ROCK-IF Trial: Re-sensitization of Carboplatin-resistant Ovarian Cancer with Kinase Inhibition of FAK, a Phase 1/2 clinical trial

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Study Chair (Sponsor-Investigator)

Michael T. McHale, M.D.
Clinical Professor, Department of Reproductive Medicine
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093
Phone: (858) 822-6275
Fax: (858) 822-6319
E-mail: mtmchale@ucsd.edu

Research Coordinating Center
UCSD Moores Cancer Center
3855 Health Sciences Drive #0698
La Jolla, CA 92093-0698

Project Manager: Sara Neugroschl
Phone: (858) 822-7952
Email: saneugroschl@ucsd.edu

Study Agent:	Defactinib (VS-6063 from Verastem Inc.)
IND Holder Name:	Michael McHale, M.D., UC San Diego Health
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LIST OF INVESTIGATORS

PRINCIPAL INVESTIGATOR

Michael T. McHale, M.D.
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093
Phone: (858) 822-6275
Fax: (858) 822-6319
E-mail: mtmchale@ucsd.edu

SUB-INVESTIGATORS

David D. Schlaepfer, Ph.D.
University of California, San Diego
Moores Cancer Center
Division of Gynecologic Oncology
3855 Health Sciences Drive #0803
La Jolla, CA 92093
Phone: (858) 822-3444
Fax: (858) 822-7519
E-mail: dschlaepfer@ucsd.edu

Cheryl C. Saenz, M.D.
University of California, San Diego
Moores Cancer Center
Division of Gynecologic Oncology
3855 Health Sciences Drive #0987
La Jolla, CA 92093
Phone: (858) 822-6275
Fax: (858) 822-6319
E-mail: csaenz@ucsd.edu

Steven C. Plaxe, M.D.
University of California, San Diego
Moores Cancer Center
Division of Gynecologic Oncology
3855 Health Sciences Drive #0987
La Jolla, CA 92093
Phone: (858) 822-6199
Fax: (858) 822-6319
Email: splaxe@ucsd.edu

Ramez Eskander, M.D.
University of California, San Diego
Moores Cancer Center
Division of Gynecologic Oncology
3855 Health Sciences Drive #0987
La Jolla, CA 92093
Phone: (858) 822-6199
Fax: (858) 822-6319
Email: reskander@ucsd.edu

Pratibha S. Binder, M.D.
University of California, San Diego
Moores Cancer Center
Division of Gynecologic Oncology
3855 Health Sciences Drive #0987
La Jolla, CA 92093
Phone: (858) 822-6199
Fax: (858) 822-6319
Email: pbinder@ucsd.edu

Dwayne G. Stupack, Ph.D.
University of California, San Diego
Moores Cancer Center
Division of Gynecologic Oncology
3855 Health Sciences Drive #0803
La Jolla, CA 92093
Phone: (858) 822-1150
Fax: (858) 822-7519
dstupack@ucsd.edu

Varun Gupta, M.D.
Division of Hematology/Oncology
Eisenhower Health
Lucy Curci Cancer Center
39000 Bob Hope Dr
Rancho Mirage, CA 92270
Phone: (760) 346-7655
Fax: (760) 346- 3037
E-mail: vgupta@eisenhowerhealth.org

Joshua Cohen, M.D.
Department of Obstetrics and Gynecology
University of California, Los Angeles
Ronald Reagan Medical Center
200 UCLA Medical Plaza Suite 220
Los Angeles, CA 90095
Phone: (310) 794- 7274
Fax: (310) 794-9110
Email: jgcohen@mednet.ucla.edu

Biostatisticians:

Xinlian Zhang, PhD
University of California, San Diego
Moores UCSD Cancer Center
3855 Health Sciences Drive #0987
La Jolla CA, 92093-0987
Phone: 858-822-4838
E-mail: xizhang@ucsd.edu

Jing Zhang, M.S.
University of California, San Diego
Moores UCSD Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA, 92093-0987
Phone 858-534-2098
Email: jiz277@ucsd.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

UCSD Principal Investigator/Study Chair

_____
Printed Name

_____ _____
Signature Date

Participating Site Principal Investigator

_____ _____
Printed Name Institution

_____ _____
Signature Date

Participating Site Principal Investigator

_____ _____
Printed Name Institution

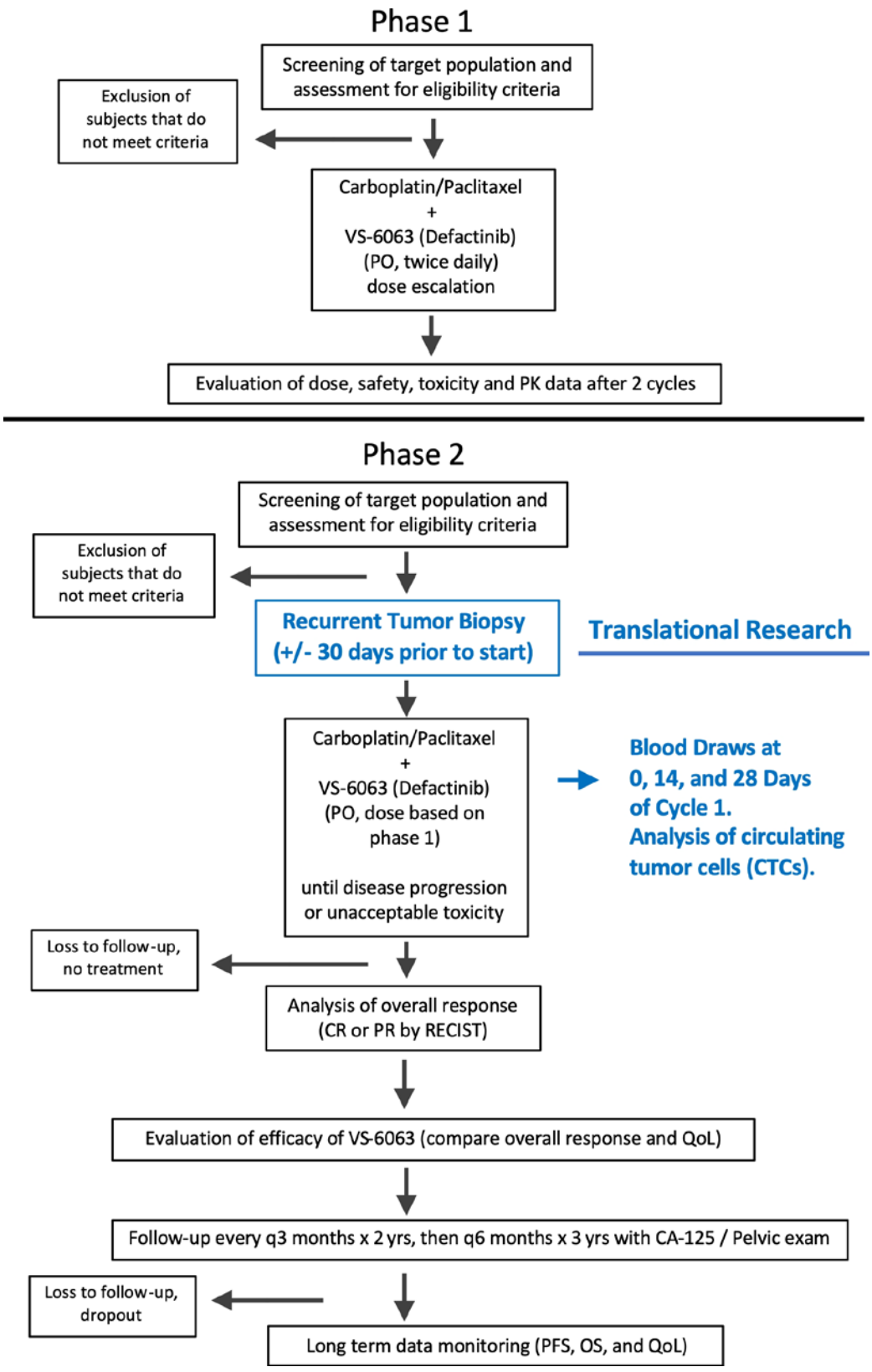
_____ _____
Signature Date

I. TABLE OF CONTENTS

II. LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute Neutrophil Count
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the curve
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
FAK	Focal Adhesion Kinase
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GOG	Gynecologic Oncology Group
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IRB	Institutional Review Board
I.V.	Intravenous
NCI	National Cancer Institute
OC	Ovarian Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PO	per os/by mouth/orally
PR	Partial Response
PT	Prothrombin Time
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
ULN	Upper Limit of Normal

