminate the study. The study will end following the last patient's last visit.

Figure 1: Study Schema



BID = twice daily; RP2D = recommended Phase 2 dose.

Table 1: Schedule of Assessments

Assessments / Procedures[a]	Screening[c]	Cycle 1			Cycles ≥2			EOT Visit[f]	30 Day Safety Follow-up[f]
Cycle Day	**-28 to -1**	**1** (Baseline)	**8** (±2 days)	**15** (±2 days)	**1** (±2 days)	**8[e]** (±2 days)	**15[e]** (±2 days)	**1** (+7 days)	**1** (+7 days)
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical and Cancer History	X								
Prior Medications/Procedures[g]	X								
Pregnancy Test[h]	X	X			X			X	
Hematology[b]	X[c]	X[d]	X	X	X	X	X	X	
Serum Chemistries[b]	X[c]	X[d]	X	X	X	X	X	X	
Coagulation[i]	X[c]	X[d]			X			X	
Urinalysis[j]	X[c]	X[d]			X			X	
Physical Examination[k]	X	Examinations will be driven by clinical findings and/or patient complaints						X	
ECOG PS	X	X	X	X	X			X	
Vital Signs and Weight[l]	X	X	X	X	X	X	X	X	
Height	X								
12-lead ECG[m]	X	X		X	X			X	
Echocardiogram/MUGA[n]	X				X[n]			X	
Ophthalmologic Examination[0]	X				X			X	
Adverse Event Reporting	Continuous from signing informed consent through 30 Day Safety Follow-up								
Concomitant Medications/ Procedures	Continuous from signing informed consent through 30 Day Safety Follow-up								
NCI-PRO-CTCAE[p]		X	X	X	X		X	X	
EORTC-QLQ-C30[p]		X	X	X	X		X	X	
GP-5 from FACT-G[p]		X	X	X	X		X	X	
Dosing of Rebastinib[q]		Continuous from Cycle 1 Day 1 (Baseline) through end of treatment							
Dosing of Paclitaxel[r]		X[r]	X	X[r]	X	X	X		
Radiologic Imaging[s]	X				X[s]			X	
Tumor Markers[t]	X[c]	X			X			X	
PK Sampling[u, v]		X		X	X			X	

Assessments / Procedures[a]	Screening[c]	Cycle 1			Cycles ≥2			EOT Visit[f]	30 Day Safety Follow-up[f]
Cycle Day	**-28 to -1**	**1** (Baseline)	**8** (±2 days)	**15** (±2 days)	**1** (±2 days)	**8**[e] (±2 days)	**15**[e] (±2 days)	**1** (+7 days)	**1** (+7 days)
Archived Tissue Sample[w]	X								
Fresh Tumor Biopsy[x]	X[x]				X[x]			X	
Pharmacogenomics		X							
Whole Blood Immunophenotyping Biomarker Samples[y]		X		X	X[y]			X	
Plasma Biomarker Samples[y]		X		X	X[y]			X	

AE = adverse event; BID = twice daily; CA-125 = cancer antigen 125; CNS = central nervous system; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = End of Treatment; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NCI-PRO-CTCAE = National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors.

a. Additional unscheduled safety or efficacy assessments may be performed at any time as clinically indicated to determine the relevance of specific findings and/or the duration of AEs.

b. Hematology and serum chemistries may be performed up to 3 days prior to the corresponding study visit.

c. Screening must occur within 28 days prior to the first dose of study drug. Screening samples for hematology, serum chemistries, coagulation, urinalysis, and tumor markers, if applicable, must be drawn within 14 days prior to the first dose of study drug. Standard procedures performed as part of the practice of medicine prior to consent (e.g., imaging, physical exam) may be used to determine eligibility if completed within 28 days prior to the initial dose of study drug (see Sections 6.1 and 6.8).

d. If the screening clinical laboratory testing and ECOG PS were performed within 3 days before the Cycle 1 Day 1 dose, the assessments need not be repeated on Cycle 1 Day 1. Similarly, if clinical laboratory testing and ECOG was performed within 3 days prior to the start of a new cycle, then the testing need not be repeated on Day 1

e. For patients that are unable to tolerate paclitaxel, rebastinib may be administered as a single agent starting in Cycle 2. If paclitaxel is discontinued, visits on Day 8 and Day 15 are not required in Cycle 2 and beyond.

f. The EOT Visit should be performed within 7 days after a patient's last dose of study drug. Patients should be contacted between 30 and 37 days after the last dose of study drug, or prior to initiation of new anticancer therapy, to collect new information pertaining to AEs and concomitant medications/procedures. These assessments can be performed over the phone.

g. Any medication or non-drug therapy or procedure taken or performed within 30 days prior to screening and before the first dose of study drug.

h. A serum pregnancy test will be performed at screening for female patients of childbearing potential (see Section 6.8.8). A negative result must be documented within 3 days prior to the first dose of study drug; results from screening tests performed within this timeframe may be used in lieu of a Cycle 1 Day 1 (Baseline) result. In addition, a urine or serum pregnancy test will be performed pre-dose on Day 1 of every cycle and at the EOT Visit. Patients must be counseled to inform the Investigator of any pregnancy that occurs during study treatment and for 120 days after the last dose of the study drug.

i. Coagulation testing will be performed on Day 1 of each cycle and at the time of a tumor biopsy.

j. If urinalysis testing is abnormal, a microscopic analysis will be performed.

k. A full physical examination will be performed at screening and the EOT Visit. At all other visits, examinations will be driven by clinical findings and/or patient complaints. If the patient reports a complaint or a possible AE, a targeted physical examination may be conducted at the Investigator's discretion. After consent, any clinically significant abnormal findings in physical examinations must be reported as AEs (see Sections 6.8.1 and 7).

l. Vital sign measurements will be collected after the patient has been at rest (seated or supine position) for at least 5 minutes. Measurements will include sitting blood pressure, heart rate, respiratory rate, and temperature. On days when PK sampling is performed, vital sign measurements should be obtained as indicated in Table 2 and Table 3. In addition, weight will be obtained at each study visit.

m. 12-lead ECGs will be performed with central over-reading after the patient has been at rest (supine or semi-recumbent position) for at least 5 minutes (see Section 6.8.4).

n. An echocardiogram or multigated acquisition (MUGA) scan will be performed during screening, Day 1 of Cycles 2, 3, 6, every third cycle thereafter (i.e., Day 1 of Cycles 9, 12, 15, etc.), and at the EOT Visit. The same modality (echocardiogram or MUGA scan) used during screening should be used for all subsequent assessments (see Section 6.8.5). Assessments may be performed up to 7 days prior to the corresponding study visit or post-dose at the corresponding study visit. Additionally, an assessment done within 14 days prior to the last dose of study drug can be used in lieu of an EOT assessment. A MUGA scan should not be performed on the same day as the draw of the PK sample. If a MUGA scan is chosen, it must be performed at least 24 hours before the corresponding PK sample.

o. Ophthalmologic examinations will be performed during screening, Day 1 (±7 days) of every third cycle thereafter (i.e., Cycles 3, 6, 9, etc.), and EOT Visit (±7 days). This examination does not have to be repeated during screening if there is documentation of an examination that met protocol criteria within 60 days prior to the first dose of study drug and after the last dose of previous anticancer treatment. Additionally, an examination done within 30 days prior to the last dose of study drug can be used in lieu of an EOT exam (see Section 6.8.6).

p. The NCI-PRO-CTCAE (Part 1 and 2), EORTC-QLQ-C30 (Part 2 only) and GP5 from FACT-G (Part 2 only) questionnaires should be completed prior to any other study assessments when possible (see Sections 6.13.1, 6.13.2, and 6.13.3). Only English-speaking patients will complete the questionnaires. Patient entered data will not be modified by the Investigator or site staff, ePRO vendor, CRO, or Sponsor.

q. Rebastinib will be administered orally per assigned dose level (either 50 mg BID, 100 mg BID, or 75 mg BID) in 28-day cycles. On days of planned study visits, patients will take the study drug at the study site after pre-dose assessments are completed and prior to the paclitaxel infusion.

r. Paclitaxel will be administered on Day 1, Day 8 and Day 15 of repeated 28-day cycles. Rebastinib will be administered orally prior to the paclitaxel infusion. All paclitaxel infusions may be administered ±2 days to the corresponding study visit however each infusion much be at least 5 days apart. All paclitaxel infusions will be administered at the study site. If the retreatment criteria are not met and a dose of paclitaxel is missed, a single make-up dose of paclitaxel may be administered on Day 22. Assessments required on Day 8 of the corresponding cycle must be performed (see Section 5.2.2).

s. CT or MRI scans of the pelvis, abdomen, and chest will be performed at screening. Subsequent scans will be performed on Day 1 of Cycles 3, 5, every 3 cycles thereafter (i.e., Day 1 of Cycles 8, 11, etc.), and at the EOT Visit. Imaging may be performed up to 7 days prior to the corresponding study visit. EOT imaging will only be performed on patients if imaging was not performed within the previous 12 weeks. Determination of objective tumor response will be performed by the Investigator according to the RECIST Version 1.1. Assessments should be completed regardless of dosing delays or additional unscheduled imaging assessments. An MRI of the brain will be performed at screening and subsequent imaging time points if CNS metastases are present at screening or signs and symptoms suggests CNS metastases. MRI or CT scans without contrast can be used for patients who are allergic to radiographic contrast media. Throughout the study, the same assessment technique must be used (see Section 6.10.1).

t. CA-125 should be measured for ovarian cancer patients at screening and Day 1 of each cycle or approximately at the same time they undergo radiologic assessment. Ovarian cancer patients experiencing CA-125 response must have a confirmatory test performed at least 28 days after the initial response is documented. For other disease indications, results of tumor marker(s) performed based on standard of cares will be collected.

u. PK sampling will be performed as described in Table 2 and Table 3. An unscheduled PK sample may be taken at the time of the onset of a new suspected, treatment-related adverse event.

v. On serial PK sampling days (i.e., Cycle 1 Day 1 and Cycle 1 Day 15), paclitaxel will be administered following the completion of the required PK sampling as indicated in Table 2 and Table 3. If the associated paclitaxel infusion cannot be administered at the study visit (e.g., due to scheduling conflicts), it may be performed on the following day (i.e., Day 2, Day 16). Pre-infusion and end-of-infusion ECGs, vitals and PK samples would be required.

w. Tumor tissue samples will be collected for all patients enrolled onto the study. If an archived tumor tissue sample is unavailable, a fresh tumor biopsy is required prior to the first dose of study drug.

x. A fresh tumor biopsy will be collected at screening (if archival tumor tissue is unavailable) and Cycle 3 Day 1 (±7 days). An optional tumor biopsy may be performed upon progression if a patient responded to treatment (CR/PR) and then progressed, and has provided consent for undergoing tumor biopsy. Fresh biopsies will be performed for patients whose tumor is safe and accessible and should only be collected if a patient qualifies for the study based on all other entry criteria. Aspiration cytology samples, such as fine-needle aspirates, are not acceptable.

y. Whole Blood Immunophenotyping Biomarker and Plasma samples will be collected pre-dose at Cycle 1 Day 1 (Baseline), Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1 and every three cycles thereafter (i.e., Cycle 6, 9, 12, etc.), and at the EOT Visit. Details on sample collection, processing, and shipping of the samples, including any exceptions, will be provided in a separate Laboratory Manual.

Table 2: Schedule of Electrocardiograms, Vitals and Pharmacokinetic Sampling (Part 1)

Study Visit[a]	Cycle 1, Day 1 (Baseline)			Cycle 1, Day 15			≥Cycle 2, Day 1			EOT Visit		
Time Point (hours)	**ECG[b]**	**Vitals[b]**	**PK**	**ECG[b]**	**Vitals[b]**	**PK[d]**	**ECG[b]**	**Vitals[b]**	**PK[d]**	**ECG[b]**	**Vitals[b]**	**PK[d]**
Pre-rebastinib dose[c]	X	X		X	X	X	X	X	X	X	X	X
1 hour post-rebastinib dose (± 10 min)	X	X	X	X	X	X						
2 hours post-rebastinib dose (± 10 min)			X			X						
4 hours post-rebastinib dose (± 30 min)			X			X						
6 hours post-rebastinib dose (± 30 min)	X	X	X	X	X	X						
Pre-paclitaxel infusion (within 10 minutes of start)			X			X						
End of paclitaxel infusion (within 10 minutes of end)	X	X	X	X	X	X						

AE = adverse event; ECG = electrocardiogram; min = minute; PK = pharmacokinetic.

a. If PK sampling cannot be performed at a study visit (e.g., due to scheduling conflicts, AE, etc.), it may be performed on another study day, provided that the patient, Investigator, and Sponsor are in agreement. Additionally, if the associated paclitaxel infusion cannot be administered at the study visit (e.g., due to scheduling conflicts), it may be performed on the following day. Pre-infusion and end-of-infusion ECGs, vitals and PK samples would be required.

b. ECG and vital sign assessments will be completed before the collection of the corresponding PK sample.

c. Pre-dose assessments should be obtained within 60 minutes prior to rebastinib administration.

d. An unscheduled PK sample may be taken at the time of the onset of a new suspected, treatment-related AE.

Table 3: Schedule of Electrocardiograms, Vitals and Pharmacokinetic Sampling (Part 2)

Study Visit[a]	Cycle 1, Day 1 (Baseline)			Cycle 1, Day 15			≥Cycle 2, Day 1			EOT Visit		
Time Point (hours)	**ECG[b]**	**Vitals[b]**	**PK**	**ECG[b]**	**Vitals[b]**	**PK[d]**	**ECG[b]**	**Vitals[b]**	**PK[d]**	**ECG[b]**	**Vitals[b]**	**PK[d]**
Pre-rebastinib dose[c]	X	X		X	X	X	X	X	X	X	X	X
Pre-paclitaxel infusion (within 10 minutes prior to start)[e]			X			X						
End of paclitaxel infusion (within 10 minutes after the end)[e]	X	X	X	X	X	X						

AE = adverse event; ECG = electrocardiogram; min = minute; PK = pharmacokinetic.

a. If PK sampling cannot be performed at a study visit (e.g., due to scheduling conflicts, AE, etc.), it may be performed on another study day, provided that the patient, Investigator, and Sponsor are in agreement. Additionally, if the associated paclitaxel infusion cannot be administered at the study visit (e.g. due to scheduling conflicts), it may be performed on the following day. Pre-infusion and end-of-infusion ECGs, vitals and PK samples would be required.

b. ECG and vital sign assessments will be completed before the collection of the corresponding PK sample.

c. Pre-dose assessments should be obtained within 60 minutes prior to rebastinib administration.

d. An unscheduled PK sample may be taken at the time of the onset of a new suspected, treatment-related AE.

e. A PK sample should be obtained within 10 minutes prior to the start and after the end-of-infusion.

LIST OF ABBREVIATIONS

Abbreviation	Definition
β-hCG	Beta-human chorionic gonadotropin
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ANG	Angiopoietin
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
AUC_{0-4h}	AUC from 0 to 4 hours
BID	Twice daily
CA	Cancer antigen
CA-125	Cancer antigen-125
CAP	College of American Pathologists
CBR	Clinical benefit rate
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CMC	Carboxymethylcellulose
C_{min}	Minimum plasma concentration
$C_{min,ss}$	Minimum plasma concentration at steady state
CML	Chronic myeloid leukemia
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTC	Circulating tumor cells
CYP	Cytochrome P450
DFS	Disease-free survival
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status

Abbreviation	Definition
eCRF	Electronic case report form
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30 item
EOT	End of Treatment
FACIT	Functional Assessment of Chronic Illness Therapies
FACT-G	Functional Assessment of Cancer Therapy - General
FDA	Food and Drug Administration
FIH	First-in-human
FLT3	FMS-related tyrosine kinase 3 ligand
FSH	Follicle-stimulating hormone
GCIG	Gynecological Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	Granulocyte macrophage-colony stimulating factor
HER2	Human epidermal growth factor receptor 2
hERG	Human ether-à-go-go related gene
Hgb	Hemoglobin
HPLC/MS	High performance liquid chromatography/mass spectrometry
HR	Hazard ratio
IB	Investigator's Brochure
IBC	Inflammatory breast cancer
IEC	Independent Ethics Committee
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemical
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
ISH	*In situ* hybridization
ITD	Internal tandem duplication
IV	Intravenous
KM	Kaplan-Meier
LVEF	Left ventricular ejection fraction

Abbreviation	Definition
MDR1	Multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
MMMT	Malignant mixed Müllerian tumor
mPFS	Median progression free survival
MTD	Maximum-tolerated dose
MRI	Magnetic resonance imaging
MSI-H	Microsatellite Instability - High
MUGA	Multigated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-PRO-CTCAE	National Cancer Institute Patient Reported Outcomes Common Toxicity Criteria for Adverse Events
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PD	Pharmacodynamics
PFI	Platinum-free interval
PFS	Progression-free survival
P-gp	P-glycoprotein
Ph+	Philadelphia chromosome positive
PIC	Powder-in-capsule
PK	Pharmacokinetic
PO	Orally
PPI	Proton pump inhibitors
PR	Partial response
PRO	Patient reported outcome
PT-INR	Prothrombin time adjusted for the international normalized ratio
PTT	Partial thromboplastin time
PyMT	Polyoma middle T antigen
QD	Once daily
QOL	Quality of life
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SD	Stable disease
SOP	Standard operating procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction
$T_{1/2}$	Half-life
T315I	Threonine 315 to isoleucine
TAMs	Tumor-associated macrophages
TEAE	Treatment-emergent adverse event
TEMs	TIE2-expressing macrophages
TIE2	Tunica internal endothelial cell kinase 2
TKI	Tyrosine kinase inhibitor
T_{max}	Time to maximum plasma concentration
$T_{max,ss}$	Time to maximum plasma concentration at steady state
TMEM	Tumor microenvironment of metastasis
TTP	Time to progression
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
Vd	Volume of distribution
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WCT PVG	Worldwide Clinical Trials Pharmacovigilance

TABLE OF CONTENTS

LIST OF TABLES IN THE TEXT

LIST OF FIGURES IN THE TEXT

1. INTRODUCTION AND RATIONALE

1.1. Introduction

The angiopoietin (ANG)/tunica internal endothelial cell kinase 2 (TIE2) kinase signaling pathway is a pivotal angiogenic signaling axis in endothelial cells. TIE2 is also expressed on a subset of macrophages (i.e., TIE2-expressing macrophages [TEMs]) which not only promote cancer growth, cancer cell survival, and motility, but also can limit the efficacy of the tumor response to chemotherapy or radiotherapy. In particular, TEMs are known to be proangiogenic, prometastatic, and immunosuppressive in the tumor microenvironment (Coffelt et al, 2011; Condeelis et al, 2006; De Palma et al, 2005; Harney et al, 2015; Ibberson et al, 2013; Mazzieri et al, 2011; Robinson et al, 2009; Rohan et al, 2014; Wyckoff et al, 2007). Since TIE2 expression is restricted to endothelial cells and highly protumoral TEMs, TIE2 is an attractive target for interrupting tumor cell/microenvironment interactions (Hanahan et al, 2012; Lewis et al, 2011). Regarding its role in tumor angiogenesis, TIE2 signaling is necessary for upregulation and function of protumoral TEMs that mediate angiogenesis in breast cancer and pancreatic islet tumors syngeneic mouse models, and adaptive or evasive revascularization in pancreatic neuroendocrine cancer treated with anti-vascular endothelial growth factor (VEGF) therapy (Mazzieri et al, 2011; Rigamonti et al, 2014). Proangiogenic TEMs have also been shown to limit therapeutic effectiveness of vascular disrupting agents (Rigamonti et al, 2014; Welford et al, 2011).