1.0 STUDY SCHEMA



2.0 **STUDY SUMMARY**

Title	ROCK-IF Trial: Re-sensitization of Carboplatin-resistant Ovarian Cancer with Kinase Inhibition of FAK, a Phase 1/2 clinical trial
Short Title	ROCK-IF Trial for platinum-resistance
Phase	Phase 1 and Phase 2
Methodology	Initial safety lead-in followed by an open-label, single-arm treatment design
Study Duration	Estimated duration 4 years
Study Center(s)	Multi-center: Moores Cancer Center, University of California, La Jolla, CA Lucy Curci Cancer Center, Eisenhower Hospital, Palm Desert, CA David Geffen School of Medicine at UCLA, Westwood, CA
Objectives	Phase 1: To assess the safety and tolerability of VS-6063 plus paclitaxel and carboplatin chemotherapy using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Phase 2: To evaluate the anti-tumor activity of VS-6063 plus paclitaxel and carboplatin in patients with recurrent ovarian, fallopian tube or primary peritoneal cancer primarily through the objective response rate (ORR), using best ORR by RECIST 1.1.
Number of Subjects	Approximately 80-90 patients will be enrolled (72 patients in Phase 2).
Diagnosis and Main Inclusion Criteria	Main clinical diagnosis: recurrent or persistent platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma Key inclusion criteria: 1) ≥ 18 years of age and able to give consent 2) Patients must have recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal carcinoma, diagnosed within 6 months of completing their most recent platinum-containing chemotherapy. 3) All patients must have measurable disease as defined by RECIST 1.1. 4) Patients must have a GOG Performance Status of 0, 1, or 2. 5) Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. 6) Patients must have NOT received more than three total prior lines of cytotoxic chemotherapy for management of recurrent or persistent disease, including retreatment with initial chemotherapy regimens.
Study Product(s), Dose, Route, Regimen	Phase 1: • First 3 patient cohort: VS-6063 200 mg PO twice daily, plus paclitaxel 60 mg/m2 infused IV continuously over 1 hour on days 1, 8, and 15 and carboplatin (AUC of 4 mg/mL/min) IV infused continuously over 1 hour on day 1 of a 28 day cycle until progression or other discontinuation criteria are met.

	• IF TOLERATED, Second 3 patient cohort: VS-6063 400 mg PO twice daily, plus paclitaxel 60 mg/m2 infused IV continuously over 1 hour on days 1, 8, and 15 and carboplatin (AUC of 4 mg/mL/min) IV infused continuously over 1 hour on day 1 of a 28 day cycle. Phase 2: VS-6063 dose based on phase 1 results, PO twice daily, plus paclitaxel 60 mg/m2 infused continuously over 1 hour on days 1, 8, and 15 and carboplatin (AUC of 4 mg/mL/min) infused continuously over 1 hour on day 1 of a 28 day cycle until disease progression or unacceptable toxicity. Subjects experiencing paclitaxel related toxicities requiring cessation of cytotoxic therapy, who have at least stable disease, may continue to receive oral VS-6063 twice daily until disease progression or other discontinuation criteria have been met.
Duration of Administration	The total duration of drug administration across Phase 1 and Phase 2 is to be determined by the efficacy and tolerability of the drug combination, as treatment will continue until disease progression or toxicity.
Reference Therapy	Therapy will be compared to the historical reference standard of weekly paclitaxel 80 mg/m2.
Statistical Methodology	Phase 1: A 3 + 3 study design will be employed. Phase 2: The primary endpoint of objective response rate will be compared to that of the historical control (weekly paclitaxel). The secondary endpoints of progression-free survival and overall survival will be evaluated using Kaplan-Meier estimates.

3.0 SCHEDULE OF EVENTS

	Phase 1							Surveillance	
	Days -28 to 0	Days 1-28		Days 29-56		Days 57+		Months 0-24 following treatment	Months 25-60 following treatment
Procedures	**Screening**	Chemo Cycle 1 (VS-6063 BID[H]) Plus Paclitaxel 60 mg/m^2 and Carboplatin (AUC 4) Day 1	Cycle 1 Day 8 and Day 15 (Paclitaxel 60 mg/m^2)	Chemo Cycle 2 (VS-6063 BID[H]) Plus Paclitaxel 60 mg/m^2 and Carboplatin (AUC 4) Day 1	Cycle 2 Day 8 and Day 15 (Paclitaxel 60 mg/m^2)	Chemo Cycle 3+ [F,G] (VS-6063 BID[H]) Plus Paclitaxel 60 mg/m^2 and Carboplatin (AUC 4) Day 1	Cycle 3 Day 8 and Day 15 (Paclitaxel 60 mg/m^2)	Post-treatment surveillance (Visits q 3 months)	Post-treatment surveillance (Visits q 6 months)
Eligibility Screening									
Informed Consent	X								
GOG Performance Status	X	X[A]							
Vital Signs	X	X							
Height/Weight/BMI	X	X	X	X	X	X	X		X
Complete Medical History/ Baseline Demographics	X	X	X	X	X	X	X		X
Concomitant Medications[J]	X	X	X	X	X	X	X		
Adverse Effects (AE)[J]		X	X	X	X	X	X	X[J]	
Physical Examination (Complete)	X	X						X	X
Physical Exam (Targeted, Including Bimanual/Pelvic Exam by Gynecologic Oncologist)				X		X			
Laboratory **Pre-Chemo Labs:**									
- Complete Metabolic Panel	X	X	X	X	X	X	X		
- CBC With Differential	X	X	X	X	X	X	X		
Baseline Labs:									
- Inr, Pt, Ptt	X	X							
- Urine Pregnancy Test	X[B]	X[B]							
CA-125 Serum Level	X[A]	X[A]		X		X	X		X
Imaging									
CT Scan with RECIST Assessments	X[A]						X[D]		

	Phase 1								Surveillance	
	Days -28 to 0	Days 1-28		Days 29-56		Days 57+			Months 0-24 following treatment	Months 25-60 following treatment
Procedures	**Screening**	Chemo Cycle 1 (VS-6063 BID[H]) Plus Paclitaxel 60 mg/m^2 and Carboplatin (AUC 4) Day 1	Cycle 1 Day 8 and Day 15 (Paclitaxel 60 mg/m^2)	Chemo Cycle 2 (VS-6063 BID[H]) Plus Paclitaxel 60 mg/m^2 and Carboplatin (AUC 4) Day 1	Cycle 2 Day 8 and Day 15 (Paclitaxel 60 mg/m^2)	Chemo Cycle 3+ [F,G] (VS-6063 BID[H]) Plus Paclitaxel 60 mg/m^2 and Carboplatin (AUC 4) Day 1	Cycle 3 Day 8 and Day 15 (Paclitaxel 60 mg/m^2)	Post-treatment surveillance (Visits q 3 months)	Post-treatment surveillance (Visits q 6 months)
Treatment									
Chemotherapy Infusion (Carbo/Taxol)		x	x	X	x	X	x		
Oral VS-6063		x	x	x	x	x	x		
Research Specimens									
Tissue Collection (Archival)	x								

	Phase 2								Surveillance	
	Days -28 to 0	Days 1-28		Days 29-56		Days 57+			Months 0-24 following treatment	Months 25-60 following treatment
Procedures	**Screening**	Chemo Cycle 1 (VS-6063 BID[H]) Plus Paclitaxel 60 mg/m^2 and Carboplatin (AUC 4) Day 1	Cycle 1 Day 8 and Day 15 (Paclitaxel 60 mg/m^2)	Chemo Cycle 2 (VS-6063 BID[H]) Plus Paclitaxel 60 mg/m^2 and Carboplatin (AUC 4) Day 1	Cycle 2 Day 8 and Day 15 (Paclitaxel 60 mg/m^2)	Chemo Cycle 3+ [F,G] (VS-6063 BID[H]) Plus Paclitaxel 60 mg/m^2 and Carboplatin (AUC 4) Day 1	Cycle 3 Day 8 and Day 15 (Paclitaxel 60 mg/m^2)	Post-treatment surveillance (Visits q 3 months)	Post-treatment surveillance (Visits q 6 months)
Eligibility Screening									
Informed Consent	x								
GOG Performance Status	X	x[A]							
Vital Signs	X	x							
Height/Weight/BMI	X	x	x	x	x	x	x		x
Complete Medical History/ Baseline Demographics	X	x	x	x	x	x	x		x
Concomitant Medications[J]	X	x	x	X	x	x	x		

Adverse Effects (AE)[J]		x	x	X	X	x	x	x[J]	
Physical Examination (Complete)	X	x						x	x
Physical Exam (Targeted, Including Bimanual/Pelvic Exam by Gynecologic Oncologist)				x		x			
Laboratory									
Pre-Chemo Labs:									
- Complete Metabolic Panel	x	x	x	x	x	x	x		
- CBC With Differential	x	x	x	x	x	x	x		
Baseline Labs:									
- Inr, Pt, Ptt	x	x							
- Urine Pregnancy Test	x[B]	x[B]							
CA-125 Serum Level	x[A]	x[A]		x		x	x		x
Imaging									
CT Scan with RECIST Assessments	x[A]						x[D]		
Treatment									
Chemotherapy Infusion (Carbo/Taxol)		x	x	x	x	x	x		
Oral VS-6063		X	X	X	X	X	X		
Research Specimens									
Tumor Tissue (Archival)	X								
Tumor Biopsy Prior To Phase 2, Cycle 1 Day 1 (Within 30 Days)	X								
Whole Blood		x	x[E]	x[E]					
Patient Reported Outcomes									
Quality of Life Survey	x					X[C]			x[C]

Superscript notation on Schedule of Events Table.

A. Only if NOT done within screening window prior to visit.
B. Reproductive aged women only.
C. Quality of Life questionnaires to be completed every third cycle (i.e. cycle 3, 6, 9, etc), and at 3, 6, 9, 12 and 24 months following treatment.
D. In addition to baseline, CT scans to be obtained following every third cycle (i.e. cycle 3, 6, 9, etc).
E. Phase 2 research samples: whole blood collected at Day 0 of cycle 1 (+- 2 days), Day 14 of cycle 1 (+-2 days), and Day 28 of cycle 1 (+/- 2 days).
F. Treatment regimen remains the same for all subsequent cycles, unless dose reduction indicated. For patients initially enrolled in Phase 1 who are on treatment upon opening of the Phase 2 portion of the trial, the numbering of cycles initiated in Phase 1 will continue into Phase 2.
G. Treatment to be continued until disease progression or unacceptable toxicity. Subjects experiencing paclitaxel related toxicities requiring cessation of cytotoxic therapy, who have at least stable disease, may continue to receive oral VS-6063 twice daily until disease progression or other discontinuation criteria have been met.
H. Exact VS-6063 dose in Phase 2 is to be determined by Phase 1 safety data
I. Dose of VS-6063 based on Phase 1 Cohort enrollment. VS-6063 to be taken twice daily for the 28 day cycle**.**
J. Only collected up to 3 months post treatment.

4.0 BACKGROUND AND RATIONALE

4.1.1 Epithelial Ovarian Cancer

Ovarian cancer (OC) remains the leading cause of death from gynecologic malignancies and ranks as the fifth most common cause of cancer deaths among women[1]. In 2018, ~22,000 new cases were reported in the United States and more than 200,000 women were diagnosed worldwide[2].

Approximately 90% of ovarian cancers are epithelial in origin, arising from the cell layers covering the ovaries and/or fallopian tubes[3,4]. In many patients, OC is diagnosed at an advanced stage, with disease that has spread beyond the pelvis. Disease metastasis to other parts of the abdomen is associated with significant morbidity and decreased survival[5]. Five-year relative survival for OC is 46%, with a median progression free-survival (PFS) of 16 to 21 months[6].

Standard of care for patients with OC is debulking surgery followed by six cycles of platinum and taxane combination chemotherapy[7]. Although the majority of patients initially respond well, 80% of patients with a complete response will recur within the first 24 months of treatment[8]. Most patients recur multiple times, eventually developing platinum-resistant tumors and succumbing to disease. Platinum-resistant disease is defined as disease that recurs within 0-6 months of prior platinum-containing chemotherapy.

There are few treatments for recurrent OC approved by the US Food and Drug Administration (FDA). Thus, re-treatment using a prior regimen has become common, and outcomes remain poor[5]. In patients with platinum- and taxane-resistant OC, re-treatment with weekly paclitaxel (80 mg/m^2/week) has activity as a second-line treatment with an objective response rate of 21% and 46% of patients achieving stable disease[9]. The management of 'platinum-resistant' disease remains challenging and better strategies to overcome drug resistance are needed[10,11].

OC recurrence and chemotherapy resistance is associated with the presence of highly malignant cells that possess stem cell-like qualities[12]. These cancer stem cells (CSCs) can become enriched in response to cisplatin chemotherapy exposure[13]. Several cellular metabolic changes are associated with chemotherapy resistance, and CSC biomarker expression such as aldehyde dehydrogenase (ALDH) or the CD133 antigen are often elevated in OCs resistant to platinum or taxane therapy[14,15]. Blocking signals that drive CSC enrichment is a novel approach to anti-tumor therapy.

5.0 DESCRIPTION OF THE TARGET AND INTERVENTION

Focal adhesion kinase (FAK) is a cytoplasmic protein tyrosine kinase that is activated by various cell stimuli to modulate intracellular signaling pathways controlling cell growth, survival, and movement[16]. Increased tyrosine (Y) phosphorylation at FAK Y397 is a marker of FAK activity. In human squamous cell carcinoma, mesothelioma, and breast carcinoma cell lines, inhibition of FAK activity decreases CSC generation[17-19].

The FAK (*PTK2)* gene is located at 8q24.3, within a high grade serous ovarian carcinoma (HGSOC) susceptibility locus[20] and common site of DNA copy gain[21]. Greater than 95% of HGSOC tumors contain inactivating mutations in the p53 tumor suppressor but relatively few (<20%) known targetable mutations (ie. *BRCA1/2*). Alternately, *PTK2* gains occur in greater than 70% of HGSOC tumors[22]. High FAK mRNA levels are associated with significantly worse

overall patient survival[23,24] and metastatic HGSOC micro-environments are enriched with matrix proteins that activate FAK[25].