It has been demonstrated that TEMs mediate invasion and metastasis in the polyoma middle T antigen syngeneic breast cancer model (PyMT) (Mazzieri et al, 2011), and that TIE2 expression correlates with poor overall survival (OS) and a high risk of metastasis in breast cancer patients (Rohan et al, 2014). Perivascular TEMs assemble into special structures with endothelial and tumor cells termed tumor microenvironment of metastasis (TMEM) to promote tumor cell intravasation into the blood stream, leading to circulating tumor cells (CTCs) and systemic dissemination and metastasis (Harney et al, 2015; Robinson et al, 2009). Moreover, chemotherapy increases the density and activity of TMEM sites and promotes distant metastasis in the PyMT and patient-derived xenografts (Karagiannis et al, 2017). Chemotherapy-induced TMEM activity and cancer cell dissemination were reversed by administration of the TIE2 inhibitor rebastinib. Analysis of clinical breast cancer specimens obtained from neoadjuvant treatment with paclitaxel, doxorubicin, or cyclophosphamide shows that TMEM density increased by treatment (Welford et al, 2011). Taken together, inhibition of TMEM function may improve clinical benefits of chemotherapy in the neoadjuvant setting or in metastatic disease.

1.2. Clinical Indications

In this study, rebastinib will be evaluated for the treatment of patients with advanced or metastatic solid tumors in combination with paclitaxel. In Part 1, patients with histologically confirmed, locally advanced or metastatic solid tumor where paclitaxel may be considered appropriate treatment, and which is refractory to standard therapies such as breast, ovarian, endometrial, non-small cell lung, and pancreatic cancer will be enrolled. In Part 2, five indication-specific cohorts in triple-negative breast, inflammatory breast, ovarian, and endometrial cancers, as well as gynecological carcinosarcoma will be open once the recommended Phase 2 dose (RP2D) of rebastinib in combination with weekly paclitaxel is

established. Although the aforementioned role of TEMs in tumor growth and metastasis has been demonstrated in models of breast cancer and pancreatic neuroendocrine tumor, the role of TEMs and the effect of rebastinib are considered as indication-independent. Diseases to be evaluated in Part 2 have been selected mainly based on use of paclitaxel and treatment options available currently.

1.2.1. Breast Cancer

Paclitaxel is commonly used in combination or as single agent in the neoadjuvant, adjuvant, and metastatic setting for treatment of breast cancer patients. Approved dosages and administration are 175 or 135 mg/m^2 given every 3 weeks. However, weekly administration at lower doses has been tested and demonstrated better efficacy and/or safety. Several Phase 2 studies in metastatic breast cancer have shown that weekly paclitaxel produced significant response rates (Gori et al, 2002; Green et al, 2005; Lombardi et al, 2004; Sato et al, 2003; Seidman et al, 1998). The largest of these reported a 21.5% response rate and a 41.8% overall clinical benefit (Perez et al, 2001). Studies in early breast cancer have also demonstrated the superiority of weekly paclitaxel compared to administration every 3 weeks. In the adjuvant setting, a Phase 3 study of 4950 patients with node-positive or high-risk node-negative breast cancer after adjuvant therapy with doxorubicin-cyclophosphamide then randomized to either paclitaxel or docetaxel given weekly or every 3 weeks was conducted. This Intergroup E-1199 Investigators showed disease-free survival (DFS) significantly improved and OS marginally improved only for the weekly paclitaxel (hazard ratio [HR] = 0.84; p-value = 0.011 and HR = 0.87; p-value = 0.09, respectively) and every-3-week docetaxel arms (HR = 0.79; p-value = 0.001 and HR, 0.86; p-value = 0.054, respectively). Weekly paclitaxel improved DFS and OS (HR = 0.69; p-value = 0.010 and HR = 0.69; p-value = 0.019, respectively) in triple-negative breast cancer (Sparano et al, 2015). In patients with metastatic breast cancer, Seidman and the Cancer and Leukemia Group B of 9840 Investigators, showed that weekly paclitaxel was superior to paclitaxel given every 3 weeks for the treatment of metastatic breast cancer. In fact, weekly paclitaxel doubled the time to progression and increased the response rate from 29% to 42% compared to paclitaxel given every 3 weeks without affecting patients' quality of life (QOL) (Seidman et al, 2008). Taken together, these results suggest that weekly paclitaxel is the optimal way of treating breast cancer patients in a variety of settings.

1.2.2. Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is rare. It accounts approximately for 0.5 to 2 percent of invasive breast cancers (Anderson et al, 2005; Hance et al, 2005). In the United States (US), its incidence appears to be increasing, particularly among white women (Anderson et al, 2005; Hance et al, 2005; Tai et al, 2005). As compared with locally advanced breast cancer, IBC is diagnosed at an earlier age (a median of 59 versus 66 years of age). The incidence of IBC is higher in black Americans compared with whites, and black women are diagnosed at a younger age. IBC is an aggressive form of locally advanced breast cancer. In general, women with IBC without distant metastatic disease are approached similarly to those with non-inflammatory locally advanced breast cancer. Metastatic IBC is also managed similarly to metastatic non-IBC.

1.2.3. Ovarian Cancer

Advanced ovarian cancer is treated with carboplatin-based combination therapies including carboplatin/paclitaxel combination. Despite initial therapy, the majority of women with advanced-stage ovarian cancer will relapse and require additional treatment. Subsequent management of patients is based on the amount of time that has elapsed between the completion of platinum-based treatment and the detection of relapse, known as the platinum-free interval (PFI). If PFI is 6 months or more, the disease is considered as platinum sensitive. Those platinum sensitive patients will receive platinum-based combination therapy with bevacizumab, an anti-VEGF antibody. If PFI is less than 6 months (platinum-resistant), patients are recommended to be treated with paclitaxel with or without bevacizumab. The weekly administration of paclitaxel has been investigated as treatment of platinum-resistant ovarian cancer by several groups with reports suggesting that approximately 10–20% of patients will achieve an objective response to the regimen (Alvarez et al, 2003; Ozols, 1999; Tiersten et al, 2004).

1.2.4. Endometrial Cancer

For women who develop metastatic endometrial cancer, platinum-based combination regimens are used. The two most commonly used regimens to treat metastatic endometrial cancer are carboplatin plus paclitaxel or the triple drug combination of cisplatin, doxorubicin, plus paclitaxel (Harris et al, 2007). Upon progression, paclitaxel (175 mg/m^2 every 3 weeks) is an option in the second-line setting, particularly in patients who were not previously treated with this agent in the first-line setting. In one study, paclitaxel resulted in a 25% objective response rate (ORR) among 48 paclitaxel-naive patients (Lincoln et al, 2003). However, weekly administration (80 mg/m^2) is also a reasonable option, particularly in patients who were previously treated with paclitaxel. This is based on data showing activity with weekly treatment in women with platinum and paclitaxel-resistant ovarian cancer (Markman et al, 2006).

1.2.5. Gynecological Carcinosarcomas

Gynecological carcinosarcomas (previously called malignant mixed Müllerian tumors [MMMTs]) are rare and aggressive cancers that are dedifferentiated (metaplastic) carcinomas comprised of carcinomatous and sarcomatous elements arising from a single malignant epithelial clone. For women with previously untreated metastatic carcinosarcoma, carboplatin and paclitaxel have activity in carcinosarcoma and cause less toxicity than ifosfamide-based regimens (Homesley et al, 2007; Sutton et al, 2000).

For women who experience disease progression following receipt of adjuvant or first-line chemotherapy, single-agent chemotherapy is preferred. A choice between agents should be individualized, taking into account the prior toxicities the patient has experienced and the toxicities associated with an alternative agent. However, in light of the limited evidence of survival benefit with treatment, hospice care is also reasonable, particularly for patients at risk for significant treatment-related toxicity (Gynecologic Oncology Group et al, 2006; Sigurdsson et al, 1986).

1.3. Overview of Rebastinib

1.3.1. Nonclinical Experience

Please refer to the Investigator's Brochure (IB) for a more detailed summary of the nonclinical experience with rebastinib.

1.3.1.1. Pharmacology

Primary Pharmacodynamic Studies

The pharmacological properties of rebastinib were investigated in a series of experiments using cell-free enzyme assays, whole cell assays, and animal cancer models. Rebastinib potently inhibited recombinant TIE2 protein kinase *in vitro*. TIE2 activity was also inhibited in a series of cellular assays designed to determine the phosphorylation state of the protein. Rebastinib blocked capillary tube formation driven by TIE2 in endothelial cell lines, and inhibited TEM-dependent tumor cell intravasation through an endothelial monolayer.

In vivo, rebastinib was evaluated in the PyMT syngeneic breast cancer model in mice. Tumor vascularization and metastasis in this model are known to be modulated by TEMs (Harney et al, 2017). Rebastinib treatment led to a significant decrease in the growth rate of the primary breast cancers, and to a decrease in the levels of tumoral TIE2 staining by immunohistochemical (IHC) analysis. Single-agent rebastinib also led to a significant decrease in the rate of occurrence of lung metastases in this model. Furthermore, rebastinib led to a dramatic reduction in the function of perivascular TEMs and in levels of CTCs.

Recently it has been demonstrated that chemotherapy such as paclitaxel induces the structure terms TMEM consisting of invasive tumor cells, TEMs, and endothelial cells facilitating systemic dissemination of tumor cells. In addition, the combination of rebastinib and paclitaxel led to a significant, dose-dependent decrease in the number of lung metastases compared with treatment with paclitaxel alone. Rebastinib led to reduction or ablation of primary tumor vascular permeability and CTCs in the PyMT spontaneous breast tumor model (Harney et al, 2017). Rebastinib was also evaluated in combination with eribulin, another marketed inhibitor of microtubules. Rebastinib in combination with eribulin led to a significant increase in OS compared with single agent eribulin therapy in the PyMT implant breast tumor model (Harney et al, 2017).

Safety Pharmacology

Rebastinib was evaluated in a series of core battery studies according to International Conference on Harmonization (ICH) S7A guidelines that included evaluation of central nervous system (CNS) effects and respiratory function in rats, cardiovascular effects in dogs, and an *in vitro* human ether-à-go-go related gene (hERG) assay.

There were no significant changes in respiratory function in rats up to a maximum dose of 100 mg/kg (600 mg/m^2), in the CNS in rats up to a maximum dose of 100 mg/kg (600 mg/m^2), and in cardiovascular function in dogs up to a maximum dose of 200 mg/kg (4000 mg/m^2).

Cardiac electrophysiological parameters also were not affected *in vitro* in HEK-293 cells expressing the hERG-encoded potassium channel when exposed to concentrations of up to 10,000 nM.

1.3.1.2. Pharmacokinetics and Absorption, Distribution, Metabolism, and Excretion Profile

Preliminary screening studies indicated high plasma protein binding of rebastinib. In addition, membrane permeability studies indicated that the parent free base of rebastinib readily crosses biological membranes by passive diffusion.

Rebastinib is a substrate for P-glycoprotein (P-gp) and has the potential to interact with other drugs known to be substrates or inhibitors of P-gp (e.g., ketoconazole, verapamil, and erythromycin).

Rebastinib was found to be a potent inhibitor of cytochrome P450 (CYP)2C9 and to a lesser degree CYP2C19, indicating a potential for interference with clearance of known substrates of these isoenzymes. Primary routes of metabolism were hydroxylation of the t-butyl group and on the quinoline moiety. The carboxylate metabolite derived from further oxidation of the t-butyl group was also observed. Secondary metabolites were found in bile after oral dosing in bile duct cannulated rats. These metabolites were tentatively identified by high performance liquid chromatography/mass spectrometry (HPLC/MS) as the glucuronide conjugates of the t-butyl hydroxyl metabolite and the glucuronide ester of the carboxylate metabolite. Cytochrome P450 (CYP) reaction profiling indicated that hepatic metabolism of rebastinib occurs primarily by CYP3A4 oxidation with minor oxidation by CYP2D6. These results indicate that rebastinib exposure could potentially be altered by co-administration of a CYP3A4 inhibitor or inducer.

In vivo studies in rats indicated no significant induction of hepatic metabolism from repeated dosing with rebastinib at 10 and 75 mg/kg by oral gavage daily for 5 days.

1.3.1.3. Toxicology

Exploratory multi-dose studies were conducted with rats and dogs, and definitive 4-week and 13-week multi-dose studies were conducted in rats and dogs in compliance with Good Laboratory Practice (GLP) guidelines. Exploratory and definitive 4- and 13-week toxicology studies were conducted using orally administered rebastinib in 0.5% carboxymethylcellulose (CMC [vehicle]).

The repeated dose no-observed-adverse-effect level (NOAEL) was 10 mg/kg/day (60 mg/m^2/day) in rats and 25 mg/kg/day (500 mg/m^2/day) in dogs.

Deaths were seen with repeated dosing at ≥100 mg/kg (600 mg/m^2) in rats. Clinical signs in animals at 75 and 125 mg/kg in the 13-week studies primarily included thin appearance, decreased activity and changes in fecal color or consistency. Dogs did not show the abdominal hardness or distension seen in some rats. These data indicated that dosing of rebastinib should be carefully monitored or discontinued if significant weight loss, serious gastrointestinal (GI) stasis or distress, or unexpected overall weaknesses are observed.

Although generally mild in severity and reversible, liver findings in the nonclinical testing suggest that liver function should be monitored in rebastinib clinical trials.

There were no ocular findings in the animal safety studies. Degenerative cardiomyopathy was seen at doses of ≥25 mg/kg (150 mg/m^2) in rats but not in dogs. Exposures at those doses were substantially above the exposures obtained in the first-in-human (FIH) trial of patients with chronic myeloid leukemia (CML) and acute myeloid leukemia (AML). Rebastinib also did not result in adverse alterations in the ICH-recommended battery of genetic toxicology tests. Based on extensive nonclinical safety experience, clinical dosage/exposure extrapolations and on previous clinical experience in CML and AML, these data support the evaluation of rebastinib in further clinical trials.

1.3.2. Clinical Experience

Please refer to the IB for a more detailed summary of the clinical experience with rebastinib.

Clinical Study DCC-2036-01-001 (NCT00827138) was a FIH, multicenter Phase 1 study to determine the safety, tolerability, and pharmacokinetic (PK) profile of rebastinib in patients with Philadelphia chromosome positive (Ph+) leukemia or (FMS-related tyrosine kinase 3 ligand [FLT3]/internal tandem duplication [ITD]) + AML. Patients with Ph+ CML who 1) had the threonine 315 to isoleucine (T315I) mutation (BCR-ABL mutant, imatinib, dasatinib, nilotinib resistant), or 2) were refractory to or intolerant of more than two tyrosine kinase inhibitor [TKI] treatments, or 3) were refractory to or intolerant of 1 TKI and were unwilling or unable to receive treatment with other TKIs were enrolled.

Study DCC-2036-01-003 is an open-label Phase 1b/2 multicenter study in patients with advanced or metastatic solid tumors where paclitaxel is considered appropriate treatment. Rebastinib is administered in combination with weekly paclitaxel in repeated 28-day cycles. The study consists of two parts (Part 1 and Part 2). The primary objectives of Part 1 are to evaluate the safety and tolerability of 50 mg and 100 mg of rebastinib twice daily (BID) when administered in combination with paclitaxel, and to determine the recommended phase 2 dose (RP2D) of rebastinib in combination with paclitaxel. The primary objectives of Part 2 are to evaluate the safety and tolerability of rebastinib at the RP2D in combination with paclitaxel, and to evaluate efficacy of rebastinib in combination with paclitaxel in 5 different diseases.

Study DCC-2036-01-004 is an open label Phase 1b/2 multicenter study in patients with advanced or metastatic solid tumors for which carboplatin is considered appropriate treatment. Rebastinib will be administered in combination with carboplatin in repeated at least 21-day cycles. The study consists of two parts: dose escalation and dose expansion. The primary objectives of the dose escalation phase are to establish the maximum tolerated dose (MTD) or RP2D of rebastinib and carboplatin in combination, and to evaluate the safety and tolerability of rebastinib when administered in combination with carboplatin. The primary objectives of the dose expansion phase are to further evaluate the safety and tolerability of rebastinib when administered in combination with carboplatin and evaluate the efficacy of rebastinib in combination with carboplatin in 3 different diseases.