Orally-available small molecule FAK inhibitors have been developed[16]. Phase 1 dose escalation clinical trials find that FAK inhibitors are generally well tolerated with confirmed reductions in FAK Y397 phosphorylation[26-28]. Defactinib (VS-6063) is FAK inhibitor developed by Verastem Inc. In a Phase 1 trial of forty-six patients with advanced solid malignancies across nine dose levels (12.5-750 mg bid), grade 1-2 adverse events included nausea (37%), fatigue (33%), vomiting (28%), diarrhea (22%) and headache (22%)[26]. Grade 3 adverse events of headache (n=1), fatigue (n=1) and unconjugated hyperbilirubinemia (n=3) occurred at the 300- or 425-mg bid dose level and were reversible. Disease stabilization at ~12 weeks occurred in 6 of 37 (16%) patients. Among the eight patients with ovarian cancer in the study, four (50%) had stable disease. In a separate trial, defactinib was administered across three dose levels, with no dose-limiting toxicities and stable disease achieved in 33% of patients[29]. The recommended defactinib Phase 2 dose is 400 mg bid taken with food.

A Phase I/Ib study in ovarian cancer analyzed the safety of defactinib in combination with weekly paclitaxel (NCT 01778803). No dose-limiting toxicities and no grade 4 or 5 adverse events (AEs) were observed at 400 mg bid[30]. Most frequent adverse events were fatigue (59%), anemia (45%), hyperbilirubinemia (45%), and gastrointestinal side effects including nausea, vomiting, and diarrhea (all 32%). Concurrent defactinib administration did not alter paclitaxel pharmacokinetic exposure. Interim analyses showed 9 of 22 patients (41%) exhibiting stable disease at six months (NCT 01778803). Among these, three achieved a partial response and two had complete responses. These results support the notion that defactinib is not strongly cytotoxic and may be used in combination with paclitaxel.

6.0 STUDY RATIONALE

FAK interacts with a number of different proteins, is activated by multiple stimuli, and functions to support tumor-intrinsic signaling changes as well as extrinsic effects on the tumor micro-environment[16]. A key ongoing research question is to find tumor dependence on FAK that may link to a targetable vulnerability.

The Schlaepfer lab has recently developed an aggressive mouse ovarian tumor model with spontaneous DNA copy number alterations, but not increased target mutation, similar to HGSOC[22]. These tumor cells termed KMF (for *KRas*, *Myc*, and *FAK* amplified) possess intrinsically elevated resistance to cisplatin. This resistance was dependent on FAK signaling activity and involved FAK-dependent regulation of stem cell and DNA repair genes. A *PTK2* target gene signature was identified as a poor HGSOC patient prognostic.

Via genetic and pharmacological inhibition analyses, FAK signaling was found to be essential for KMF tumorsphere proliferation and this acquired dependence on FAK activity was a common phenotype of platinum resistant HGSOC tumorspheres. FAK activity sustained intrinsic and acquired resistance to cisplatin. In patient samples, increased FAK activation was observed within HGSOC patient tumors surviving neo-adjuvant chemotherapy - suggestive that FAK activation can occur in tumors surviving chemotherapy. The combination of FAK inhibitor with platinum triggered platinum-resistant cell apoptosis *in vitro* and prevented the growth of platinum-resistant tumors in mice[22].

These studies support an oncogenic role for FAK activation (and indirectly FAK copy number gains) in ovarian cancer. This trial proposal will test the hypothesis that defactinib (FAK inhibition), in combination with carboplatin and paclitaxel, can provide clinical benefit for

recurrent platinum-resistant ovarian cancer. Molecular analyses of collected patient research samples will provide key insights into FAK signaling and markers of FAK inhibition.

7.0 STUDY OBJECTIVES

7.1.1 Phase 1: Primary Objective:

7.1.1.1 To assess the safety and tolerability of VS-6063 plus paclitaxel and carboplatin chemotherapy using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

7.1.2 Phase 2: Primary Objectives:

7.1.2.1 To evaluate the anti-cancer activity of VS-6063 plus paclitaxel and carboplatin in patients with recurrent ovarian, fallopian tube or primary peritoneal cancer primarily through the objective response rate (ORR), using best ORR by RECIST1.1.

7.1.3 Phase 2: Secondary Objectives:

7.1.3.1 To assess the toxicity and adverse event profile of VS-6063 plus paclitaxel and carboplatin chemotherapy.

7.1.3.2 To describe health-related quality-of-life (QoL) outcomes of patients receiving VS-6063 plus paclitaxel and carboplatin chemotherapy.

7.1.3.3 To determine the effect of VS-6063 on progression free survival (PFS).

7.1.3.4 To estimate the effect of VS-6063 on overall survival (OS).

7.1.3.5 To assess change in FAK Y397 phosphorylation in circulating tumor cells between Day 0, Day 14, and Day 28 within cycle 1 of Phase 2.

7.1.3.6 To assess change in circulating tumor cell numbers between Day 0, Day 14, and Day 28 within cycle 1 of Phase 2.

7.1.3.7 To assess DNA mutations and copy number alterations by DNA sequencing in recurrent platinum resistant tumors obtained from biopsies.

7.1.3.8 To assess gene expression by RNA sequencing in recurrent platinum resistant tumors obtained from biopsies.

7.1.3.9 To assess markers of FAK signaling by immunohistochemical staining in recurrent platinum resistant tumors obtained from biopsies.

8.0 ENDPOINTS

The goal of Phase 1 is to assess the safety and tolerability of VS-6063 plus paclitaxel and carboplatin chemotherapy using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).

Phase 2 will estimate the anti-tumor activity of VS-6063 in patients with platinum-resistant ovarian cancer. We will do this primarily by measuring objective tumor response rates and CA-125 measurements, but we will also secondarily evaluate progression free survival and overall survival. The objective tumor response rate will be defined by the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Complete response (CR) is defined as the disappearance of all tumor lesions. Partial response (PR) includes at least a 30% decrease in the sum of the longest diameter of target lesions or the complete disappearance of target lesions with persistence of one or more non-target lesions. Stable disease (SD) will also be

assessed and describes disease in which no new lesions are discovered and existing lesions show neither shrinkage nor growth.

Progression free survival is defined as the time from the date of study randomization to the date of first determined progressive disease or death from any cause. Patients not showing any disease progression will be censored at the date of the last examination. Tumor progression or recurrence is monitored through serial assessment using clinical exam and serum CA-125 levels, followed by confirmation of suspected recurrence with computed tomography (CT) imaging. Overall survival is defined as the time from study enrollment to the date of death from any cause.

9.0 PATIENT ELIGIBILITY

9.1.1 Inclusion Criteria:

9.1.1.1 ≥ 18 years of age and able to give consent to participate in a clinical trial.

9.1.1.2 Patients must have recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal carcinoma, diagnosed within 6 months of completing their most recent platinum-containing chemotherapy. Histologic documentation of the original primary tumor is required via a pathology report.

9.1.1.3 Patients with the following histologic cell types are eligible:

Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.).

9.1.1.4 All patients must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest Xray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

9.1.1.5 Patients must have at least one “target lesion” to be used to assess response on this protocol as defined by RECIST 1.1 (Appendix G). Tumors within a previously irradiated field will be designated as “nontarget” lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

9.1.1.6 Patients must have a GOG Performance Status of 0, 1, or 2.

9.1.1.7 Patients of childbearing potential must have a negative serum pregnancy test prior to study entry and be practicing an effective form of contraception.

9.1.2 Patients must have adequate:

9.1.2.1 Bone marrow function: Absolute neutrophil count ≥ 1,500 cells/uL and platelets ≥ 100,000/uL, equivalent to Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) grade 1.

9.1.2.2 Renal function: Serum creatinine level less than or equal to 1.5 x institutional upper limit normal (ULN) (CTCAE v4.03 grade 1) or a glomerular filtration rate (GFR) > 60 mL/min.