Additionally, an Investigator sponsored Phase 1b study (NCT02824575) entitled “Phase Ib study of rebastinib plus antitubulin therapy with paclitaxel or eribulin in patients with metastatic breast cancer” has tested rebastinib at 50 and 100 mg BID in combination with paclitaxel or eribulin in metastatic breast cancer. The study has two phases: dose escalation and dose expansion phases (Anampa et al, 2018).

1.4. Overview of Paclitaxel

Paclitaxel is the first member of the taxane family (a drug class that acts by disrupting the microtubular network essential for cell division) to receive marketing approval for cancer treatment. Paclitaxel has demonstrated clinical activity both as single-agent therapy and in combination with other chemotherapeutic agents in a variety of cancer types, including breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer, endometrial cancer and pancreatic cancer. In metastatic breast cancer, paclitaxel has demonstrated ORRs of 19 and 25% in two Phase 3 studies (Gradishar et al, 2005; Jones et al, 2005). ORRs of paclitaxel in platinum-resistant, recurrent ovarian cancers have been reported as approximately 20% in multiple studies (Kumar et al, 2010). As the second line treatment of endometrial cancer, paclitaxel has reached an ORR of 27% (Lincoln et al, 2003). Paclitaxel can be administered weekly (80 to 100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) or every three weeks (135 to 175 mg/m^2).

1.5. Rationale

1.5.1. Study Rationale

The ANG/TIE2 kinase signaling pathway is a pivotal angiogenic signaling axis in endothelial cells. TIE2 is also expressed on a subset of macrophages (i.e., TEMs). TEMs not only promote cancer growth, cancer cell survival, and motility, but can limit the efficacy of the tumor response to chemotherapy or radiotherapy. In particular, TEMs are known to be proangiogenic, prometastatic, and immunosuppressive in the tumor microenvironment.

Rebastinib is a potent, small molecule inhibitor of TIE2. Although rebastinib has much higher activity against TIE2 compared to BCR-ABL and FLT3 (approximately 100 fold more selective), the FIH Phase 1 Study DCC-2036-01-001 (NCT00827138) of rebastinib was conducted by enrolling patients with Ph+ CML (52 patients) and FLT3-ITD positive AML (5 patients). Exposure of rebastinib was dose-proportional. A retrospective analysis of levels of ANG2, a ligand for TIE2, in plasma samples obtained from patients in study DCC-2036-01-001 pre- and post-treatment with rebastinib (100 – 200 mg BID) revealed more than 2-fold increases in circulating ANG2 levels, indicating TIE2 receptor engagement in these patients. An MTD was established as 150 mg BID.

Paclitaxel has demonstrated clinical activity both as single-agent therapy and in combination with other chemotherapeutic agents in a variety of cancer types, including breast cancer, NSCLC, ovarian cancer, and pancreatic cancer. In addition to arresting tumor growth, paclitaxel also disrupts the vascular endothelium and produces a hypoxic tumor environment. Hypoxia induces recruitment of bone marrow derived TEMs to reestablish the tumor vasculature, leading to tumor regrowth. Rebastinib in combination with paclitaxel significantly reduced tumor growth in a murine model of breast cancer. This anti-tumor activity correlated with a reduction in TEMs in the tumor and that in the formation of lung metastases. As described above, perivascular TEMs assemble into special structures with endothelial and tumor cells termed TMEM to promote tumor cell intravasation into the blood stream, leading to CTCs and systemic dissemination and metastasis. Moreover, chemotherapy including paclitaxel increases the density and activity of TMEM sites and promotes distant metastasis in the PyMT and patient-derived xenografts. Chemotherapy-induced TMEM activity and cancer cell dissemination were reversed by administration of the TIE2 inhibitor rebastinib. Analysis of clinical breast cancer specimens

obtained from neo-adjuvant treatment with paclitaxel, doxorubicin, or cyclophosphamide shows that TMEM density increased by treatment (Rigamonti et al, 2014).

Based on these findings, the Investigator sponsored Phase 1b study entitled "Phase Ib study of rebastinib plus antitubulin therapy with paclitaxel or eribulin in patients with metastatic breast cancer" was initiated. As described above, rebastinib at 50 and 100 mg BID in combination with weekly dosed paclitaxel was tolerated and showed a hint of clinical activity in breast cancer. Thus, although this Investigator sponsored study will continue evaluating the combination with eribulin, further evaluation of safety, efficacy, PK and pharmacodynamics (PD) is warranted for the combination with paclitaxel in various cancer types where paclitaxel-based therapies are used.

1.5.2. Dose, Regimen, and Treatment Duration Rationale

In the FIH study of rebastinib, an MTD of 150 mg BID was established as described above. This study was performed in CML/AML patients, investigating rebastinib as a BCR-ABL and FLT3 inhibitor. In the current study, rebastinib will be investigated as a TIE2 receptor tyrosine kinase inhibitor with a picomolar potency for blocking not only TIE2 enzymatic activity, but also functional cellular activity in TEMs and endothelial cells. Due to the approximately 100-fold higher potency against TIE2 compared to BCR-ABL or FLT3, it is expected that the optimum biologic dose is below the MTD established from that CML/AML clinical study. In addition, ANG2 levels were examined in CML and AML patients before and after treatment with 100-200 mg BID rebastinib. On Day 22 after starting rebastinib treatment, increases in ANG2 were observed in 19/20 patients and a >2-fold increase in ANG2 plasma levels was observed in 14/20 (70%) patients suggesting pharmacological inhibition of TIE2 by rebastinib at 100 mg BID.

Based on safety analysis in the same study, muscular weakness/musculoskeletal disorders, peripheral neuropathy, cardiomyopathy/cardiac disorders, and visual abnormalities/eye disorders were considered to be of particular clinical interest and were further analyzed as Adverse Events of Special Interest (AESI). Exposure-response relationship analysis for rebastinib and selected AESIs listed below were conducted (Table 4). The values for either C_{max} or AUC from 0 to 4 hours (AUC_{0-4h}) of evaluable patients were divided into low, middle, and high thirds. Patients were analyzed based on the highest toxicity grade for an AE category within each C_{max} or AUC_{0-4h} value. Incidences of AESIs with higher grades were increased in patients exposed to the high range of C_{max} or AUC_{0-4h}. PK analysis shows that geometric mean C_{max} and AUC_{0-4h} values of 100 and 150 mg BID are in the low and medium range, respectively.

In addition, in the Investigator sponsored Phase 1b study, the combination was found tolerable in 3 patients at the 50 mg BID dose level, and in 3 patients at the 100 mg BID dose level (as described in Section 1.3.2).

Taken together, although 150 mg BID was determined as the MTD in the study with CML and AML patients, 100 mg BID should be deemed as an appropriate dose for the combination with paclitaxel given the positive PD effect on ANG2 levels and the exposure-dependent safety profile with a significantly reduced frequency of Grade 3 or 4 AEs at the dose level. In addition, 50 mg BID will be explored simultaneously in Part 1 for determining the RP2D. Both dose levels have been tested and tolerated in combination with paclitaxel in 3 breast cancer patients each. In

the case where 100 mg BID rebastinib in combination with paclitaxel were not tolerated, 75 mg BID may be tested.

Table 4: Treatment-emergent Adverse Events of Special Interest by Worst CTCAE Grade and Rebastinib C_{max} and AUC_{0-4h} Subgroup during Cycles 1 and 2

		Low		Medium		High	
SOC	**Worst CTC Grade of Adverse Event**	**C_{max} Subgroup (N = 17) n (%)**	**AUC_{0-4h} Subgroup (N = 15) n (%)**	**C_{max} Subgroup (N = 15) n (%)**	**AUC_{0-4h} Subgroup (N = 14) n (%)**	**C_{max} Subgroup (N = 18) n (%)**	**AUC_{0-4h} Subgroup (N = 18) n (%)**
Cardiac disorders	Grade 1	1 (6%)	1 (7%)	1 (7%)	1 (7%)	2 (11%)	2 (11%)
	Grade 2	0	0	0	0	0	0
	Grade 3	1 (6%)	1 (7%)	0	0	1 (6%)	1 (6%)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
	Total	2 (12%)	2 (13%)	1 (7%)	1 (7%)	3 (17%)	3 (17%)
Eye Disorders	Grade 1	3 (18%)	3 (20%)	5 (33%)	4 (29%)	2 (11%)	2 (11%)
	Grade 2	0	0	0	0	2 (11%)	1 (6%)
	Grade 3	0	0	0	0	1 (6%)	1 (6%)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
	Total	3 (18%)	3 (20%)	5 (33%)	4 (29%)	5 (28%)	4 (22%)
Musculo-skeletal Disorders	Grade 1	4 (24%)	3 (20%)	1 (7%)	1 (7%)	3 (17%)	4 (22%)
	Grade 2	0	0	2 (13%)	2 (14%)	2 (11%)	2 (11%)
	Grade 3	1 (6%)	0	4 (27%)	4 (29%)	5 (28%)	3 (17%)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
	Total	5 (29%)	3 (20%)	7 (47%)	7 (50%)	10 (56%)	9 (50%)
Nervous system Disorders	Grade 1	2 (12%)	2 (13%)	5 (33%)	5 (36%)	6 (33%)	6 (33%)
	Grade 2	1 (6%)	1 (7%)	1 (7%)	0	3 (17%)	3 (17%)
	Grade 3	0	0	1 (7%)	1 (7%)	1 (6%)	1 (6%)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
	Total	3 (18%)	3 (20%)	7 (47%)	6 (43%)	10 (56%)	10 (56%)

		Low		Medium		High	
SOC	**Worst CTC Grade of Adverse Event**	**C_{max} Subgroup (N = 17) n (%)**	**AUC_{0-4h} Subgroup (N = 15) n (%)**	**C_{max} Subgroup (N = 15) n (%)**	**AUC_{0-4h} Subgroup (N = 14) n (%)**	**C_{max} Subgroup (N = 18) n (%)**	**AUC_{0-4h} Subgroup (N = 18) n (%)**
Any of the above	Grade 1	6 (35%)	5 (33%)	6 (40%)	6 (43%)	6 (33%)	7 (39%)
	Grade 2	0	0	3 (20%)	2 (14%)	2 (11%)	3 (17%)
	Grade 3	2 (12%)	1 (7%)	4 (27%)	4 (29%)	7 (39%)	5 (28%)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
	Total	8 (47%)	6 (40%)	13 (87%)	12 (86%)	15 (83%)	15 (83%)

AUC_{0-4h} = area under the plasma concentration-time curve from zero to 4 hours; C_{max} = mean peak plasma concentration; CTCAE = Common Toxicity Criteria Adverse Event; SOC = system organ class; CTCAE Version 3.0

2. STUDY OBJECTIVES

2.1. Part 1

2.1.1. Primary Objectives

- To evaluate the safety and tolerability of 50 mg and 100 mg rebastinib BID when administered in combination with paclitaxel.
- To determine the RP2D of rebastinib in combination with paclitaxel.

2.1.2. Secondary Objectives

- To assess the preliminary efficacy of rebastinib administered in combination with paclitaxel by evaluating the ORR.
- To assess the PK of rebastinib and paclitaxel when administered in combination.
- To evaluate efficacy measures, such as progression-free survival (PFS), clinical benefit rate (CBR), response duration, time to response, time to progression (TTP), and OS of rebastinib in combination with paclitaxel.

2.2. Part 2

2.2.1. Primary Objectives

- To evaluate the safety and tolerability of rebastinib at the RP2D in combination with paclitaxel.
- To evaluate the ORR as the primary efficacy measure of rebastinib in combination with paclitaxel.

2.2.2. Secondary Objectives

- To assess the PK of rebastinib and paclitaxel when administered in combination.
- To evaluate efficacy measures, such as PFS, CBR, response duration, time to response, TTP, and OS of rebastinib in combination with paclitaxel.

2.3. Parts 1 and 2

2.3.1. Exploratory Objectives

- To evaluate changes in select blood and plasma biomarkers when rebastinib is administered in combination with paclitaxel.
- To evaluate changes in the tumor tissue microenvironment (e.g., changes in the composition of infiltrating mononuclear cells) when rebastinib is administered in combination with paclitaxel.
- To assess polymorphisms in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of rebastinib in combination with paclitaxel.
- Assess the effects of rebastinib administered in combination with paclitaxel using patient reported outcome (PRO) measures.

3. STUDY DESIGN

3.1. Overview of Study Design

This is an open-label Phase 1b/2 multicenter study in patients with advanced or metastatic solid tumors where paclitaxel is considered appropriate treatment. Rebastinib will be administered in combination with paclitaxel in repeated 28-day cycles to primarily assess the safety, tolerability and preliminary efficacy of the combination. Adverse events will be assessed, and laboratory values, vital sign measurements, electrocardiograms (ECGs), ophthalmologic examinations, physical examinations and Eastern Cooperative Oncology Group performance status (ECOG PS) will be obtained to evaluate the safety and tolerability of rebastinib when administered in combination with paclitaxel. Pharmacokinetic and PD samples will be collected at pre-specified time points.

The study consists of two parts (Part 1 and Part 2). In Part 1, patients will be assigned to one of two pre-defined dose levels of rebastinib (50 or 100 mg BID) in combination with paclitaxel administered by intravenous (IV) infusion at 80 mg/m^2. Each arm is planned to enroll at least 12 evaluable patients. Additionally, if rebastinib at 100 mg BID is deemed unsafe, an additional arm dosing at 75 mg BID of rebastinib in combination with paclitaxel may be initiated. Up to 36 evaluable patients will be dosed in Part 1. Safety will be continuously monitored and any arm may be terminated early if deemed intolerable by the Sponsor.

Safety and tolerability, PK and PD, and preliminary efficacy data obtained in Part 1 will be used to determine the RP2D. Data for at least 12 evaluable patients through Cycle 1 must be available in an arm to declare the dose as the RP2D. Patients must receive ≥80% of planned doses of rebastinib and paclitaxel in Cycle 1 to be considered evaluable. Enrollment of patients will pause for determination of the RP2D prior to initiation of Part 2. An RP2D will be chosen by the Sponsor in consultation with the Investigators.

Upon determination of the RP2D, Part 2 will be initiated to dose up to 165 evaluable patients using the RP2D across five indication-specific cohorts. A Simon two-stage design will be applied to Part 2 to further evaluate the safety, tolerability, and preliminary efficacy of rebastinib in combination with paclitaxel in triple-negative breast (Cohort 1), inflammatory breast (Cohort 2), ovarian (Cohort 3), endometrial (Cohort 4), and gynecological carcinosarcoma (Cohort 5) cancers.

Each cohort will initially enroll up to 18 evaluable patients in the first stage. Patients must receive at least 1 dose of the combination and have 1 post-baseline assessment, or be discontinued prior to the post-baseline disease assessment due to an AE at least possibly related to rebastinib, to be considered evaluable. Tumor response will be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. The decision to enroll patients beyond the first stage will be based on response assessments obtained after the first post-dose response assessment of the last patient enrolled in the first stage of a cohort. Patients who meet criteria defined in Section 8.3 will be replaced and not be included in the responder analysis. If >4 responses (defined as PR or complete response [CR]) are seen in a cohort, additional patients will be enrolled for a total of up to 33 patients. If ≤4 responses are seen in a cohort, the cohort will be terminated. If >4 responses are seen prior to the last evaluable patient

in the first stage, expanding the cohort may be triggered earlier. Enrollment in each cohort will pause between the first and second stage of the Simon two-stage for evaluation of response.

3.2. Number of Patients

A total of approximately 201 patients (up to 36 evaluable patients in Part 1 and up to 165 evaluable patients in Part 2) may be enrolled in this study. The study will be conducted at approximately 7 centers in the US during Part 1 and approximately 20 centers in the US during Part 2.

3.3. Duration of Study

Patients will receive study treatment until they develop progressive disease, experience unacceptable toxicity, or withdraw consent.

Patients will be eligible to receive study treatment for as long as the Investigator and the Sponsor agree that the patient is showing clinical benefit and for as long as rebastinib is being developed to support the indication and continuation of treatment does not conflict with the Sponsor's right to terminate the study. The study will end following the last patient's last visit.

4. STUDY POPULATION

4.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible to enroll in the study:

1. Male or female patients ≥18 years of age at the time of informed consent.
2. Part 1, All Arms
   i. Histologically confirmed diagnosis of a locally advanced or metastatic solid tumor for which paclitaxel is considered appropriate treatment.
   ii. Patients who have progressed despite standard therapies, or for whom conventional therapy is not considered effective or tolerable, as judged appropriate by the investigator.
3. Part 2
   A. Part 2, Cohort 1: Triple-Negative Breast Cancer
      i. Histologically confirmed metastatic triple-negative breast cancer based on the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Hammond et al, 2010)
      ii. Received at least one prior line but no more than three prior lines of systemic chemotherapy in the metastatic setting.
      iii. Has not received taxane-containing regimens within 6 months prior to the first dose of study drug.
   B. Part 2, Cohort 2: Inflammatory Breast Cancer (IBC)
      i. Histologically or cytologically confirmed stage IV breast carcinoma with a previous clinical diagnosis of IBC based on the presence of inflammatory changes in the involved breast, such as diffuse erythema and/or edema (peau d'orange), with or without an underlying palpable mass and involving the majority of the skin of the breast; pathological evidence of dermal lymphatic invasion should be noted but is not required for diagnosis.
      ii. Received at least one prior line of systemic chemotherapy in the metastatic setting.
      iii. Has not received taxane-containing regimens within 6 months prior to the first dose of study drug.
   C. Part 2, Cohort 3: Ovarian Cancer
      i. Histologically confirmed, recurrent epithelial ovarian, peritoneal or fallopian tube carcinoma. Note: patients with low grade serous, mucinous or clear cell histology will be excluded.
         a. Progressed or relapsed within 6 months after the completion of a platinum-containing chemotherapy regimen.
         b. Patients that progressed during treatment or within 1 month after the completion of the first platinum-containing chemotherapy regimen (primary platinum refractory) are excluded.

ii. Received no more than five prior lines of systemic anticancer therapy.
    a. Neoadjuvant and/or adjuvant is considered one regimen.
    b. Maintenance therapy, including Poly (ADP-Ribose) Polymerase (PARP) inhibitors, is considered part of the preceding regimen.
    c. Hormonal therapy is not considered a prior systemic regimen.

iii. Must have received prior treatment with a PARP inhibitor if patients have a BRCA1 or 2 germline or somatic mutation(s). Patients who have refused therapy with a PARP inhibitor may be considered for enrollment, following consultation with the Sponsor.

D. Part 2, Cohort 4: Endometrial Cancer

i. Histologically confirmed adenocarcinoma of the endometrium.

ii. Received at least one prior line of platinum-based therapy in the recurrent, metastatic, or high-risk disease setting.
    a. For patients with known microsatellite instability-high (MSI-H) or mismatch repair deficiency, progressed after a regimen including an anti-PD1 agent.

E. Part 2, Cohort 5: Gynecological Carcinosarcoma

i. Histologically confirmed advanced (stage III or IV), persistent, or recurrent gynecological carcinosarcoma.
    a. Homologous or heterologous type carcinosarcoma (MMMT) are allowed.

ii. Must have received at least 1 prior chemotherapy regimen (including high-dose, consolidation, or extended therapy after surgical or nonsurgical assessment for gynecological carcinosarcoma).

4. At least one measurable lesion according to RECIST Version 1.1.
5. ECOG PS of ≤2.
6. Able to provide a tumor tissue sample; if an archival tumor tissue sample is unavailable, a fresh tumor biopsy is required prior to the first dose of study drug, only if tumor biopsy is safe and accessible as judged by the Investigator.
7. Adequate organ function and bone marrow reserve as indicated by the following laboratory assessments performed within 14 days prior to the first dose of study drug:

i. Bone marrow function: absolute neutrophil count (ANC) ≥1500/μL; hemoglobin ≥9 g/dL; platelet count ≥100,000/μL.

ii. Hepatic function: total bilirubin ≤1.5×the upper limit of normal (ULN) or <3×ULN for Gilbert's syndrome; aspartate transaminase (AST)/alanine transaminase (ALT) ≤2.5×ULN (≤5×ULN in the presence of hepatic metastases).

iii. Renal function: serum creatinine ≤1.5×ULN or creatinine clearance ≥30 mL/min based either on urine collection or Cockcroft Gault estimation.

iv. Coagulation profile: prothrombin time adjusted for the international normalized ratio (PT-INR) and partial thromboplastin time (PTT) ≤1.5×ULN. Patients on a stable, maintenance regimen of anticoagulant therapy for at least 30 days prior to study drug administration may have PT-INR measurements >1.5×ULN if, in the opinion of the Investigator, the patient is suitable for the study. An adequate rationale must be provided to the Sponsor prior to enrollment.

8. If a female of childbearing potential, must have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening and agree to use two methods of contraception, with one of them being highly effective, prior to the first dose of study drug and for at least 120 days following the last dose of study drug as outlined in Section 6.8.9.
9. If male, must agree to use two methods of contraception, with one of them being highly effective, and refrain from sperm donation prior to the first dose of study drug through 120 days following the last dose of study drug as outlined in Section 6.8.9.
10. Patient must provide signed consent to participate in the study and is willing to comply with study-specific procedures.

4.2. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Received prior anticancer or other investigational therapy within 28 days or 5 × the half-life (whichever is shorter) prior to the first dose of study drug. See Section 5.11.6 for further details.
2. Not recovered from all toxicities from prior therapy to Grade ≤1 (or baseline) within 1 week prior to first dose of study drug (excluding alopecia and ≤Grade 3 clinically asymptomatic alkaline phosphatase).
3. Peripheral neuropathy of any etiology >Grade 1.
4. Patients with a prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of this clinical trial.
5. Known active CNS metastases defined as:
    i. Unstable (i.e., evidence of progression by magnetic resonance imaging [MRI]) within 4 weeks prior to the first dose of study drug.
    ii. Neurologic symptoms within 2 weeks prior to the first dose of study drug and required use of enzyme-inducing antiepileptic drugs.
    iii. Patients who require steroids must be on a stable dose for 2 weeks prior to the first dose of study drug.
6. Use of systemic corticosteroids within 7 days prior to the first dose of study treatment or an existing condition that requires the concomitant use during the course of the study, unless the dose is no more than the equivalent of prednisone 15 mg/day. See Section 5.11.6 for further details.
7. Known retinal neovascularization, macular edema or macular degeneration.

8. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, history of class III or IV congestive heart failure according to New York Heart Association classification, unstable angina or poorly controlled arrhythmia as determined by the Investigator, or myocardial infarction within 6 months prior to the first dose of study drug.
9. QT interval corrected for heart rate at screening using Fridericia's formula (QTcF) >450 ms in males or >470 ms in females or history of QT interval corrected for heart rate (QTc) prolongation.
10. Left ventricular ejection fraction (LVEF) <50% at screening.
11. Arterial thrombotic or embolic events such as cerebrovascular accident (including ischemic attacks) or moderate hemoptysis within 6 months prior to the first dose of study drug.
12. Venous thrombotic event (e.g., deep vein thrombosis) within the 3 months prior to the first dose of study drug; following a venous thrombotic event of ≥3 months prior to the first dose of study drug, must be on a stable dose of anticoagulation therapy, if clinically indicated.
13. Active infection ≥Grade 3 requiring IV anti-infective treatment within 7 days prior to the first dose of study drug.
14. Known human immunodeficiency virus or hepatitis C infection only if the patient is taking medications that are excluded per protocol, active hepatitis B, or active hepatitis C infection.
15. Use of proton pump inhibitors (PPI) within 4 days prior to the first dose of study drug or an existing condition that requires the concomitant use of a proton pump inhibitor during the course of the study.
16. If female, the patient is pregnant or lactating.
17. Major surgery 4 weeks prior to the first dose of study drug; following major surgeries >4 weeks prior to the first dose of study drug, all surgical wounds must be healed and free of infection or dehiscence.
18. Manifestation of malabsorption due to prior gastrointestinal surgery, disease or other illness which could affect oral absorption as judged by Investigator and Sponsor.
19. Known allergy or hypersensitivity to any component of rebastinib or any of its excipients.
20. Any other clinically significant comorbidities, such as uncontrolled pulmonary disease, active infection, or any other condition which, in the judgment of the Investigator, could compromise compliance with the protocol, interfere with the interpretation of study results, or predispose the patient to safety risks.

5. STUDY DRUG ADMINISTRATION AND MANAGEMENT

5.1. Study Drug Description

5.1.1. Rebastinib

Rebastinib will be provided by the Sponsor as tablets for oral administration containing 25 mg and 75 mg of active rebastinib. The tablets also contain microcrystalline cellulose, lactose, polyethylene glycol 3350, poloxamer 407, crospovidone, colloidal silicon dioxide, PRUV®, and butylated hydroxytoluene.

5.1.2. Paclitaxel

Paclitaxel will be provided by the Sponsor. Please refer to the paclitaxel label or prescribing information (US Prescribing Information) for more details.

5.2. Study Drug Dose and Administration

5.2.1. Rebastinib

Rebastinib may be dispensed only under the supervision of the Investigator or an authorized designee and only for administration to study patients. In Part 1, patients will be enrolled to receive 50 mg BID or 100 mg BID of rebastinib orally (PO) in combination with paclitaxel in repeated 28-day cycles. If 100 mg BID is deemed intolerable, a cohort of 75 mg BID in combination with paclitaxel will be initiated. In Part 2, rebastinib will be administered at the RP2D in combination with paclitaxel. For patients that are unable to tolerate paclitaxel, rebastinib may be administered as a single agent starting in Cycle 2.

The Investigator or designee must instruct the patient to take rebastinib as per protocol.

- Patients should be instructed to take their assigned dose at the same time each day, approximately 12 hours apart (minimum of 6 hours apart).
- Patients should take their study drug dose with a 6-ounce glass of water.
- All doses of rebastinib should be taken at least 1 hour before or at least 2 hours after a meal.
- Patients must be instructed to swallow the tablets whole. Tablets must not be crushed, chewed, or dissolved in liquid or food.
- On days of PK sample collection, the morning dose of study drug must be administered at the site after pre-dose assessments have been completed. The date, amount taken and time of study drug administration must be recorded in the patient's diary.
- On days of paclitaxel administration, patients must take the dose of rebastinib prior to infusion of paclitaxel. Premedication will be administered prior to or after the rebastinib dose.
- If a patient forgets to take a dose at the scheduled time, the patient can take the scheduled dose if taken within 6 hours of the scheduled time that was missed. If more than 6 hours have passed after the scheduled time, then that missed dose must be omitted and the patients must continue treatment with the next scheduled dose.

- If vomiting occurs immediately after taking a dose, that dose must not be "made up," and the patient may be offered prophylactic anti-emetics prior to their next dose. For information on overdose, refer to Section 7.12.
- Patients must be instructed to avoid medications that increase gastric pH (e.g., H2 receptor antagonists and antacids) within 2 hours before or after administration of rebastinib. H2 receptor antagonists administered during the required premedication for each paclitaxel infusion are allowed.

5.2.2. Paclitaxel

Paclitaxel will be administered by IV infusion at 80 mg/m^2 over approximately 60 minutes on Day 1, Day 8 and Day 15 of repeated 28-day cycles. Rebastinib will be administered orally prior to the paclitaxel infusion. All paclitaxel infusions may be administered ±2 days to the corresponding study visit however each infusion much be at least 5 days apart. All paclitaxel infusions will be administered at the study site.

Patients should be pre-medicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions per institutional practices. On serial PK sampling days during Part 1, paclitaxel will be infused after the required PK sampling (see Table 2).

To initiate each weekly treatment, the following is needed:

- ANC ≥500/µL
- Platelets ≥75,000/µL

If the retreatment criteria are not met and a dose of paclitaxel is missed, a single make-up dose of paclitaxel may be administered on Day 22 of a given cycle as long as retreatment criteria are met. Assessments required on Day 8 of the corresponding cycle must be performed.

For patients that are unable to tolerate paclitaxel, rebastinib may be administered as a single agent starting in Cycle 2.

5.3. Dose Interruption/Modification and Management of Toxicities

Study drugs may be interrupted or modified (i.e., dose reduced) at the discretion of the Investigator at any time due to AE, to accommodate palliative treatment, or for other reasons after consultation with the Sponsor. Dose reduction steps of rebastinib and paclitaxel will be completed according to Table 5 and Table 6, respectively. Recommended dose interruptions and modifications as well as management of toxicities are identified in Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, and Table 14. A Grade 1 or Grade 2 AE will not require dose interruption or medication unless specified in these tables.

The causal relationship of each AE should be assessed in relation to rebastinib and to paclitaxel separately so that dose modifications can be made accordingly. Upon resumption following a dose interruption, the Investigator must continue with the patient's original visit schedule calculated from Cycle 1 Day 1 (Baseline). Re-escalation of rebastinib or paclitaxel will be done by one dose-level at time upon agreement between the Sponsor and Investigator.

Permanent discontinuation of the study drugs should be considered for any severe or life-threatening event. Upon experiencing any of following conditions, a patient should discontinue

study drug treatment permanently except when the Investigator determines that the patient is obtaining clinical benefit and has discussed this with the Sponsor:

- Any Grade 4 AE excluding hematological AEs defined in Table 7.
- Requirement for more than 2 dose reductions from the assigned dose at enrollment to manage AEs.
- Rebastinib: treatment interruption for >14 days due to treatment-related AEs.
- Paclitaxel: treatment interruption for >21 days due to treatment-related AEs.

Sites must follow up with patients at least weekly during drug interruptions.

Table 5: Dose Reduction Steps for Rebastinib

Starting Dose of Rebastinib	1st Dose Reduction	2nd Dose Reduction
50 mg BID	25 mg BID	Discontinue
100 mg BID	75 mg BID	50 mg BID
75 mg BID	50 mg BID	25 mg BID

Sites must follow-up with patients at least weekly during drug interruptions.

Table 6: Dose Reduction Steps for Paclitaxel

Starting Dose of Paclitaxel	1st Dose Reduction	2nd Dose Reduction
80 mg/m^2	70 mg/m^2	60 mg/m^2

Sites must follow-up with patients at least weekly during drug interruptions.

Table 7: Recommended Dose Modification for Hematological Adverse Events

Adverse Event	Grade	Occurrence	Rebastinib	Paclitaxel
Based on the causal relationship, dose interruption/modification will apply to rebastinib only, paclitaxel only or both study drugs.				
Neutrophil Count Decrease	4	Any	Continue the same dose unless the AE is deemed related to rebastinib. If related: • Hold rebastinib until ANC≥500 /µL. • Restart at the same dose.	Hold paclitaxel. • Until ANC ≥500 /µL. • Restart at the same dose. • If Grade 4 neutropenia does not resolve within 7 days, reduce one dose level.
Platelet Count Decrease	≥2	Any	Continue the same dose unless the AE is deemed related to rebastinib. If related: • Hold rebastinib until Platelets ≥75,000 /µL. • Restart at the same dose.	Hold paclitaxel. • Until Platelets ≥75,000 /µL. • Restart at the same dose. • If Grade 3 thrombocytopenia does not resolve within 7 days, reduce one dose level. • If AE is Grade 4, reduce one dose level.
Anemia	≥3	Any	Continue the same dose unless the AE is deemed related to rebastinib only. If related: • Hold rebastinib until Hgb ≥9.0 g/dL. • Restart at the same dose.	Hold paclitaxel until Hgb ≥9.0 g/dL. • If resolved in ≤7 days, maintain the same dose • If resolved in >7 days, reduce one dose level. • If AE is Grade 4, reduce one dose level.
Febrile Neutropenia	3	1st and 2nd	Hold rebastinib until ANC ≥1,500/µL. • Restart the same dose unless AE is worsening. • If worsening, reduce one dose level.	Hold paclitaxel until ANC ≥1,500/µL. • Reduce one dose level with G-CSF or GM-CSF.
		3rd	• The same as above.	• Permanently discontinue paclitaxel treatment.

Hgb = hemoglobin; G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte macrophage-colony stimulating factor.
Sites must follow up with patients at least weekly during drug interruptions.

Table 8: Recommended Dose Modification for Peripheral Sensory Neuropathy

Adverse Event	Grade	Occurrence	Rebastinib	Paclitaxel
Based on the causal relationship, dose interruption/modification will apply to rebastinib only, paclitaxel only or both study drugs.				
Peripheral Sensory Neuropathy	2	1st	Continue the same dose unless AE is worsening. • If worsening, reduce one dose level.	Hold paclitaxel until AE resolves to Grade <2. • Reduce one dose level. • If AE is worsening with each infusion, even if it remains Grade 1, reduce one more dose level.
		2nd and subsequent occurrence(s)	Continue the same dose unless AE is worsening. • If worsening, reduce one dose level.	Permanently discontinue paclitaxel.
	3	1st	Hold rebastinib until AE resolves to Grade <2. • Reduce one dose level.	Hold paclitaxel until AE resolves to Grade <2. • Reduce one dose level. • If AE is worsening with each infusion, even if it remains Grade 1, reduce one more dose level.
		2nd and subsequent occurrence	Hold rebastinib until AE resolves to Grade <2. • Reduce one dose level.	Permanently discontinue paclitaxel.

Sites must follow-up with patients at least weekly during drug interruptions.

Table 9: Recommended Dose Modification for Muscular Weakness

Adverse Event	Grade	Occurrence	Rebastinib	Paclitaxel
Based on the causal relationship, dose interruption/modification will apply to rebastinib only, paclitaxel only or both study drugs.				

Muscular Weakness	2	1st	Hold rebastinib until toxicity resolves to Grade <2:
			• If AE persists at Grade 2 >5 days after dose interruption:
			  ○ Refer patient to a neurologist for evaluation and management
			• If AE resolves in ≤14 days, **continue the same dose level**
			• If AE does not resolve in >14 days, **consider permanent discontinuation**
				Hold paclitaxel until toxicity resolves to Grade <2:
				• If AE persists at Grade 2 >5 days after dose interruption:
				  ○ Refer patient to a neurologist for evaluation and management
				• If AE resolves in ≤14 days, **continue the same dose level**
				• If AE does not resolve in >14 days, **consider permanent discontinuation**

		2nd	Hold rebastinib until toxicity resolves to Grade <2: • Refer patient to a neurologist for evaluation and management • If AE resolves in ≤14 days, **reduce 1 dose level** • If AE does not resolve in >14 days, **consider permanent discontinuation**	Hold paclitaxel until toxicity resolves to Grade <2: • Refer patient to a neurologist for evaluation and management • If AE resolves in ≤14 days, **reduce 1 dose level** • If AE does not resolve in >14 days, **consider permanent discontinuation**
		3rd	Permanently discontinue study treatment	
	3	1st	Hold rebastinib until toxicity resolves to Grade <2: • Refer patient to a neurologist for evaluation and management • If AE resolves in ≤14 days, **reduce 1 dose level** • If AE does not resolve in >14 days, **consider permanent discontinuation**	Hold paclitaxel until toxicity resolves to Grade <2: • Refer patient to a neurologist for evaluation and management • If AE resolves in ≤14 days, **reduce 1 dose level** • If AE does not resolve in >14 days, **consider permanent discontinuation**
		2nd	Permanently discontinue study treatment	

Sites must follow-up with patients at least weekly during drug interruptions.

Table 10: Recommended Dose Modification for Ocular Events (Except Asymptomatic Intraocular Pressure Increases)

Adverse Event	Grade	Occurrence	Rebastinib	Paclitaxel
Based on the causal relationship, dose interruption/modification will apply to rebastinib only, paclitaxel only or both study drugs.				
Ocular AEs and Visual AEs[a]	2	1st	Implement close monitoring and hold rebastinib until AE resolves to Grade <2. • Resume at the same dose.	Continue the same dose. • If AE is worsening with each infusion, reduce one dose level.
		2nd	Hold rebastinib until AE resolves to Grade <2. • Reduce one dose level • Perform ophthalmological assessment as clinically indicated.	Continue the same dose. • If AE is worsening with each infusion, reduce one dose level.
		3rd	A patient will be discontinued from the study.	
	3	1st	Hold rebastinib until AE resolves to Grade <2 • Reduce one dose level • Perform ophthalmological assessment as clinically indicated.	Hold paclitaxel until AE resolves to Grade <2 • Resume at the same dose. • If AE is worsening with each infusion, reduce one dose level.
		2nd	A patient will be discontinued from the study.	
Retinal Vein Occlusion or Macular Edema	Any	1st	A patient will be discontinued from the study.	

a. Includes optic nerve disorder, papilledema, vision blurred, visual field defect, visual impairment. Retinal vein occlusion and macular edema are described separately.