9.1.2.3 Hepatic function: Serum bilirubin less than or equal to 1.5 x ULN (CTCAE v3.0 grade 1). SGOT (AST) less than or equal to 3 x ULN and alkaline phosphatase less than or equal to 2.5 x ULN (CTCAE v4.03 grade 1).

9.1.2.4 Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE v4.03 grade 1.

9.1.3 All persistent clinically significant toxicities from prior chemotherapy must be less than or equal to Grade 1**.**

9.1.4 Patients must have recovered from effects of recent surgery, radiotherapy, or chemotherapy.

9.1.4.1 Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).

9.1.4.2 Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration.

9.1.4.3 Any other prior therapy directed at the malignant tumor, including biological and immunologic agents, must be discontinued at least three weeks prior to registration.

9.1.5 Prior Therapy.

9.1.5.1 Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included intraperitoneal therapy, high-dose therapy, consolidation, noncytotoxic agents or extended therapy administered after surgical or non-surgical assessment.

9.1.5.2 Patients must have NOT received more than three total prior lines of cytotoxic chemotherapy for management of recurrent or persistent disease, including retreatment with initial chemotherapy regimens.

9.1.5.3 Patients may have received one additional non-cytotoxic regimen for management of recurrent or persistent disease according to the following definition: Non-cytotoxic (biologic or cytostatic) agents include (but are not limited to) hormones, monoclonal antibodies, cytokines, and small molecule inhibitors of signal transduction.

9.1.5.4 Patients must be considered platinum resistant according to standard GOG criteria, which defines patients as having had a treatment-free interval following platinum of less than 6 months.

9.1.6 Inclusion of Women and Minorities: This study will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire ovarian, fallopian tube, or primary peritoneal cancer population treated by participating institutions.

9.1.7 Exclusion Criteria.

9.1.7.1 Platinum-refractory ovarian, fallopian tube, or primary peritoneal carcinoma.

9.1.7.2 Known second primary or prior malignancy diagnosed within 5 years of study start date (other than previously treated non-melanoma skin cancer).

9.1.7.3 Current treatment with chemotherapy or radiation therapy. Any prior therapy directed at the malignant tumor, including biologic and immunologic agents, must be discontinued at least three weeks prior to registration.

9.1.7.4 History of treatment with known kinase inhibiting agents.

9.1.7.5 History of gastrointestinal fistula, hemorrhage, perforation or peptic ulcer disease.

9.1.7.6 Patients who are pregnant or breastfeeding.

10.0 TREATMENT PLAN

10.1.1 Study Design.

The study is a multi-center, phase 1/2 trial with an initial safety lead-in period followed by a single treatment arm design. We plan to evaluate the antitumor activity of the FAK inhibitor VS-6063 defactinib combined with weekly paclitaxel and carboplatin chemotherapy in recurrent or persistent, platinum-resistant epithelial ovarian cancer.

Note: All eligible patients will have received at least one platinum-based line of chemotherapy, but not more than three prior lines of cytotoxic chemotherapy. Some of these patients will be experiencing a first recurrence of disease, while others will be experiencing a second recurrence; in the latter case, patients are eligible for the trial whether the first recurrence was platinum-sensitive or –recurrent. In counseling patients for treatment options for the present recurrence of disease, the provider will offer treatment options as recommended by the National Comprehensive Cancer Network (NCCN) Guidelines, Version 2.2017. Accordingly, many patients will have already been exposed to bevacizumab as part of treatment for either a platinum-sensitive recurrence (together with platinum-based chemotherapy as in the OCEANS trial) [31] or a platinum-resistant recurrence (as a doublet with a non-platinum cytotoxic agent, as in the AURELIA trial)[32]. However, for patients who have not yet received bevacizumab for prior recurrent disease, or for whom the present is the first recurrence of disease, patients will be offered NCCN guideline care, which includes participation in a clinical trial or standard chemotherapy with bevacizumab as discussed above.

All initial and continuing reviews must be submitted to the UCSD Clinical Trials Regulatory Office.

Before patient entries will be accepted, the following documents must be submitted to the UCSD Regulatory Office:

- Documentation of IRB approval
- IRB-approved informed consent
- Institutional Biosafety Committee (IBC) approval letter or documentation of IBC declination of review; or if no IBC is available for the site, documentation of protocol review by institution's Infection Control Committee, or other relevant institutional oversight committee.

10.1.2 Phase 1: Study Design.

Phase 1 of the study is the safety lead-in portion designed to assess the safety and tolerability of all three drugs when given concomitantly. This will be a non-blinded, traditional rule-based design with cohorts of three patients each, utilizing a total of at least six patients to confirm the tolerability of the three drugs at their recommended doses.

10.1.3 Phase 1 Treatment Dosage and Administration: In this portion of the study, all patients will receive paclitaxel 60 mg/m2 and carboplatin AUC of 4 mg/mL/min. The VS-6063 dose will then be escalated after the first 3 patient cohort, if tolerated. The regimens for each cohort are listed below:

10.1.3.1 First 3 patient cohort: VS-6063 200 mg PO twice daily, plus paclitaxel 60 mg/m2 infused IV continuously over 1 hour on days 1, 8, and 15 and carboplatin (AUC of 4 mg/mL/min) IV infused continuously over 1 hour on day 1 of a 28 day cycle.

10.1.3.2 IF TOLERATED, Second 3 patient cohort: VS-6063 400 mg PO twice daily, plus paclitaxel 60 mg/m2 infused IV continuously over 1 hour on days 1, 8, and 15 and carboplatin (AUC of 4 mg/mL/min) IV infused continuously over 1 hour on day 1 of a 28 day cycle.

10.1.3.3 All patients will undergo clinical assessments following chemotherapy cycles 1 and 2 to determine the safety and tolerability of the combined regimen.

10.1.3.4 Patients enrolled in Phase 1 will continue treatment at the same dose.

10.1.3.5 The treatment regimen will be repeated until disease progression or unacceptable toxicity.

10.1.3.6 Subjects experiencing carboplatin and/or paclitaxel related toxicities requiring cessation of paclitaxel administration, who have at least stable disease, may continue to receive oral VS-6063 twice daily until disease progression or other discontinuation criteria have been met.

10.1.3.7 The principal investigators and the safety monitoring committee will review the safety and tolerability data of the patients who received the escalated VS-6063 dose of 400mg twice daily. If the data indicate this combination was tolerable, then this will be the recommended regimen and we will proceed with phase 2 portion of the trial.

10.1.3.8 Patients who are receiving active study treatment and do not experience a dose-limiting toxicity after completion of Phase 1 may be enrolled into Phase 2 if desired. The numbering of treatment cycles initiated in Phase 1 will be continued into Phase 2 and their dose will remain the same.

10.1.4 Phase 2: Study Design.

Phase 2 of the study will only commence once safety and dosing data from the safety lead-in has been confirmed. Patients fitting eligibility criteria, including biopsy confirming recurrent disease and baseline CT scan, will then start the treatment arm.

10.1.5 Phase 2 Treatment Dosage and Administration. Patients will be administered the following regimen:

10.1.5.1 Therapy Regimen: VS-6063 dose based on Phase 1 results, PO twice daily, plus paclitaxel 60 mg/m2 IV infused continuously over 1 hour on days 1, 8, and 15 and carboplatin (AUC of 4 mg/mL/min) IV infused continuously over 1 hour on day 1 of a 28 day cycle.

10.1.5.2 The treatment regimen will be repeated until disease progression or unacceptable toxicity.

10.1.5.3 Subjects experiencing carboplatin and/or paclitaxel related toxicities requiring cessation of cytotoxic therapy, who have at least stable disease, may continue to receive oral VS-6063 twice daily until disease progression or other discontinuation criteria have been met.