Sites must follow up with patients at least weekly during drug interruptions.

Table 11: Recommended Dose Modification and Management of Asymptomatic Intraocular Pressure Increases

Condition	Management
Elevated intraocular pressure (IOP) and IOP of both eyes still ≤21 mmHg	• Continue the same dose of rebastinib and paclitaxel. • If the increase is >5 mmHg from baseline, monitor IOP as needed.
IOP of either of eyes >21 mmHg but ≤30 mmHg	• Continue the same dose of rebastinib and paclitaxel. • Consult with an ophthalmologist: o May initiate treatment of elevated IOP with a medication(s): starting with a topical prostaglandin and then adding a medication(s) such as a beta blocker, alpha adrenergic agonist, and carbonic anhydrase inhibitor as appropriate to reduce and maintain IOP of both eyes ≤21 mmHg. o Perform monitoring of IOP as necessary to adjust medications (e.g., weekly). o If IOP cannot be reduced to ≤21 mmHg with 3 topical medications, ▪ Hold rebastinib until IOP of both eyes is reduced to ≤21 mmHg. • If not recovered within 14 days, consider permanent discontinuation. • If recovered, reduce rebastinib by one dose level. ▪ Paclitaxel can be administered at the same dose per discretion of the Investigator. o If dose reduction of rebastinib with medications cannot lower IOP ≤21 mmHg, then a patient will be discontinued from the study.
IOP of either of eyes >30 mmHg	• Hold rebastinib until IOP of both eyes is reduced to ≤21 mmHg. o Consult with an ophthalmologist. o Paclitaxel can continue being administered at the same dose per discretion of the Investigator. o Resume rebastinib at the same dose. ▪ Consider prescribing a medication(s) as described above to prevent IOP (>21 mmHg). ▪ Perform monitoring of IOP (e.g., weekly) and adjust medications as necessary. o If IOP cannot be maintained at ≤21 mmHg with 3 topical medications, ▪ Reduce rebastinib by one dose level. o If dose reduction of rebastinib with medications cannot lower IOP ≤21 mmHg, then a patient will be discontinued from the study.

Sites must follow up with patients at least weekly during drug interruptions.

Table 12: Recommended Dose Modification for Cardiovascular Events

Adverse Event	Grade	Occurrence	Rebastinib	Paclitaxel
Based on the causal relationship, dose interruption/modification will apply to rebastinib only, paclitaxel only or both study drugs.				
Cardiac Disorders[a]	1	Any	Continue the same dose.	Continue the same dose.
			Perform cardiovascular assessment and monitoring.	
	2	1st	Continue the same dose unless AE is worsening. • If worsening, reduce one dose level.	Hold paclitaxel until AE resolves to Grade <2. • Reduce one dose level. • If AE is worsening with each infusion, even if it remains Grade 1, reduce one more dose level.
			Perform cardiovascular assessment and monitoring.	
		2nd	Hold rebastinib until AE resolves to Grade <2. • Reduce one dose level.	Hold paclitaxel until AE resolves to Grade <2. • Reduce one dose level. • If AE is worsening with each infusion, even if it remains Grade 1, hold paclitaxel.
			Perform cardiovascular assessment and monitoring.	
		3rd	A patient will be discontinued from the study.	
	3	1st	A patient will be discontinued from the study.	
Hypertension	2 and systolic BP ≥150 or diastolic BP ≥95	Any	Hold rebastinib. • If BP is <150/95 mmHg, restart the same dose.	Continue the same dose.
	3	Any	Hold rebastinib and initiate anti-hypertensive therapy. • If BP is <150/95 mmHg, restart the same dose.	Hold paclitaxel and initiate anti-hypertensive therapy. • If BP is <150/95 mmHg, restart the same dose.
			A patient will be discontinued from the study if hypertension is not controlled.	

a. Includes cardiac disorders system organ class.

Sites must follow up with patients at least weekly during drug interruptions.

Table 13: Recommended Dose Modification for Gastrointestinal Adverse Events

Adverse Event	Grade	Occurrence	Rebastinib	Paclitaxel
Based on the causal relationship, dose interruption/modification will apply to rebastinib only, paclitaxel only or both study drugs.				
Nausea[a, b] **Vomiting**[a, b]	3	1st and 2nd	Continue the same dose unless AE is worsening. • If worsening, hold rebastinib until AE resolves to Grade <2.	Hold paclitaxel until Grade 1 • Reduce one dose level. • If AE is worsening with each infusion, even if it remains Grade 1, reduce one more dose level. • Dose re-escalation by one dose level at time if deemed safe.
		3rd and subsequent occurrence	Hold rebastinib until AE resolves to Grade <2. • Reduce one dose level. • Dose re-escalation by one dose level at time if deemed safe.	Permanently discontinue paclitaxel treatment.
Diarrhea[a, c] **Mucositis**[a]	2	Any	Continue the same dose unless AE is worsening. • If worsening, reduce one dose level.	Hold paclitaxel until Grade <2 • Resume paclitaxel at the same dose.
	3	1st and 2nd	Continue the same dose unless AE is worsening. • If worsening, reducing one dose level.	Hold paclitaxel until Grade <2 • Reduce one dose level. • If AE is worsening with each infusion, even if it remains Grade 1, reduce one more dose level. • Dose re-escalation by one dose level at time if deemed safe.
		3rd and subsequent occurrence	Hold rebastinib until AE resolves to Grade <2. • Reduce dose by one dose level. • Dose re-escalation by one dose level at time if deemed safe.	Permanently discontinue paclitaxel treatment.

a. Excludes Nausea, Vomiting, Diarrhea and Mucositis resolved to ≤ Grade 1 or baseline within 1 week after optimal treatment.
b. Prophylactic antiemetics should be used at the discretion of the Investigator.
c. Anti-diarrheal agents are encouraged.
Sites must follow up with patients at least weekly during drug interruptions.

Table 14: Recommended Dose Modification for Other Grade 3 Non-Hematological Adverse Events

Adverse Event	Grade	Occurrence	Rebastinib	Paclitaxel
Based on the causal relationship, dose interruption/modification will apply to rebastinib only, paclitaxel only or both study drugs.				
Other Non-Hematologic[a]	3	Any	Hold rebastinib until AE resolves to Grade <2. • Reduce dose by one dose level. • Dose re-escalation by one dose level at a time if deemed safe.	Hold paclitaxel until the AE resolves to Grade <2. • Reduce on dose level dose. • If AE is worsening with each infusion, even if it remains Grade 1, reduce one more dose level. • Dose re-escalation by one dose level at a time if deemed safe.

a. The following AEs are exceptions to the above:
- Grade 3 nausea, vomiting, and diarrhea resolved to Grade 1 or baseline within 1 week with optimal treatment,
- Transient Grade 3 fatigue (lasting <1 week) and,
- Any other Grade 3 non-hematologic AE that can be controlled to Grade 1 or baseline within 1 week with appropriate treatment.

Sites must follow up with patients at least weekly during drug interruptions.

5.4. Packaging and Labeling

Rebastinib will be supplied by the Sponsor as formulated drug in tablets for oral administration containing 25 mg and 75 mg of active rebastinib. The 75 mg tablets will be supplied in 30-count blister packs. The 25 mg tablets will be supplied in 28-count blister packs. Study drug labeling will be in accordance with applicable local and national regulations.

Paclitaxel 100 mg (16.7 mL) multidose vials will be supplied by the Sponsor. Paclitaxel is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to IV infusion. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of Polyoxyl 35 Castor Oil, NF, 49.7% (v/v) Dehydrated Alcohol, USP and 2 mg Citric Acid, USP.

Study drug will be provided and replaced via the Interactive Response Technology (IRT). Study drug dispensation instructions will be provided in the Pharmacy Manual.

5.5. Storage Conditions

Instructions regarding the storage, handling and administration will be on the label and/or in the Pharmacy Manual.

Rebastinib: Store at controlled room temperature between 20° to 25°C (68° to 77°F). Retain in the original package to protect from light and moisture.

Paclitaxel: Store in original cartons at controlled room temperature between 20° to 25°C (68° to 77°F) at clinical sites. The original packaging should be retained during storage and the vials should be protected from light.

For both study drugs, refer to United States Pharmacopeia [USP] Controlled Room Temperature.

5.6. Study Drug Compliance

To ensure study drug compliance, the Investigator or designee must supervise all study drug dosing that occurs at the site. At each visit, site personnel must review that the patient is compliant with at-home study drug dosing and remind the patient of study drug dosing requirements. Compliance must also be assessed by ongoing study drug count.

If a patient demonstrates continued noncompliance of at-home study drug dosing despite educational efforts, the Investigator must contact the Sponsor to discuss discontinuation of the patient from the study.

5.7. Study Drug Accountability

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator must ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the study drug's delivery date to the site, study drug inventory at the site, study drug dispensed to each patient, study drug returned by each patient, and study drug returned to the Sponsor or study drug destruction on site must be maintained by the clinical site. Accountability records must include

dates, quantities, bottle numbers, and patient numbers. The Sponsor or its designee must review drug accountability at the site on an ongoing basis during monitoring visits. If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

Patients must be instructed to return all unused, partially used, and used study drug blister packs to the site at each visit. The Study Monitor must verify study drug records and inventory throughout the study.

5.8. Disposal, Return, or Retention of Unused Study Drug

Patients must be instructed to return all used, partially used, and full study drug blister packs. The site staff or pharmacy personnel (as appropriate) must retain all materials returned by the patients until returned to Sponsor/designee or destroyed by the study site. If the study drug will be destroyed at the study site, the site must have a governing standard operating procedure (SOP) documenting the process to be followed when destroying investigational product (IP) on site. The Sponsor must review this SOP and give approval prior to destruction of IP at the site. The Investigator or designee, must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. Destruction must be adequately documented.

5.9. Method of Assigning Patients to Treatment

In Part 1, patients will be assigned to the dose of rebastinib according to the arm in which they are enrolled. In Part 2, patients will be assigned to the RP2D of rebastinib and enrolled into the appropriate indication-specific cohort.

5.10. Blinding

This is an open-label study.

5.11. Prior and Concomitant Treatment and Procedures

5.11.1. Prior Medications and Procedures

Information regarding any medication or non-drug therapy or procedure taken or performed within 30 days prior to screening and before the first dose of study drug must be documented in the patient's source documents and the electronic case report form (eCRF).

5.11.2. Prior Anticancer Medications and Procedures

Any prior anticancer medication or procedure must be documented in the patient's source documents and the eCRF.

5.11.3. Concomitant Medications

All medications, including vitamin supplements, over-the-counter medications, and oral herbal preparations; non-drug therapies taken on or after the first day of study drug dose through the 30 Day Safety Follow-up Visit, or initiation of new anticancer therapy must be documented in the patient's source documents and the eCRF. In addition, any new medications taken after the

last dose of study drug through the 30 Day Safety Follow-up Visit, or initiation of new anticancer therapy, must be documented in the patient's source documents and the eCRF.

5.11.4. Permitted Medication

Medications that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded.

Supportive care agents, such as blood products, antiemetics, and pain medications are permitted as needed per ASCO guidelines (Hammond et al, 2010) or local institutional practices.

Medications used only as premedication for paclitaxel infusion per institutional practices are permitted even if listed as to avoid or take with caution, or prohibited.

5.11.5. Medications to Avoid or Take with Caution

The following medications must be avoided or taken with caution:

- Medications that are strong inhibitors, and inducers of CYP3A4 and CYP2C8.
    - For patients that have permanently discontinue paclitaxel and are being treated with rebastinib as a single agent, substrates, inhibitors and inducers of CYP2C8 may be taken without restriction.
    - Non-Medication CYP inhibitors, including the following herbal supplements and foods, must be avoided or taken with caution:
        - Herbal supplements and foods that are strong inhibitors of CYP3A4 including, but not limited to, grapefruit and grapefruit juice, Seville orange juice, or other products containing Seville oranges.
        - Strong inducers of CYP3A4 including, but not limited to, St. John’s wort.
        - Patients taking any of the above listed supplements and foods must be closely monitored for any potential interactions with rebastinib.
- Medications that are known inhibitors, or inducers of P-gp/multidrug resistance protein 1 (MDR1).
- Medications that increase gastric pH (e.g., H_2 receptor antagonists and antacids), with the exception of PPIs, may be taken provided they are not administered within 2 hours before or after administration of rebastinib. H_2 receptor antagonists administered during the required premedication for each paclitaxel infusion are allowed.
- Warfarin and low molecular weight heparin.
- Medications that are CYP2C19 and CYP2C9 substrates with a narrow therapeutic index
- Medications which are associated with conditional or possible risk of QT prolongation.

Patients taking any of the above listed medications must be closely monitored for any potential drug-drug interactions.

5.11.6. Prohibited Medications and Substances

The following medications must be excluded during the study:

- Anticancer therapies, including investigational therapy, concurrent radiation therapy (with the exception of radiotherapy for palliative radiation due to pre-existing bone metastases), or any other investigational therapy is not permitted during the study.
    - Palliative radiation during study treatment must be discussed with the Sponsor prior to implementation.
    - Hormonal therapy including octreotide or bone targeted therapy such as bisphosphonates or a receptor activator of nuclear factor-kappa B (RNAK) ligand inhibitor is not considered as anticancer therapy.
- Any other investigational therapy
- Proton pump inhibitors (PPIs): PPIs must be discontinued 4 days prior to the first dose of study drug.
- Medications that are known to prolong the QTc interval.
    - Antiemetics, known to prolong the QTc interval such as ondansetron are permitted only as premedication for paclitaxel infusion in accordance with institutional practice.
- Systemic corticosteroids or requirement chronically on study drugs, unless the dose is no more than the equivalent of prednisone 15 mg/day.
    - Inhaled, intranasal, intra-ocular, topical, and intra-articular injections are allowed.
    - Premedication with steroids, in accordance with institutional practice (including dexamethasone) is permitted prior to paclitaxel dosing.

5.11.7. Concomitant Procedures

All procedures performed on or after the first dose of study drug through the 30 Day Safety Follow-up Visit, or initiation of new anticancer therapy, must be documented in the patient's source documents and the eCRF.

Investigational procedures of any kind are excluded during the study. Surgical resection during study treatment must be discussed with the Sponsor prior to implementation.

5.12. Other Precautions

Formal photosensitivity studies have not been performed, however a potential for photoirritation/phototoxicity exists based absorption properties of rebastinib in the ultraviolet visible range (above 290 nm). In order to mitigate the potential risk of photoirritation/phototoxicity, patients must be instructed to avoid strong sunlight, sunlamps, and other sources of ultraviolet radiation for the duration of the study. Prophylactic skin care recommendations for all patients on study drug include sunscreen with sun protection factor ≥30, hypoallergenic moisturizing creams or ointments for dry skin, and gentle skincare with fragrance-free soaps and detergents.

6. STUDY ASSESSMENTS

The study specific assessments are detailed in this section and the Schedule of Assessments is outlined in Table 1 (Schedule of Assessments). Additional unscheduled safety or efficacy assessments may be performed at any time as clinically indicated to determine the relevance of specific findings and/or the duration of events.

6.1. Screening

Screening must occur within 28 days prior to the first dose of study drug to confirm that patients meet the selection criteria for the study. The assessments to be conducted at screening are provided in Table 1 (Schedule of Assessments).

6.2. Treatment Period

Patients will be registered in the study after confirmation of all eligibility criteria. The first dose of study drug must be administered in the clinic on Cycle 1 Day 1 (Baseline). The treatment period is defined as the time of first dose of study through the End of Treatment (EOT) Visit. Study visits during the treatment period will occur as shown in Table 1 (Schedule of Assessments). All visits must occur within the windows specified.

Patients who prematurely discontinue study drug must return for an EOT Visit within 7 days after the last dose of study drug.

6.3. Safety Follow-Up

Patients should be contacted between 30 and 37 days after the last dose of study drug, or prior to initiation of new anticancer therapy, to collect new information pertaining to AEs and concomitant medications and procedures as outlined in Table 1 (Schedule of Assessments). These assessments can be performed over the phone.

6.4. Lost to Follow-Up

A patient will be considered lost to follow up if both of the following occur:

- Patient misses two consecutive study visits and is subsequently unable to be contacted by phone call (after three documented attempts by phone within 2 weeks following the second missed visit).
- Patient does not respond within 2 weeks to a registered letter sent after the three attempted phone contacts.

6.5. Informed Consent Procedure

Each patient must sign and date a study-specific informed consent form (ICF) before any study specific procedures can be performed. The ICF will comply with all applicable regulations governing the protection of patients. An ICF, approved by the Sponsor and the site's Institutional Review Board (IRB) must be used. The Investigator or designee must document the consenting process, including the date when the ICF was signed in the patient’s source document.

6.6. Patient Identification and Registration

A unique patient identification number (patient number) will be assigned to each patient once informed consent is obtained. If a patient is rescreened, the patient retains the original patient number.

Patients who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria (Section 4.1 and Section 4.2) have been satisfied and that the patient is eligible for participation in this clinical study.

6.7. Demographics and Medical History

Demographic information must be collected at screening.

Cancer history and prior treatment (including reason for discontinuation), must be obtained during screening. Cancer history will include:

- Known histologic diagnosis.
- All prior cancer treatment regimens, including:
  - Surgery: include date(s), site(s), and extent of resection (e.g., tumor tissue sample only, R0, R1, or R2).
  - Systemic therapy: include dates of treatment, agents (including dose and dosing regimen), reason for treatment (e.g., adjuvant therapy or for metastatic disease), response, date of disease progression or date and reason for treatment discontinuation other than disease progression.
  - Radiation therapy: include the site(s) treated, total dose(s), date(s) of treatment, and response(s).
  - Other procedures, such as radiofrequency ablation (if applicable).

Medical history, including any significant conditions or diseases that stopped at or prior to informed consent, must be elicited from each patient during screening. Based on the medical history, the patient must be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history shall include a complete review of systems, past medical and surgical histories, and any allergies. Ongoing conditions are considered concurrent medical conditions; if possible, the start date for these comorbidities must be documented.

6.8. Safety

The safety profile will be assessed based on:

- Overall AEs
- SAEs
- AESIs
- Dose reduction or discontinuation of study drug due to toxicity
- Physical examinations

- ECOG PS
- Ophthalmic examinations
- Changes from baseline in laboratory parameters
- Electrocardiogram (ECGs)
- Echocardiograms or multigated acquisition (MUGAs)
- Vital signs

6.8.1. Physical Examinations and Height and Weight

A full physical examination will be performed at screening, and the EOT Visit. A full physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. At all other visits, examinations will be driven by clinical findings and/or patient complaints. If the patient reports a complaint or a possible AE, a targeted physical examination may be conducted at the Investigator's discretion. After consent, any clinically significant abnormal findings in physical examinations must be reported as AEs (Section 7).

6.8.2. Eastern Cooperative Oncology Group (ECOG) Performance Status

Eastern Cooperative Oncology Group (ECOG) PS (Oken et al, 1982) will be assessed according to the Schedule of Assessments in Table 1.

6.8.3. Vital Signs, Weight, and Height

Vital sign measurements, height, and weight will be performed according to the Schedule of Assessments in Table 1. Vital sign measurements will consist of sitting blood pressure, heart rate, respiratory rate, and body temperature. These will be assessed following a 5-minute rest (seated or supine position). On study visits when PK blood samples will be collected, assessment of vital signs will be conducted according to the schedule shown in Table 2 (Part 1) and Table 3 (Part 2). Vital sign assessments will be completed before the collection of the corresponding PK sample.

6.8.4. Electrocardiograms

Digital, 12-lead ECGs will be performed with central over-reading according to the Schedule of Assessments in Table 1. All sites will be provided with an ECG machine and associated materials by the central ECG diagnostic service. On study visits when PK blood samples will be collected, assessment of ECG will be conducted according to the schedule shown in Table 2 (Part 1) and Table 3 (Part 2). Assessment of ECG will be performed prior to PK sampling.

Performance of all ECGs must adhere to the following guidelines:

- All standard digital ECGs must be performed after the patient has been in the supine or semi-recumbent position for at least 5 minutes.
- An ECG must be performed before the collection of corresponding PK samples and prior to the dose of study drug.

- A hard copy of both the initial ECG tracing and central over-read copy must be printed and signed by the Investigator at the site.

6.8.5. Echocardiograms/Multigated Acquisition Scans

Echocardiograms or MUGA scans will be performed according to the Schedule of Assessments in Table 1. The same modality (echocardiogram or MUGA scan) must be used throughout the study. Left ventricular ejection fraction (LVEF) must be documented in the patient's source documents and eCRF.

6.8.6. Ophthalmologic Examination

Ophthalmologic examinations will be performed by a licensed ophthalmologist according to the Schedule of Assessments in Table 1. This examination does not have to be repeated during screening if there is documentation of an examination that met protocol criteria within 60 days prior to the first dose of study drug and after the last dose of previous anticancer treatment. Additionally, an examination done within 30 days prior to the last dose of study drug can substitute one required on the EOT Visit.

Examinations will include slit lamp examination of anterior structures (including eyelids, conjunctiva, cornea, anterior chamber, iris, and lens) and posterior structures (including optic nerve, macula, retinal vessels, the retinal periphery, and the vitreous); assessment of intraocular pressure by Goldmann Applanation Tonometry in each eye; assessment of visual acuity in each eye using best spectacle-corrected Snellen visual acuity at distance; assessment of visual fields based on Humphrey automated visual field testing using static automated perimetry testing with a 24-2 test pattern, but if not available a 30-2 test pattern; color vision testing using the Ishihara test; and, fundoscopy with mandatory digital photography of the fundus. Copies of digital photography of the fundus will be collected by the Sponsor and stored centrally. In addition to the scheduled examinations, ophthalmologic examinations will be performed as clinically indicated based on the occurrence of visual symptoms. Examinations prompted by visual disturbances should include fundus fluorescein angiography, optical coherence tomography, and electroretinogram as clinically indicated.

6.8.7. Clinical Laboratory Tests

Blood and urine samples will be collected according to the Schedule of Assessments in Table 1 and analyzed at the site's local laboratory. All blood samples must be collected while patients are in a seated or supine position. Laboratory test results that are abnormal and considered clinically significant must be reported as AEs (Section 7). Screening laboratory results must be available before the first dose of study drug. All samples must be collected in accordance with acceptable laboratory procedures, and graded for toxicity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0. (CTCAE 2017).

The safety laboratory tests are provided in Table 15.

Table 15: Safety Laboratory Tests

Serum Chemistry	Hematology	Urinalysis[b]
Alanine aminotransferase	Hemoglobin	Urine protein
Albumin	Hematocrit	Urine blood
Alkaline phosphatase	Platelets	Specific gravity
Aspartate aminotransferase	Leukocytes	Urine ketones
Bicarbonate	Differential	Urine glucose
Blood urea nitrogen	• Eosinophils	
Calcium	• Basophils	
Chloride	• Neutrophils	
Creatinine	• Lymphocytes	
Creatine Phosphokinase	• Monocytes	
Follicle-stimulating hormone[a]		
Glucose	**Coagulation Studies**	
Lactate dehydrogenase	Activated partial thromboplastin time	
Magnesium	Prothrombin time	
Phosphorus	International Normalized Ratio	
Potassium		
Sodium		
Total and direct bilirubin[c]		
Total protein		

a. This may be required to demonstrate a patient is non-childbearing potential as defined in Section 6.8.8.
b. If any result is abnormal, a microscopic analysis must be performed by the local laboratory.
c. Indirect bilirubin must be calculated and documented at the site.

6.8.8. Pregnancy Test

A serum β-hCG test to rule out pregnancy in women of childbearing potential will be obtained at screening. A urine or serum pregnancy test will be performed at all other visits as outlined in Table 1 (Schedule of Assessments).

Pregnancy testing will not be required for patients who are non-childbearing females; defined as one who is post-menopausal (amenorrhoeic for ≥12 months with a follicle-stimulating hormone (FSH) ≥40 mIU/mL) or is surgically sterile (has documented bilateral oophorectomy or hysterectomy).

6.8.9. Contraception and Pregnancy Avoidance Measures

6.8.9.1. Contraception

The effects of rebastinib on sperm, conception, pregnancy, and lactation are not known. Participation in this study requires patients to agree to use two methods of contraception, with one of the methods being highly effective. Methods of contraception must be in successful use prior to the first dose of study drug and until 120 days following the last dose of study drug.

Contraception for the patient is waived for the following:

True abstinence for the patient, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and postovulation methods) and withdrawal are not acceptable methods of contraception.

If the male has documented bilateral orchiectomy or is considered infertile as documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before the first dose of the study drug.

If the female is of non-childbearing potential, per the following:

- Postmenopausal: spontaneous amenorrhea for at least 12 consecutive months and have a serum FSH level ≥40 mIU/mL.
- Surgically sterile defined as documented bilateral oophorectomy or hysterectomy.

NOTE: All other female patients (including patients with tubal ligations and patients who do not have a documented hysterectomy) will be considered to be of childbearing potential.

Acceptable highly effective methods of contraception:

- Vasectomy 6 months or more previously, with a negative post-vasectomy semen analysis for sperm.
- Bilateral tubal ligation performed at least 6 months previously.
- Continuous use of an intrauterine device.
- Combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
  - injectable
  - implantable

Acceptable methods of contraception:

- Male and female condom with or without spermicide.
- Barrier contraception (such as diaphragm, cervical cap, or sponge) and spermicide.

Additional notes:

- Acceptable methods of contraception listed above are examples. Local requirements may prohibit the use of some of these examples. Please contact the Sponsor with any questions.
- Female condom cannot be used with male condom (as a double method of contraception) due to risk of tearing.
- Male and female patients who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.
- Male patients must not donate sperm after the first dose of study drug, throughout the study, and for 120 days following the last dose of study drug.

- Female patients and female partners of male patients must not plan to become pregnant during the study through 120 days following the last dose of study drug.
- Male patients whose female partner becomes pregnant through well-documented *in vitro* fertilization (donated sperm) or banked sperm (collected before the patient received study drug), must be compliant with the contraception requirements. In this scenario, the male patient must commit to using acceptable methods of contraception (to ensure there is no exposure of the fetus to study drug) for the duration of the study and until 120 days after the last dose of study drug.

Unique situations that may not fall within the above specifications must be discussed with the Sponsor.

If there is any question that a woman of childbearing potential or male patient will not reliably comply with the requirements for contraception, that patient must not be entered into the study.

6.8.9.2. Pregnancy

Patients must be counseled to inform the Investigator of any pregnancy that occurs during study treatment and for 120 days after the last dose of the study drug.

If a female patient becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. If the female partner of a male patient becomes pregnant while participating in the study, the patient must notify the Investigator immediately. The Investigator must notify the Sponsor and IQVIA Pharmacovigilance within 24 hours from the point in time when the Investigator becomes aware of the patient's (or partner's) pregnancy.

The patient or partner must be followed until the end of the pregnancy and the infant must be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF must be provided to explain these follow up activities. Pregnancy itself does not constitute an AE.

6.8.10. Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH Good Clinical Practice (GCP) guidelines. Section 7 outlines the definitions, collection periods, criteria and procedures for documenting, grading, and reporting AEs.

6.8.11. 30 Day Safety Follow-Up

All patients must be followed for AEs, medications, including any anticancer treatments, and procedures from last dose of study drug through the 30 Day Safety Follow-up Visit (30 [+7] days after last dose of study drug) or prior to the initiation of a new anticancer therapy, whichever occurs first.

6.9. Pharmacokinetics

6.9.1. Sample Collection

At the visits indicated in Table 1 (Schedule of Assessments), Table 2 (Part 1) and Table 3 (Part 2), blood samples will be collected for the determination of the concentrations of rebastinib and paclitaxel.

Details on sample collection, processing, and shipping of the samples, including any exceptions, will be provided in a separate protocol-specific Laboratory Manual.

For each visit with a PK blood draw, a record of study drug administration must be collected as described in Section 5.2. The collection date and time that each PK blood sample is drawn must also be recorded.

Samples from the PK sampling will be kept frozen by the Sponsor or its designee until all analyses have been completed and then disposed of according to the Sponsor or designee SOPs.

6.9.2. Sample Assessment

The following PK parameters will be calculated using non-compartmental methods of plasma rebastinib and paclitaxel, obtained after single and repeated dose administration. The parameters will include, but may not be limited to C_{max}, T_{max}, AUC, and $T_{1/2}$.

6.10. Efficacy

6.10.1. Radiologic Imaging

All patients will have radiographic tumor evaluation by CT or MRI scans of the chest, abdomen, and pelvis according to the Schedule of Assessments in Table 1. MRI or CT scans without contrast can be used for patients who are allergic to radiographic contrast media. Throughout the study, the same assessment technique should be used.

Determination of objective tumor response will be performed by the Investigator according to the RECIST Version 1.1. Assessments should be completed regardless of dosing delays or additional unscheduled imaging assessments. An MRI of the brain will be performed at screening and subsequent imaging time points if CNS metastases are present at screening or signs and symptoms suggests CNS metastases.

Imaging may be performed up to 7 days prior to the corresponding study visit. EOT imaging will only be performed on patients if imaging was not performed within the previous 12 weeks.

6.10.2. Response Assessment Using CA-125 (Ovarian Cancer Patients Only)

CA-125 should be collected for all patients with ovarian cancer according to the Schedule of Assessments in Table 1. Patients experiencing CA-125 response must have a confirmatory test performed at least 28 days after initial response is documented. Response assessment using RECIST Version 1.1 and CA-125 response criteria will be performed by the Investigator according to the Gynecological Cancer Intergroup (GCIG) guidelines (Rustin et al, 2011).

6.10.3. Relevant Tumor Markers

Data of relevant tumor markers such as CA-15.3, CA-125, CA-19-9, CA-27.29, prostate-specific antigen, and carcinoembryonic antigen will be collected as appropriate for disease assessment and if performed as a part of the standard of care.

6.11. Biomarker Research Studies

6.11.1. Sample Collection

Biomarker samples will be collected according to the schedule in Table 1 (Schedule of Assessments). Sampling may be discontinued at any time by the Sponsor contingent on data.

A Laboratory Manual describing the details of collecting, storing, and shipping of the samples, including any exceptions, will be provided.

Remaining biomarker samples, including archival samples, will be stored for up to 15 years. These samples will be used for further analysis intended to address scientific questions related to study drug and/or cancer. A decision to perform such exploratory biomarker research studies will be based on data obtained from rebastinib clinical studies, new scientific findings related to the drug class or disease, and/or reagent and assay availability.

6.11.2. Sample Assessments

6.11.2.1. Tumor Tissue Samples

At screening, an archival tumor tissue sample is required for all patients enrolled onto the study. If archival tumor tissue is unavailable, a fresh tumor biopsy will be collected prior to the first dose of study drug. Additionally, a fresh tumor biopsy will be collected at Cycle 3 Day 1. An optional tumor biopsy may be performed upon progression if a patient responded to treatment (CR/PR) and then progressed, and has provided consent for undergoing tumor biopsy. Fresh biopsies are only required for patients whose tumor is safe and accessible as judged by the Investigator and should only be collected if a patient qualifies for the study based on all other entry criteria. Aspiration cytology samples, such as fine-needle aspirates, are not acceptable.

Tissue samples will be used to assess changes in the tumor microenvironment (e.g., changes in the composition of infiltrating mononuclear cells including tumor-associated macrophages) when rebastinib is administered in combination with paclitaxel.

6.11.2.2. Whole Blood and Plasma Samples

Whole blood samples will be collected for immunophenotyping of peripheral blood mononuclear cells. Plasma samples will be collected to measure circulating levels of chemokines/cytokines. Changes in chemokines/cytokines will be monitored to investigate the impact of rebastinib in combination of paclitaxel on systemic immune response.

6.12. Pharmacogenomic Measurements

6.12.1. Sample Collection

A pharmacogenomic sample will be collected according to the schedule of study assessments in Table 1 (Schedule of Assessments). A Laboratory Manual describing the details of collecting, storing, and shipping the sample, including any exceptions, will be provided. The pharmacogenomic sample will be stored and analyzed by a central laboratory, and may be stored for up to 15 years.

6.12.2. Sample Assessment

Pharmacogenomic samples will be used to assess polymorphisms in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of rebastinib in combination with paclitaxel. Additionally, polymorphisms in genes that may be associated with clinical response and/or study drug-related toxicity will be assessed.

6.13. Patient Reported Outcome Measurements

Patients will be asked to complete PRO assessments in the form of questionnaires at the investigative site prior to any other study assessments (when possible) according to the Schedule of Assessments in Table 1.

Questionnaires will only be available in English, therefore, only English-speaking patients may complete the questionnaire. Patient-entered data will not be modified by the Investigator or site staff, ePRO vendor, CRO, or Sponsor.

6.13.1. National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (NCI-PRO-CTCAE)

The NCI-PRO-CTCAE measurement system was developed to gather symptomatic AEs by patient self-reporting (Kim et al, 2017). The NCI-PRO-CTCAE library is comprised of 124 items representing 78 symptomatic AEs. The NCI-PRO-CTCAE items evaluate symptom attributes such as symptom occurrence, frequency, severity, and interference with daily activities, and are intended to be complementary to the items in the NCI's CTCAE. Patients will fill out a subset of the library to report on their symptom experience over the preceding 7 days, using specific descriptor terms for each attribute.

In this study, a subset of NCI-PRO-CTCAE items has been selected from the NCI-PRO-CTCAE item library. The time required for completion is approximately 20 minutes. Patients will be asked to complete NCI-PRO-CTCAE (using patient reported outcome software, if possible) according to the Schedule of Assessments in Table 1.

6.13.2. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC QLQ-C30)

The EORTC QLQ-C30 is a validated, standardized, patient-completed questionnaire used extensively in international clinical studies. It was developed to assess health-related QOL in patients with cancer (EORTC, 2018). The time required for completion is approximately 4 minutes. The questionnaire is composed of multi-item and single-item scales. These include 5

functional scales (physical functioning, role functioning, emotional functioning, social functioning, cognitive functioning), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health status/QOL scale.

The physical functioning and role functioning scales are completed by the patient's response to Likert scale response options of "not at all," "a little," "quite a bit," or "very much." The 2 items comprising the global health status scale also evaluate the patient's experience over the past week using numerical rating scales with 1 representing "very poor" and 7 representing "excellent".

Patients will be asked to complete EORTC-QLQ-C30 (using patient reported outcome software, if possible) according to the Schedule of Assessments in Table 1.

6.13.3. Functional Assessment of Cancer Therapy – General (FACT-G)

The Functional Assessment of Chronic Illness Therapy (FACIT) FACT-G questionnaire, is a validated, standardized, patient completed question used extensively in international clinical studies (FACIT, 2018). It was developed to assess health related QOL in patients with cancer. The time required for completion is less than 1 minute. The questionnaire will be composed of 1 question (GP5 from FACT-G) to measure the burden of side effects experienced by the patient. It is completed by the patient's selection of one of the following options of "not at all," "a little bit," "somewhat," "quite a bit," and "very much.

Patients will be asked to complete the GP5 from FACT-G (using patient reported outcome software, if possible) according to the Schedule of Assessments in Table 1.

7. ADVERSE EVENT AND SERIOUS ADVERSE EVENT DOCUMENTATION, SEVERITY GRADING, AND REPORTING

7.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product during the study, which does not necessarily have a causal relationship with the study drug. An AE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency after the ICF is signed. When there is a change in severity of an existing AE, including improvement or worsening of an event, a new AE should be reported.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was screened in the study and progression of underlying disease are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned).