10.1.6 The carboplatin dose in milligrams will be determined using the Calvert formula.

REGIMEN DESCRIPTION					
Agent	**Premedications**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Carboplatin	Premedicate with corticosteroids, diphenhydramine, and H2 antagonists	AUC 4mg/mL/min	IV over 1 hour	Day 1	4 weeks (28 days)
Paclitaxel	Premedicate with corticosteroids, diphenhydramine, and H2 antagonists	Phase 1: 60 mg/m2 Phase 2: 60 mg/m2	IV over 1 hour before carboplatin	Days 1, 8, 15	
VS-6063	Not applicable	Phase 1: 200mg bid (first three patients), then 400 mg bid Phase 2: 400mg bid	PO	Twice daily	

10.1.7 Definition of Dose-Limiting Toxicity (DLT) (Phase 1).

10.1.7.1 Dose-Limiting Neutropenia (DLT-ANC) is defined by the occurrence of febrile neutropenia or any Grade 4 neutropenia persisting ≥7 days. Febrile neutropenia is defined within the CTCAE as a disorder characterized by an ANC <1000/ uL and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour.

10.1.7.2 Dose-limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of Grade 4 thrombocytopenia (<25,000/uL) or bleeding associated with Grade 3 thrombocytopenia (25,000 to <50,000/uL). There will be no modifications for uncomplicated Grade 3 thrombocytopenia except as above.

10.1.7.3 Dose-limiting neuropathy is defined as Grade 2 (or greater) peripheral neuropathy as described by the CTCAE.

10.1.7.4 Dose-limiting gastrointestinal toxicity is defined as ≥ Grade 3 aspartate transaminase [AST, also referred to as serum glutamic oxaloacetic transaminase (SGOT)] or alanine aminotransferase [ALT, also referred to as serum glutamic pyruvic transaminase (SGPT)] for > 7 days or increase in grade for subjects with liver metastases; or ≥ Grade 4 AST or ALT of any duration.

10.1.7.5 ≥ Grade 3 non-hematologic toxicity, except untreated nausea, vomiting, constipation, pain, hyperbilirubinemia and rash (these become DLTs if the AE persists despite adequate treatment). Alopecia will not be considered a DLT.

10.1.7.6 Any toxicity that results in a VS-6063 treatment interruption exceeding 5 consecutive days, or a treatment-related toxicity that prevents administration of three doses of paclitaxel.

10.1.7.7 In general, the occurrence of a hypersensitivity reaction to paclitaxel is not considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments in infusion rates should be made. However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study.

10.1.7.8 The target dose of VS-6063 is 400 mg PO twice daily and will be employed in Phase 2 if <2 patients experience DLT at this dose level.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 3 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose (The final determination will also take into account any cumulative or delayed toxicity). At least 6 patients must be entered at the recommended phase 2 dose.

10.1.8 Replacement patients: may be enrolled in a cohort for patients who withdraw from investigational treatment for a reason that is definitely unrelated to toxicity of the study agent (e.g. disease progression). Replacement patients will ensure enough patients are enrolled in each cohort to determine the Phase 2 dose.

10.1.9 Pre-medications: For all cycles where chemotherapy is to be administered, routine pre-medication should be provided. This regimen should include a standard dose of dexamethasone (either IV or PO), an anti-histamine H1 (diphenhydramine 50 mg IV or orally, or an equivalent dose of an alternate H1 blocker such as loratadine or fexofenadine), and a standard dose of antihistamine H2 IV (such as cimetidine, ranitidine, or famotidine). The preparative regimen can be altered at the discretion of the treating investigator.

10.1.10 Concomitant Medications.

10.1.10.1 No investigational treatment, immunotherapy or additional chemotherapy is allowed during the course of this study.

10.1.10.2 The use of blood transfusions is permitted at the discretion of the treating physician. Anticoagulant therapy is permitted.

10.1.10.3 *In vitro* studies have shown that defactinib inhibits CYP2C9 and CYP3A4 in human liver microsomes. Based on extrapolations to expected human exposure, the potential for inhibition and/or induction of CYP enzymes is considered to be low. However, as the clinical significance of these potential interaction have not been formally assessed, it is recommended that compounds that are substrates for CYP2C9 and CYP3A4 be used with caution as concomitant administration with defactinib may increase their exposure. A list of known substrates for CYP2C9 and CYP3A4 can be found in Appendix B.

Subjects taking warfarin for therapeutic anticoagulation should be monitored closely because treatment with VS-6063 may increase its exposure. If subjects can safely stop taking warfarin, they should do so. If subjects require anticoagulation an alternative to warfarin should be considered. Subjects who require anticoagulation but cannot discontinue warfarin should be monitored closely and have their INRs checked more frequently whilst on VS-6063. For subjects requiring the start of anti-coagulation therapy during the course of any VS-6063 trial, alternatives to warfarin are recommended.

In addition, as defactinib has been shown to be metabolized by CYP2C9 and CYP3A4, concomitant use of strong inhibitors and inducers of CYP2C9 and CYP3A4 should be avoided if possible or used with caution. A list of examples of examples of strong inhibitors and inducers of CYP2C9 and CYP3A4 can be found in Appendix C.

10.1.11 Toxicities and Dosing Delays/Dose Modifications. Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity (see Tables A-D).

10.1.12 Hematologic toxicity: General considerations. Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below. The use of hematopoietic cytokines and protective reagents are restricted as noted:

10.1.12.1 It is anticipated that myelosuppression may be a significant side effect of each regimen. Myeloid growth factors (filgrastim) can be used (it is recommended that NCCN and/or ASCO guidelines be consulted). If myeloid growth factors are used, it is recommended that filgrastim (dose according to institutional standard) will be administered daily subcutaneously starting 24-72 hours after the last dose of chemotherapy and continuing through hematopoietic recovery. Administration of growth factors on the same day as chemotherapy is not recommended. Pegfilgrastim is not recommended for chemotherapy regimens given less than every 2 weeks.

10.1.12.2 Patients will NOT receive prophylactic thrombopoietic agents.

10.1.12.3 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.

10.1.12.4 Patients may NOT receive amifostine or other protective reagents not mentioned in the study design.

10.1.12.5 Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

10.1.13 Hematologic toxicity: Dose modifications for carboplatin AUC 4 and paclitaxel at the 60 mg/m2 dose level (Table A)

10.1.13.1 For Day 8 and 15 of treatment, ANC must be ≥ 1000 cell/uL, and platelet count must be ≥ 75,000/uL. If these parameters are not met, dose of carboplatin and paclitaxel should be omitted (and not made up). For first occurrence, G-CSF will be added. For second occurrence, cytotoxic therapy should be discontinued.

10.1.13.2 Subsequent cycles of therapy will not begin until the ANC is ≥ 1500 cells/uL and the platelet count is ≥ 100,000/uL. Cytotoxic therapy will be delayed for at least one week and for a maximum of two weeks until these values are achieved. If fail to recover adequate counts within a two-week delay, cytotoxic therapy should be discontinued.

10.1.13.3 For first occurrence of febrile neutropenia and/or documented grade 4 neutropenia persisting ≥ 7 days, cytotoxic therapy should be discontinued.

10.1.13.4 Patients with grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia of any duration, cytotoxic therapy should be discontinued.

10.1.13.5 There will be no dose modifications on the basis of uncomplicated granulocyte nadirs lasting less than 7 days.

10.1.14 Non-hematologic toxicity: Dose modifications for carboplatin AUC 4 and paclitaxel at the 60 mg/m2 dose level (Table B).

10.1.14.1 Grade 2 (or greater) peripheral neuropathy delay in subsequent cytotoxic therapy for a maximum of 2 weeks until recovered to grade 1.