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, must not be reported as AEs. Elective surgeries or procedures must not be reported as AEs, but must be documented on the appropriate eCRF page. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an AE.

Each AE must be assessed immediately to determine if it meets the definition of serious (Section 7.8). If a SAE occurs, expedited reporting must follow local regulations, as appropriate.

7.2. Severity Assessment

The Investigator must determine and record the severity of all serious and non-serious AEs. The NCI-CTCAE, Version 5.0, must be used for grading the severity of AEs (Cancer Therapy Evaluation Program website.

The severity of an AE that does not appear in the CTCAE scale must be determined according to Table 16 (CTCAE, 2017).

Table 16: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 Severity Grading Scale

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

ADL = activities of daily living; AE = adverse event.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.3. Causality Assessment

The Investigator's assessment of relationship of the AE, if any to the study drug must be provided for all AEs. An Investigator's causality assessment is the determination of whether there is reasonable possibility that the study drug caused or contributed to an AE.

Relationship to each study drug must be determined by the Investigator according to the following criteria in Table 17.

Table 17: Relationship to Study Drug Criteria

Related	There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and causes other than the study drug has been ruled out, and/or the event re-appeared on re-exposure to the study drug.
Possibly Related	There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug, but there may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.
Unlikely Related	The event is unlikely to be related to the study drug and likely to be related to factors other than the study drug.
Not Related	The event is related to an etiology other than the study drug (the alternative etiology must be documented in the study patient's medical record).

For the purpose of the safety analyses, all AEs that are classified as at least possibly related will be considered treatment-related events.

7.4. Study Drug Action Taken

The Investigator must classify the study drug action taken with regard to the AE. The action taken must be classified according to the categories shown in Table 18.

Table 18: Classification for Study Drug Action Taken with Regard to an Adverse Event

Classification	Definition
Dose Not Changed	Study drug dose not changed in response to an AE.
Dose Reduced	Study drug dose reduced in response to an AE.
Drug Interrupted	Study drug administration interrupted in response to an AE.
Drug Withdrawn	Study drug administration permanently discontinued in response to an AE.
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" must be used during a dose hold or in circumstances such as when the study drug had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw study drug is possible.

AE = adverse event

7.5. Adverse Event Outcome

An AE must be followed until the Investigator has determined and provided the final outcome. The outcome must be classified according to the categories shown in Table 19.

Table 19: Classifications for Outcome of an Adverse Event

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms.
Recovered/Resolved with Sequelae	Resolution of an AE with residual signs or symptoms.
Recovering/Resolving	Improvement of an AE
Not Recovered/Not Resolved (Continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing.
Fatal	Outcome of an AE is death. "Fatal" must be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a patient lost to follow-up).

AE = adverse event

7.6. Treatment Given

The Investigator must ensure adequate medical care is provided to patients for any AEs. In addition, the Investigator must describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE and may include treatments such as other medications, hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

7.7. Additional Points to Consider for Adverse Events

7.7.1. Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs must be assessed and those deemed as clinically significant must be documented as an AE. When possible, a clinical diagnosis for the study assessment must be provided rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself may be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the patient has one or more of the following:

- Worsening, from baseline, concomitant signs or symptoms related to the abnormal study assessment.
- Further diagnostic testing or medical/surgical intervention is required.
- A change in the dose of study drug, if study drug is withheld, or discontinuation from study drug occurs.

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant must be made by the Investigator.

Symptoms of the disease under study must not be recorded as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease, including significant worsening unless the deterioration was unexpected, and are part of the efficacy data to be collected in the study.

7.8. Serious Adverse Events

An AE is considered serious if it meets any of the following:

- Results in death (regardless of cause), that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug.
- Is life threatening (an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in congenital anomaly/birth defect.
- Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes (i.e., allergic bronchospasm requiring intensive treatment in an

emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Clinical outcomes or symptoms related to progressive disease need to be reported as an SAE if they meet SAE criteria and occur within 30 days of the last study drug administration. They must be reported according to the diagnosis or symptom of event and not by the term “disease progression,” unless the disease progression is considered atypical, accelerated, or caused by study drug.

Clarification must be made between the terms "serious" and "severe," because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations. For example, a laboratory abnormality judged to be Grade 4, in itself, may not constitute an SAE unless the clinical status of the patient indicates a life-threatening AE.

7.9. Adverse Event of Special Interest for Study Drug

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to study drug, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such AEs may require further investigation to characterize and understand them. AESIs may be added or removed during a study by a protocol amendment.

The following AEs are considered AESIs:

- Muscular weakness (Grade 3)
- Central retinal vein occlusion

7.10. Adverse Event Reporting Periods

The AE (including SAEs and AESIs) reporting period begins from the time that the patient provides informed consent through and including 30 days after the last administration of the study drug for all enrolled patients. Any SAE or AESI occurring after the reporting period must be promptly reported if a causal relationship to study drug is suspected.

If a patient begins a new anticancer therapy, the safety reporting period ends at the time the new treatment is started; however, death must always be reported when it occurs during the safety reporting period irrespective of intervening treatment.

7.11. Adverse Event and Serious Adverse Event Reporting Requirements

Each patient must be carefully monitored for the development of any AEs. This information must be obtained in the form of non-leading questions (e.g., “How are you feeling?”) and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients.

All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures must be recorded. When possible, signs and symptoms indicating a common underlying pathology must be noted as one comprehensive event. Accompanying signs or symptoms (e.g., abnormal laboratory values) must not be reported as additional AEs. If a diagnosis is unknown, one or more symptoms may be reported as separate AEs. If an underlying diagnosis is subsequently determined for the reported symptom(s), then the reported symptom(s) term(s) must be revised to be "attributed" or "due" to the diagnosis.

All SAEs and AESIs that occur within the reporting period, regardless of causality, must be reported by the Investigator to IQVIA Pharmacovigilance **within 24 hours** from the point in time when the Investigator becomes aware of the SAE or AESI. SAEs and AESIs must be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow up is not required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it must be documented as ongoing. For purposes of regulatory safety monitoring, the Investigator is required to follow the event to resolution and report to the Sponsor the outcome of the event. Further instructions on reporting of SAEs and AESIs will be provided on the reporting form.

If there are serious, unexpected (defined as not reported in the IB), suspected adverse drug reactions (SUSARs) associated with the use of the study drug, the Sponsor or authorized designee will ensure that the appropriate regulatory agency(ies) and all participating Investigators are notified on an expedited basis. It is the responsibility of the Investigator to promptly notify the local IRB of SUSARs according to the institutional policy.

7.12. Abuse, Misuse, Overdose, and Medication Error

Occurrences of events of overdose, drug misuse, drug abuse and medication error must be reported to the Sponsor.

Abuse of a medicinal product: Persistent or sporadic, intentional excessive use of medicinal products, which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].

Misuse: Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or not within the legal status of its supply.

Overdose: Administration of a quantity of study drug given per administration or per day, which is above the assigned dose.

Medication Error: An error made in prescribing, dispensing, administration, and/or use of the study drug. Medication errors are reportable to the Sponsor as defined below.

- The dispensing, administration and/or use of the unassigned study drug.
- The administration and/or use of an expired study drug.

Note: cases of patients missing doses of the study drug are not considered reportable as medication errors.

AEs or SAEs associated with drug abuse, misuse, overdose, or medication error must be reported as appropriate (Section 7.1 and Section 7.8).

8. DISCONTINUATION AND REPLACEMENT OF PATIENTS

8.1. Discontinuation of Treatment

A patient is free to discontinue from the study drug and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a patient's involvement in the study at any time if the patient's clinical condition warrants it. The primary reason for discontinuation or withdrawal of a patient from study treatment must be determined using the following categories:

- Progressive Disease (clinical or radiological)
- Adverse event
- Withdrawal by patient from treatment
- Death
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Termination of study by Sponsor
- Any other reason that in the opinion of the Investigator, would justify removing the patient from study treatment, based on the best interest of the patient

8.2. End of Study

The end of study is defined as the date when the patient has withdrawn or completed all necessary follow-up assessments through the 30 Day Safety Follow-up Visit.

If the patient is unable to complete the 30 Day Safety Follow-up Visit, the reason will be captured in the clinical database using the following categories:

- New anticancer therapy
- Death
- Lost to follow-up
- Withdrawal by patient from study
- Termination of study by Sponsor
- Other

If a patient voluntarily withdraws from the study, the Investigator should attempt to contact the patient to determine the reason(s) for discontinuation and request the patient return for an EOT Visit and 30 Day Safety Follow-up Visit. Patients must return all used, partially used, and unused study drug blister packs.

8.3. Replacement of Patients

In Part 1, patients must receive ≥80% of planned doses of rebastinib and paclitaxel in Cycle 1 to be considered for determination of the RP2D. Patients who do not receive the requisite amount of the combination may be replaced.

In Part 2, patients who do not receive at least one dose of the combination will be replaced. Patients must receive at least 1 dose of the combination and have 1 post-baseline assessment, or be discontinued prior to the post-baseline disease assessment due to an AE at least possibly related to rebastinib, to be considered evaluable. In addition, if the study drug treatment is discontinued prior to the scheduled first post-dose tumor assessment (Cycle 3, Day 1) due to reasons other than disease progression (clinical or radiological) or AE(s) at least possibly related to rebastinib, patients may be replaced. Patients who meet these criteria will be replaced and not be included in the responder analysis.

9. STATISTICAL CONSIDERATIONS

9.1. Determination of Sample Size

Part 1 will primarily be used to evaluate the safety and tolerability of the combination. Up to 36 evaluable patients will be enrolled in total with at least 12 evaluable patients in each arm. This is considered appropriate for analysis of safety and tolerability to determine the RP2D.

A Simon two-stage design will apply to Part 2 of the study. The number of patients required for each cohort was calculated to demonstrate 20% improvement in ORR (from 20% historical ORR in the setting to 40% for the combination) under 80% power and one sided alpha of 0.05. In the initial stage, up to 18 patients will be evaluated. Greater than 4 responses will be required to enroll additional patients in order to demonstrate the target efficacy of >10 responses in a total of 33 patients. Thus, this part of study may enroll up to 165 (33 patients per indication-specific cohort) evaluable patients. If a non-evaluable rate of 10% is considered, approximately 183 patients may be enrolled.

9.2. Analysis Endpoints

9.2.1. Safety

Safety endpoints include:

- Overall AEs
- SAEs
- AESIs
- Dose reduction, dose interruptions, or discontinuation of study drug due to toxicity
- Physical examinations
- ECOG PS
- Ophthalmic examinations
- Changes from baseline in laboratory parameters
- Electrocardiogram (ECGs)
- Echocardiograms or multigated acquisition (MUGAs)
- Vital signs

9.2.2. Pharmacokinetics

Pharmacokinetic endpoints when rebastinib is administered in combination with paclitaxel and as a single agent include, but are not limited to:

- Time to maximum observed concentration (T_{max}: rebastinib only).
- Time to maximum observed concentration at steady state ($T_{max,ss}$: rebastinib only).
- Maximum observed concentration (C_{max}).

- Maximum observed concentration at steady state ($C_{max,ss}$).
- Concentration observed at the end of the dosing interval (C_{min}, trough concentration).
- Concentration observed at the end of the dosing interval at steady state ($C_{min,ss}$).
- Area under the concentration-time curve (AUC).
- Half-life ($T_{1/2}$).
- Volume of distribution (Vd).
- Clearance (CL).

9.2.3. Efficacy

Radiographic tumor assessments (CT or MRI) will be performed by RECIST Version 1.1. For ovarian patients, additional response assessments will be performed using RECIST Version 1.1 and CA-125 response criteria by the GCIG guideline (Oken et al, 1982). The endpoints for preliminary assessment of antitumor activity include:

- Objective response rate (CR + PR) of the combination therapy.
- Clinical benefit rate (CBR) (CBR = CR + PR + stable disease [SD]) at 8, 16, and 28 weeks of the combination therapy.
- Time to response (defined as time from Cycle 1 Day 1 to PR or CR).
- Progression-free-survival (PFS; defined as time from Cycle 1 Day 1 to disease progression or death due to any cause).
- Time to progression (TTP; defined as time from Cycle 1 Day 1 to the first documentation of progressive disease).
- Duration of response (DOR; time from first PR/CR to disease progression or death due to any cause).
- Overall survival (OS).

9.2.4. Pharmacogenomics

The pharmacogenomics endpoints of the study include, but are not limited to:

- Assessment of polymorphic variations in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of rebastinib.
- Assessment of polymorphisms in genes that may be associated with clinical response and/or study drug-related toxicity.

9.2.5. Pharmacodynamics

The pharmacodynamic endpoints of the study include, but are not limited to:

- Assess changes of plasma chemokines/cytokines upon treatment.
- Assess changes in monocyte population in peripheral blood.

- Evaluate changes in tumor microenvironment, including but not limited to tumor associated macrophage, tumor infiltrating lymphocytes using IHC, ISH or other fit-for-purpose assays.

9.2.6. Patient Reported Outcomes

Assess the safety profile of rebastinib in combination with paclitaxel using the NCI-PRO-CTCAE, a "treatment-bother" question (GP5) from Functional Assessment of Chronic Illness Therapy's (FACIT 2018), Functional Assessment of Cancer Therapy - General (FACT-G), as well as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC-QLQ-C30).

9.3. Populations for Analysis

Safety Population: The Safety Population is defined as all patients who have received at least one dose of either study drug. This population will be used for analysis of safety data.

Modified intent-to-treat (mITT) Population: mITT Population includes all patients who had at least one full dose of the combined study drugs, had measurable disease at baseline, and had at least one post-baseline assessment unless the patient discontinued prior to the post-baseline disease assessment due to an AE at least possibly related to rebastinib or due to clinical progression. This population will be used for analysis of efficacy data.

PK Population: The PK population will include all patients who received at least one dose of either study drug and had at least one measurable concentration in plasma for either study drug. Additionally, this population will be used for analysis of PD data, if post-dose PD data is available.

9.4. Procedures for Handling Missing, Unused, and Spurious Data

Unless specified in the individual endpoint analysis, missing data will not be imputed except for identification of TEAEs and study drug medication with missing start or end time. All available data will be presented on the data listings as collected.

A TEAE is defined as an AE that occurred on or after the time of initial study drug and within 30 days after the date of last dose of study drug.

Algorithms for imputing partial or missing dates of AEs are shown in Table 20. The same algorithm will be used for date of non-study drug medication.

Table 20: Partial or Missing Date Algorithms

Variable	Missing Day	Missing Day, Month	Missing Day, Month, Year
Date of Last Therapy/Date of Initial Diagnosis	Assign 1	Assign January 1 if prior to date of informed consent, otherwise use date of informed consent	Missing (do not impute)
Adverse Event/Start Date	Assign first day of month unless it is the month of first dose of study medication. Otherwise, assign date of first dose of study medication.	Assign January 1 unless the year is year of first dose of study medication Otherwise, assign date of first dose of study medication.	Assign date first dose of study medication.
Adverse Event End Date	Assign the last day of the month or end of study date, whichever is earlier.	Assign December 31 or end of study date, whichever is earlier.	If ongoing, end date is missing. Otherwise, assign end of study date.

9.5. Interim Analyses

No interim analysis for efficacy will be performed for this study.

9.6. Adjustment for Multiple Comparisons

Due to the exploratory nature of the study, adjustments for multiplicity will not be made.

9.7. Blinding

This is an open-label study.

9.8. Statistical Methods

9.8.1. General Methods

Data collected in this study will be documented using summary tables and patient data listings. Data may be displayed by each of the Part 1 arms and Part 2 indication-specific cohorts. Continuous variables will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequency distributions and proportions. Time-to-event data will be summarized via Kaplan Meier (KM) using medians with associated 2-sided 90% confidence intervals (CIs). Proportions, when appropriate, will be reported with exact 2-sided 90% confidence intervals.

Unless specified otherwise, baseline measurements must be the most recent value prior to receiving the first dose of study medication. If an assessment is not available, then the last assessment prior to that visit would be used.

Medical history, AEs, and concurrent procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

Unless specified, the mITT Population is used for efficacy analysis and the Safety Population is used for the safety analysis.

9.8.2. Disposition of Patients

Patient disposition will be summarized overall for all patients who entered the study (i.e., signed the informed consent for the study). In addition, the number of patients in each population (Safety, PK, and mITT) and patients that were removed from a population will be summarized. The number and proportion of patients who complete the study, as well as those who discontinue the study will be summarized along with the reason for discontinuation.

9.8.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics at study entry will be summarized for the Safety and mITT Populations.

9.8.4. Extent of Exposure

The total number of patients who received either study medication will be summarized by n and percentage. In addition, the number of cycles received will be displayed using continuous descriptive statistics. These analyses will be performed for the Safety Population.

9.9. Efficacy Analysis

Efficacy analysis for each of the Part 1 arms and Part 2 indication-specific cohorts will be performed separately. Additionally, analysis may be done by including Part 1 patients who met the inclusion criteria and received the same dose level as an RP2D selected for a given indication-specific cohort. Note that ORR is a secondary endpoint in Part 1 and a primary endpoint in Part 2.

9.9.1. Primary Endpoint

The primary endpoint in Part 2, ORR, defined as the proportion of patients with a CR or PR will be analyzed in the mITT Population as the primary analysis. Patients with unknown or missing response will be treated as non-responders, that is, they will be included in the denominator when calculating the proportion. Time to response (CR or PR) (reported in weeks) is defined as the interval between the date of first dose of study medication and the earliest date of first documented CR or PR. Patients who do not have a PR or CR will be censored at the date of the last adequate assessment. Results will be summarized for each cohort with the proportion and exact 2-sided 90% confidence intervals.

9.10. Secondary Endpoints

9.10.1. Progression-free Survival

The PFS (reported in weeks) is defined as the interval between Cycle 1 Day 1 and the earliest documented evidence of disease progression based on Investigator review, or death due to any cause. Patients who undergo surgical resection of target or non-target lesions, who have received other anticancer treatments, including surgical resection or radiation (other than palliative radiation to pre-existing bone metastases), or who do not have a documented date of progression

or death due to any cause will be censored at the date of the last assessment. Summaries for each cohort will be provided using the methods of Kaplan-Meier, and will include medians with 2-sided 90% confidence intervals.