10.1.14.2 Grade 3 (or greater) elevations in SGOT (AST), alkaline phosphatase or bilirubin requires delay in subsequent cytotoxic therapy for a maximum of 2 weeks until recovered to grade 1.

10.1.14.3 There will be no dose modifications for alopecia or fatigue.

10.1.14.4 It is expected that patients with nausea, emesis, diarrhea, or constipation will receive appropriate medical management without dose modification. However, patients with persistent (greater than 3 days) grade 3 (or greater) toxicity in spite of optimal medical management require delay in subsequent cytotoxic therapy for a maximum of 2 weeks until recovered to grade 1.

10.1.14.5 Other non-hematologic toxicities with an impact on organ function of grade 3 (or greater) require delay in subsequent cytotoxic therapy for a maximum of 2 weeks until recovered to grade 1, or pre-therapy baseline.

Table A. Dose modifications for carboplatin AUC 4 and paclitaxel at the 60 mg/m2 dose level.

	First occurrence	Second occurrence	Third occurrence
Neutropenia			
ANC 1000-1499 cells/uL on Day 1	Delay carboplatin and paclitaxel for at least 1 week. If ANC not recovered after 2 weeks, stop cytotoxic therapy	Delay carboplatin and paclitaxel for at least 1 week. If ANC not recovered after 2 weeks, stop cytotoxic therapy	Delay carboplatin and paclitaxel for at least 1 week. If ANC not recovered after 2 weeks, stop cytotoxic therapy
ANC 500-999 cells/uL on Day 8 or Day 15	Omit dose. Add G-CSF at next treatment	Discontinue protocol-directed cytotoxic therapy	
Febrile neutropenia **OR** Grade 4 (ANC <500 cells/uL) lasting 7 or more days	Discontinue protocol-directed cytotoxic therapy		
Thrombocytopenia			
Platelets <100,000/uL on Day 1	Delay carboplatin and paclitaxel for at least 1 week. If platelets not recovered after 2 weeks, stop cytotoxic therapy	Delay carboplatin and paclitaxel for at least 1 week. If platelets not recovered after 2 weeks, stop cytotoxic therapy	Delay carboplatin and paclitaxel for at least 1 week. If platelets not recovered after 2 weeks, stop cytotoxic therapy
Platelets <75,000/uL on Day 8 or Day 15	Omit dose.	Discontinue protocol-directed cytotoxic therapy	
Grade 4 thrombocytopenia **OR** Grade 3 thrombocytopenia with bleeding	Discontinue protocol-directed cytotoxic therapy		
Grade ≥2 peripheral neuropathy	Delay carboplatin and paclitaxel for up to 2 weeks until recovered to grade 1.	Stop cytotoxic therapy	
Grade ≥3 any other organ system	Delay carboplatin and paclitaxel for up to 2 weeks until recovered to grade 1.	Stop cytotoxic therapy	

10.1.15 Dose modifications for VS-6063 (defactinib) non-hematologic toxicity (Tables B and C).

10.1.15.1 Grade ≥3 non-hematologic toxicities require VS-6063 to be held for a maximum of 2 weeks until recovered to grade 1, or pre-therapy baseline. Management for second recurrence is based on the dose level and is described in Tables B and C.

10.1.15.2 Increased bilirubin has been observed with defactinib. These increases are generally transient and not associated with increases in AST or ALT. Increased bilirubin often resolves spontaneously even with continued drug treatment.

10.1.15.3 Grade ≥3 hyperbilirubinemia without grade ≥2 elevation in AST or ALT requires VS-6063 to be held for a maximum of 2 weeks until recovered to grade 1, or pre-therapy baseline. Management for second recurrence is based on the dose level and is described in Tables C and D.

10.1.15.4 Grade ≥2 accompanied by grade ≥2 elevation in AST or ALT requires permanent discontinuation of VS-6063.

Table B. Dose modifications for VS-6063 at 200 mg bid dose level.

	First occurrence	Second occurrence	Third occurrence
Bilirubin			
Grade ≥2 **WITH** Grade ≥2 AST and/or ALT	Permanently discontinue VS-6063		
Grade 3 or 4 **WITHOUT** Grade ≥2 AST or ALT	Hold VS-6063 until resolved to < grade 3.	Permanently discontinue VS-6063.	
Other non-hematologic toxicities			
Grade 3 or 4 non-hematologic toxicities (except alopecia, rash, hyperglycemia, nausea, vomiting, or diarrhea if able to optimally manage to grade 2 or less) **OR** Grade 3 or 4 nausea, vomiting, diarrhea, or skin rash persists for ≥3 days with optimal medical intervention	Hold VS-6063 until decreases to grade 1 or baseline.	Permanently discontinue VS-6063.	

Table C. Dose modifications for VS-6063 at 400 mg bid dose level.

	First occurrence	Second occurrence	Third occurrence
Bilirubin			
Grade ≥2 **WITH** Grade ≥2 AST and/or ALT	Permanently discontinue VS-6063		
Grade 3 or 4 **WITHOUT** Grade ≥2 AST or ALT	Hold VS-6063 until resolved to < grade 3.	Hold VS-6063 until resolved to < grade 3. Reduce VS-6063 one dose level at next treatment.	Permanently discontinue VS-6063.
Other non-hematologic toxicities			
Grade 3 or 4 non-hematologic toxicities (except alopecia, rash, hyperglycemia, nausea, vomiting, or diarrhea if able to optimally manage to grade 2 or less) **OR** Grade 3 or 4 nausea, vomiting, diarrhea, or skin rash persists for ≥3 days with optimal medical intervention	Hold VS-6063 until decreases to grade 1 or baseline.	Hold VS-6063 until decreases to grade 1 or baseline. Reduce VS-6063 one dose level at next treatment.	Permanently discontinue VS-6063.

Table D. Dose levels

Drug	**Regimen starting dose**	**Regimen -1 Level**
Paclitaxel	60 mg/m^2	N/A
Carboplatin	AUC 4.0	N/A
VS-6063	400mg bid	200mg bid

10.1.16 Duration of Study Treatment.

10.1.16.1 The treatment regimen will continue until disease progression or unacceptable toxicity.

10.1.16.2 If side effects are not severe, a patient may remain on study indefinitely until evidence of disease progression or unacceptable toxicity.

10.1.17 Duration of Follow Up.

10.1.17.1 Patients will be screened for recurrence or progression every 3 months x 2 years and then every 6 months x 3 years using serial serum CA-125 levels and pelvic examinations performed by trained gynecologic oncologists.

10.1.18 Discontinuation from Study Participation. Study treatment will be discontinued in patients with the following criteria:

10.1.18.1 Inability to tolerate the lowest doses of paclitaxel, carboplatin or VS-6063 because of toxicity or significant side effects.

10.1.18.2 If carboplatin and/or paclitaxel is discontinued and patient has at least stable disease, the patient may elect to continue VS-6063 monotherapy as maintenance. If a patient does not elect for this option, she will be removed from the study, and VS-6063 also discontinued.

10.1.18.3 Evidence of progressive disease.

10.1.18.4 Severe concurrent illness that prevents further administration of treatment.

10.1.18.5 Patient may withdraw consent for the study at any time for any reason. If this occurs, the patient will be removed from study treatment.

11.0 STUDY PROCEDURES

Refer to the Schedule of Events for outline and timing of procedures.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at study treatment completion/early study treatment discontinuation, and during the follow-up period.

11.1.1 Screening/Baseline Procedures. Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 40 days of registration for Phase 1, or within 28 days of registration for Phase 2, unless otherwise stated. The screening procedures include:

- Written informed consent.
- Review of inclusion and exclusion criteria.
- Complete medical/oncology history.
- Demographics.
- Documentation of concomitant medications.
- Complete physical examination, including vital signs, height, and weight.
- Performance status assessment.
- Laboratory tests (within 2 days).
- Blood collection for correlative studies.