9.10.2. Time to Progression

The secondary endpoint of TTP (reported in weeks) is defined as the interval between Cycle 1 Day 1 dose and the earliest documented evidence of disease progression based on Investigator review. Patients who undergo surgical resection of target or non-target lesions, who have received other anticancer treatments, who do not have a documented date of progression or death due to any cause, or who die prior to tumor progression will be censored at the date of the last assessment.

9.10.3. Overall Survival

Overall survival (reported in weeks) is defined as the interval between Cycle 1 Day 1 and date of death from any cause. Patients who are still alive or who are lost to follow-up will be censored at the date of last contact. Summaries for each cohort will be provided using the methods of Kaplan-Meier, and will include medians with 2-sided 90% confidence intervals. Summaries for each cohort will be provided using the methods of Kaplan-Meier, and will include medians with 2-sided 90% confidence intervals.

9.10.4. Time to Response

The time to response, as defined only for patients with PR or CR as the time from Cycle 1 Day 1 to the first PR or CR, will be summarized and displayed using the methods of Kaplan-Meier, and will include medians with 2-sided 90% confidence intervals.

9.10.5. Clinical Benefit Rate

Clinical benefit rate (CBR) will be calculated and summarized with n and percentage at 8, 16, and 28 weeks, and in the event of disease progression. Clinical benefit will be defined as having a response (complete or partial) or stable disease. Proportions with exact 2-sided 90% confidence intervals will be reported for each arm or indication-specific cohort.

9.10.6. Duration of Response

Duration of response, defined as the time from first PR/CR to disease progression or death due to any cause, will be calculated for patients who have a PR or CR. Duration of response will be summarized and displayed using the methods of Kaplan-Meier and will include medians with 2-sided 90% confidence intervals. Duration of response will be summarized only for patients who have a CR or PR.

9.11. Safety Analysis

9.11.1. Adverse Events

Adverse events will be summarized utilizing the number and proportion of patients by system organ class and preferred term for the Safety Population. All tables will only include TEAEs, where treatment emergent is defined as any AE that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug.

Adverse event toxicity grade will be classified using NCI-CTCAE Version 5.0 criteria (See Table 16). If a patient has multiple occurrences of the same system organ class (SOC) or preferred term, then only the most severe event will be summarized in the tables for that SOC and preferred term. Adverse events of ≥Grade 3 will also be summarized. A missing toxicity grade will not be imputed.

The AE analysis will be repeated for SAEs and AEs leading to dose reduction or discontinuation, and AESIs.

9.11.2. Eastern Cooperative Oncology Group Performance Status

Assessments will be summarized overall by time point utilizing continuous descriptive statistics. In addition, the change from baseline will be summarized for continuous parameters. For categorical parameters, the n and percentage will be displayed for each arm or indication-specific cohort.

9.11.3. Vital Signs

Assessments will be summarized overall by time point utilizing continuous descriptive statistics. In addition, the change from baseline will be summarized for continuous parameters. For categorical parameters, the n and percentage will be displayed for each arm or indication-specific cohort.

9.11.4. Echocardiogram/Multigated Acquisition Scans

Assessments will be summarized overall by time point utilizing continuous descriptive statistics. In addition, the change from baseline will be summarized for continuous parameters.

9.11.5. Ophthalmologic Assessments

Ophthalmologic assessments will be summarized by n and percent.

9.11.6. Clinical Laboratory Parameters

Assessments will be summarized overall by time point utilizing continuous descriptive statistics. In addition, the change from baseline will be summarized for continuous parameters. For categorical parameters, the n and percentage will be displayed for each arm or indication-specific cohort. Shift tables for labs with NCI-CTCAE grades will be presented.

9.12. Pharmacokinetic Analysis

Pharmacokinetic concentrations will be summarized utilizing continuous descriptive statistics, n, median, mean, standard deviation, minimum, and maximum. C_{max}, C_{min}, and AUC will also be summarized using geometric mean. Geometric means are standard for AUC and C_{max}.

9.13. Tumor Marker Analysis

Assessment of CA-125 in ovarian cancer will be done using GCIG criteria described in (Section 6.10.2). Otherwise, levels of tumor markers will be summarized overall by time points using descriptive statistics. In addition, changes from baseline will be summarized for each arm or indication-specific cohort.

9.13.1. Biomarker and Pharmacodynamic Analysis

Biomarkers and pharmacodynamic parameters will be summarized graphically and with descriptive statistics (mean, SD, median, min, max).

9.14. Pharmacogenomic Analysis

Pharmacogenomic analysis will explore the impact of variations in genes encoding for drug metabolism enzymes and drug transporters on patient's response to study drug.

9.15. Procedures for Reporting Deviations to Original Statistical Analysis Plan

All deviations from the original SAP will be provided in the final clinical study report.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Study Site Monitoring Visits

During study conduct, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors will review source documents to confirm that the data recorded on eCRFs is accurate. The Investigator and institution will allow the Sponsor's monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the IRB, and/or to quality assurance audits performed by the Sponsor, or companies working with or on behalf of the Sponsor, and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10.2. Protocol Compliance

The Investigator must conduct the study in compliance with the protocol provided by the Sponsor, and given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Modifications to the protocol must not be made without agreement between both the Investigator and the Sponsor. Changes to the protocol will require written IRB and the appropriate regulatory authority(ies) approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB. The Sponsor must ensure that all protocol modifications are submitted to the regulatory authority(ies) in accordance with the governing regulations.

If other unexpected circumstances arise that require deviation from protocol-specified procedures, the Investigator must consult with the Sponsor (and IRB, as required) to determine the appropriate course of action.

The site must document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site must notify the Sponsor (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessments.

11. DATA HANDLING AND RECORD KEEPING

11.1. Electronic Case Report Form

The Sponsor or designee will provide the study sites with secure access to and training on the electronic data capture application sufficient to permit site personnel to enter or correct information in the eCRFs on the patients for which they are responsible.

An eCRF is required and must be completed for each enrolled patient. The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms. Source documentation supporting the eCRF data must indicate the patient's participation in the study and must document the dates and details of study procedures, AEs, other observations, and patient status.

The Investigator, or designated representative, must complete the eCRF as soon as possible after information is collected.

The audit trail will show the user's identification information and the date and time of the any correction. The eCRFs must be signed electronically by the Investigator to attest that the data contained on the eCRFs, including any changes made to the eCRFs, is correct and endorse the final submitted data for the patients for whom the Investigator is responsible.

The completed eCRFs are the sole property of the Sponsor and must not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

The Sponsor will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be provided to the site for placement in the Investigator's study file.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), all signed ICFs, SAE forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records must be retained by the Investigator according to the ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor must be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association.

In addition, the study will be conducted in accordance with the protocol, ICH GCP, and applicable local regulatory requirements and laws.

The Investigator must ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21CFR Part 312, 21 CFR Part 314 and ICH GCP E6.

12.2. Patient Information and Consent

All parties must ensure protection of patient personal data and must not include patient names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, the Sponsor must maintain high standards of confidentiality and protection of patient personal data.

The ICF must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The ICF used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and the Sponsor before use.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The Investigator, or a person designated by the Investigator, must obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed.

12.3. IRB

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, ICFs, and other relevant documents from the IRB. All correspondence with the IRB must be retained in the Investigator Site File.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB and the Sponsor in writing immediately after the implementation.

12.4. Patient Confidentiality

The Sponsor and designees affirm and uphold the principle of the patient’s right to protection against invasion of privacy. Throughout this study, a patient’s source data must only be linked to the Sponsor’s clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or

date of birth may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA), the Sponsor's designated auditors, and the appropriate IRBs to review the patient's original medical records (source data or documents), including, but not limited to, any genetic/genomic data the patient might have from testing done prior to entering the study, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (Section 12.2).

Copies of any patient source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., patient name, address, and other identifier fields not collected on the patient's eCRF).

12.5. Reporting of Safety Issues or Serious Breaches of the Protocol or International Conference on Harmonization Good Clinical Practice

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the study drug, the Sponsor must be informed immediately.

In addition, the Investigator must inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that comes to the attention of the Investigator.

12.6. Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

13. STUDY TERMINATION

When the Sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drug, as well as other important information that may affect proper conduct of the clinical study, the Sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reason to the Investigator.

If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor of the discontinuation and the reason for it.

13.1. Criteria for Suspension or Premature Termination of the Study

Criteria for either temporary suspension or premature termination of the study include:

1. New information regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for patients participating in the study.
2. Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises patient safety.
3. The Sponsor may suspend or prematurely terminate the study for reasons not related to the conduct of the study.

13.2. Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found to be in significant violation of GCP, protocol, contractual agreement, or is unable to ensure adequate performance of the study.

13.3. Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

14. PUBLICATION OF STUDY RESULTS

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere must be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and therefore may be disclosed as required to other clinical Investigators, business partners and associates, the FDA, and other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the Investigator and/or the Investigator's institution.

15. REFERENCES

1. Alvarez AA and Clarke-Pearson DL. Platinum-resistant and refractory ovarian cancer. *Am J Cancer.* 2003;2:1.
2. Anampa J, Xue X, Oh S, Kornblum N, Sadan S, Oktay M, et al. Phase 1b study of rebastinib plus antitubulin therapy with paclitaxel (P) or eribulin(E) in patients with HER2-negative metastatic breast cancer (MBC). Presented at the 2018 American Association of Cancer Research Annual Meeting. April 14-18.
3. Anderson W, Schairer C, Chen B, Hance KW, Levine PH: Epidemiology of inflammatory breast cancer. *Breast Dis.* 2005–2006;22:9–23.
4. Coffelt SB, Chen YY, Muthana M, Welford AF, Tal AO, Scholz A, et al. Angiopoietin 2 stimulates TIE2-expressing monocytes to suppress T cell activation and to promote regulatory T cell expansion. *J Immunol.* 2011;186(7):4183-90.
5. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017. National Cancer Institute, National Institutes of Health. U.S. Department of Health and Human Services.
6. Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. *Cell.* 2006;124(2):263-6.
7. De Palma M, Venneri MA, Galli R, Sergi Sergi L, Politi LS, Sampaolesi M, et al. TIE2 identifies a hematopoietic lineage of proangiogenic monocytes required for tumor vessel formation and a mesenchymal population of pericyte progenitors. *Cancer Cell.* 2005;8(3):211-26.
8. EORTC Quality of Life http://groups.eortc.be/qol/eortc-qlq-c30 [accessed 16 February 2018].
9. FACIT.org http://www.facit.org/FACITOrg/Overview [accessed 27 April 2018].
10. Gori S, Mosconi AM, Basurtol C, Cherubinil R, De Angelis V, Tonato M, et al.: Weekly paclitaxel in metastatic breast cancer patients. *Tumori.* 2002;88:470-73.
11. Gradishar W, Tjulandin S. Davidson N, Shaw H, Desai N, Bhar P, et al. Phase Ill trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol.* 2005;23(31):7794-803.
12. Green MC, Buzdar AU, Smith T, Ibrahim NK, Valero V, Rosales MF, et al.: Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J Clin Oncol.* 2005;23(25):5983-992.
13. Gynecologic Oncology Group, Markman M, Blessing J, Rubin SC, Connor J, Hanjani P, et al. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol 2006;101:436.
14. Hammond MEH, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American society of clinical oncology/college of American pathologists guideline

recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Arch Pathol Lab Med.* 2010;134:907-01.

15. Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer Cell.* 2012;21(3):309-22.
16. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. *J Natl Cancer Inst.* 2005;97(13):966-75.
17. Harney AS, Arwert EN, Entenberg D, Wang Y, Guo P, Qian BZ, et al. Real-time imaging reveals local, transient vascular permeability, and tumor cell intravasation stimulated by TIE2hi Macrophage-Derived VEGFA. *Cancer Discov Online.* 2015;5(9):932-43.
18. Harney AS, Karagiannis GS, J Pignatelli J, Smith BD, Kadioglu E, Wise SC, et al. The selective Tie2 inhibitor rebastinib blocks recruitment and function of Tie2Hi macrophages in breast cancer and pancreatic neuroendocrine tumors. *Mol Cancer Ther.* 2017;16(11):2486-501.
19. Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol.* 2007;25(33):5287-312.
20. Homesley HD, Filiaci V, Markman M, Bitterman P, Eaton L, Kilgore LC, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:526.
21. Ibberson M, Bron S, Guex N, Faes-van't Hull E, Ifticen-Treboux A, Henry L, et al. TIE-2 and VEGFR kinase activities drive immunosuppressive function of TIE-2-expressing monocytes in human breast tumors. *Clin Cancer Res.* 2013;19(13):3439-49.
22. Jones SE, Erban J, Overmoyer B, Budd GT, Hutchins L, Lower L, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol.* 2005;23(24):5542-551.
23. Karagiannis GS, Pastoriza JM, Wang Y, Harney AS, Entenberg D, Pignatelli J, et al. Neoadjuvant chemotherapy induces breast cancer metastasis through a TMEM-mediated mechanism. *Sci Transl Med.* 2017;9(397): eaan0026. Erratum in: Sci Transl Med. 2017;9(399): eaao3817.
24. Kim J, Singh H, Ayalew K, Borror K, Campbell M, Johnson LL, et al. Use of PRO measures to inform tolerability in oncology trials: Implications for clinical review, IND safety reporting and clinical site inspections. *Clin Cancer Res.* 2017;13.
25. Kumar S, Mahdi, Bryant C, Shah JP, Garg G, Munkarah A. Clinical trials and progress with paclitaxel in ovarian cancer. *Intl J of Women's Health.* 2010;2:411-27.
26. Lewis CE, Ferrara N. Multiple effects of angiopoietin-2 blockade on tumors. *Cancer Cell.* 2011;19(4):431-3.
27. Lincoln S, Blessing JA, Lee RB, Rocereto TF. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2003;88(3):277-81.

28. Lombardi D, Crivellari D, Scuderi D, Magri MD, Spazzapan S, Sorio R, et al.: Long-term, weekly one-hour infusion of paclitaxel in patients with metastatic breast cancer: A phase II monoinstitutional study. *Tumori.* 2004; 90(3):285-88.

29. Markman M, Blessing J, Rubin SC, Connor J, Hanjani P, Waggoner S, Gynecologic Oncology Group. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2006;101(3):436–40.

30. Mazzieri R, Pucci F, Moi D, Zonari E, Ranghetti A, Berti A, et al. Targeting the ANG2/TIE2 axis inhibits tumor growth and metastasis by impairing angiogenesis and disabling rebounds of proangiogenic myeloid cells. *Cancer Cell.* 2011;19(4):512-26.

31. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-55.

32. Ozols RF. Oral etoposide for the treatment of recurrent ovarian cancer. *Drugs.* 1999;58(3):43.

33. Perez EA, Vogel CL, Irwin DH, Kirshner JJ, Patel R.: Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol.* 2001;19:4216-223.

34. Rigamonti N, Kadioglu E, Keklikoglou I, Wyser Rmili C, Leow CC, De Palma M. Role of angiopoietin-2 in adaptive tumor resistance to VEGF signaling blockade. *Cell Rep.* 2014;8(3):696-706.

35. Robinson BD, Sica GL, Liu YF, Rohan TE, Gertler FB, Condeelis JS, et al. Tumor microenvironment of metastasis in human breast carcinoma: a potential prognostic marker linked to hematogenous dissemination. *Clin Cancer Res.* 2009;15(7):2433-41.

36. Rohan TE, Xue X, Lin HM, D'Alfonso TM, Ginter PS, Oktay MH, et al. Tumor microenvironment of metastasis and risk of distant metastasis of breast cancer. *J Natl Cancer Inst.* 2014;106(8).

37. Rustin GJ , Vergote I , Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *Int J Gynecol Cancer.* 2011;21:419–23.

38. Sato K, Inoue K, Saito T, Kai T, Mihara H, Okubo K, et al. Multicenter phase II trial of weekly paclitaxel for advanced or metastatic breast cancer: The Saitama breast cancer clinical study group (SBCCSG-01). *Jpn J Clin Oncol.* 2003;33(8):371-76.

39. Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol.* 2008;1;26(10):1642-9.

40. Seidman AD, Hudis CA, Albanell J, Tong W, Currie V, Moynahan ME, et al. Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol.* 1998;16:3353-61.

41. Sigurdsson H, Johansson-Terje I, Aspegren K, Landberg T, Andersson T, Borgstrom S, et al. Weekly-dose doxorubicin (WDA) in advanced breast cancer. Radiother Oncol 1986;7:133.

42. Sparano JA, Zhao F, Martino S, Ligibel JA, Perez EA, Saphner T, et al. Long-term follow-up of the E1199 phase III trial evaluating the role of taxane and schedule in operable breast cancer. *J Clin Oncol.* 2015;33:2353-360.

43. Sutton G, Brunetto VL, Kilgore L, Soper JT, McGehee R, Olt G, et al. A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study. Gynecol Oncol 2000;79:147.

44. Tai P, Yu E, Shiels R, Pacella J, Jones K, Sadikov E, et al. Short- and long-term cause-specific survival of patients with inflammatory breast cancer. *BMC Cancer.* 2005;5:137.

45. Tiersten AD, Selleck MJ, Hershman DL, Smith D, Resnik EE, Troxel AB, et al. Phase II study of topotecan and paclitaxel for recurrent, persistent, or metastatic cervical carcinoma. *Gynecol Oncol.* 2004;92(2):635-8.

46. Welford AF, Biziato D, Coffelt SB, Nucera S, Fisher M, Pucci F, et al. TIE2-expressing macrophages limit the therapeutic efficacy of the vascular-disrupting agent combretastatin A4 phosphate in mice. *J Clin Invest.* 2011;121(5):1969-73.

47. Wyckoff JB, Wang Y, Lin EY, Li J, Goswami S, Stanley R, et al. Direct visualization of macrophage-assisted tumor cell intravasation in mammary tumors. *Cancer Res.* 2007;67(6):2649-56.