- Documentation of tumor staging.
- Tumor biopsy for correlative studies at Phase 2 enrollment.

11.1.2 Medical History. A complete medical, surgical and oncology history as well as history of infections are obtained at screening. Any changes from screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

11.1.3 Demographics. Demographic profile will include date of birth, gender, race, and ethnicity.

11.1.4 Review Subject Eligibility Criteria. Review of eligibility criteria as described in Section 3 to ensure subject qualification for study entry.

11.1.5 Concomitant Medications. All concomitant therapy, including anesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, received by patients prior to each chemotherapy cycle and at each follow-up visit will be recorded in the patient's medical record. If a reportable adverse event deemed related to study intervention (see Section 7) occurs within 28 days after last study dose and the patient has not started a new treatment, recording of concomitant medications related to the treatment of that adverse event should continue until resolution of the adverse event.

11.1.6 Physical Exam. A complete physical examination should include the evaluation of general appearance; evaluation of head, eyes, ears, nose, and throat (HEENT); and cardiovascular, pulmonary, abdominal, musculoskeletal, skin, lymph nodes, neurological, and genitourinary systems. Targeted physical exams will be performed prior to each chemotherapy cycle, and will include the following: cardiovascular, pulmonary, abdominal, musculoskeletal, skin, lymph nodes, neurological, and genitourinary systems.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if clinically significant.

11.1.7 Vital Signs and Height. Vital signs should include temperature, pulse, and blood pressure and weight. Height will only be collected at screening.

11.1.8 Performance status. Performance status is evaluated by the Gynecologic Oncology Group (GOG) criteria.

11.1.9 Adverse event assessment. Baseline assessment of subject status for determining adverse events. See Section 7 for Adverse Event monitoring and reporting.

11.1.10 Hematology. Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), differential, and absolute neutrophil count (ANC).

11.1.11 Serum Chemistries. The following will be obtained: comprehensive metabolic panel (CMP) to include albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. Additionally, serum CA-125 level will be obtained.

11.1.12 Coagulation. Coagulation profile includes International Normalized Ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (PTT).

11.1.13 Blood draw for translational research studies. See Section 12 for details.

11.1.14 Pregnancy test (for females of child bearing potential). See Section 9.1.1 for definition of inclusion criteria.

11.1.15 Quality of Life Questionnaire. Quality of life will be assessed by the Trial Outcome Index of the Functional Assessment of Cancer Therapy – Ovary (FACT-O) survey.

11.1.16 Tumor Assessment. Tumor burden will be assessed by physical exam, CA-125 level, and CT scan at baseline and subsequent pre-chemotherapy visits (see Section 10.1, Study Design).

11.1.16.1 Tumor assessments will be performed following every third cycle of chemotherapy (i.e. after cycle 3, 6, 9, etc).

11.1.17 Tumor Tissue Collection. See Section 12 for details

11.1.18 Procedures During Treatment. Pre-chemotherapy clinical evaluation will be performed within 7 days prior to the initiation of each chemotherapy cycle for Phase 1 and Phase 2.

11.1.19 Prior to Each Treatment Cycle.

- Documentation of concomitant medications and adverse events
- Physical exam, vital signs
- Hematology
- Serum chemistries (including CA-125 level)

11.1.20 End of treatment visit after disease progression or toxicity.

- Documentation of concomitant medications and adverse events
- Physical exam, vital signs
- Hematology
- Serum chemistries (including CA-125 level)

11.1.21 Follow-up Procedures. Following discontinuation of study treatment for any reason, we will continue to surveil every three months for two years, and every six months for an additional three years, for overall survival. Overall survival of study subjects will be recorded together with the cause of death in the case of a fatality.

12.0 TRANSLATIONAL RESEARCH STUDIES

12.1.1 Biomarker Sampling. Patients may be consented and samples will be collected as part of the UCSD IRB approved protocol Collection and Banking of Biological Samples for Use in Biomedical Research (HRP 181755) under the supervision of UCSD Biorepository. All samples will be stored by the UCSD Biorepository.

12.1.2 Primary Tumor Tissue Sample. Formalin fixed paraffin embedded tumor samples obtained at the time of initial tumor removal will obtained from Pathology (if available). Samples will consist of thin sections cut from paraffin blocks. Ten 5 to 6 micron unstained slides should be provided for IHC analysis. For DNA and RNA isolation, cut at 10 microns and provide 10 paraffin tissue roll ups in Eppendorf tubes.

12.1.3 Recurrent Tumor Biopsy. Patients enrolled in Phase 2 will undergo a biopsy to diagnose tumor recurrence no greater than 30 days prior to initiating the recommended chemotherapy regimen. Tissue samples may be collected by:

- Surgery used to remove part of the tumor.
- An endoscope used to remove part of the tumor.
- A needle used to withdraw tissue or fluid.

Samples may not stay in formalin longer than 24 hours. Sample shipping (when applicable) must occur immediately after acquisition and sent to UCSD Biorepository for processing and storage.

12.1.4 Blood Draws. Research blood draws will be performed at the start of Phase 2 (Day 0, +/- 2 days of cycle #1 chemotherapy), on Day 14 of chemotherapy (+/- 2 days), and on Day 28 (+/- 2 days prior to cycle #2 of chemotherapy). Blood will be collected and processed using standard procedures. Blood collected at sub-sites will be shipped to UCSD Biorepository with cold packs the day of acquisition for processing and storage.

12.1.5 Tumor Specimen Banking. De-identified samples will be labeled with the ROCKIF subject ID, date of collection, and sample collection type. Samples will be stored under the supervision of UCSD Biorepository personnel.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UCSD, the investigator or a collaborating researcher or entity.

13.0 MEASUREMENT OF EFFECT

13.1.1 Safety / Tolerability. Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of hematologic and non-hematologic adverse events.

13.1.2 Antitumor Effect- Solid Tumors. Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee[33]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria (see Appendix G).

13.1.3 Objective Response Rate (ORR).

13.1.3.1 Response rates (CR and PR) will be assessed and defined based on Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Complete response (CR) is defined as the disappearance of all tumor lesions. Partial response (PR) includes at least a 30% decrease in the sum of the longest diameter of target lesions or the complete disappearance of target lesions with persistence of one or more non-target lesions. Stable disease (SD) will also be assessed and describes disease in which no new lesions are discovered and existing lesions show neither shrinkage nor growth.

13.1.3.2 Tumor progression is defined according to RECIST guidelines. Events qualifying as tumor progression include the occurrence of any new lesion, at least a 20% increase in the sum of the diameters of target lesions, or death from any cause before progression is diagnosed.

13.1.3.3 At baseline, and following every third chemotherapy cycle (i.e. following cycle 3, 6, 9, etc), patients will be required to undergo a computed tomography (CT) scan to document any disease.

13.1.3.4 Following completion of treatment, patients will be screened for recurrence or progression every 3 months x 2 years and then every 6 months x 3 years using serial serum CA-125 levels and pelvic examinations performed by trained gynecologic oncologists. If either screening test is suspicious for tumor growth as defined by RECIST criteria, subjects will receive a CT scan of the abdomen and pelvis to confirm recurrence. Disease recurrence indicated by a rising serum CA-125 level will be interpreted according to the following criteria:

- Patients with elevated CA-125 which normalize following treatment must show evidence of a CA-125 greater than, or equal to, 2 times the upper limit of normal on 2 occasions, at least 1 week apart.
- Patients with elevated CA-125 which never normalize following therapy must show evidence of CA-125 greater than, or equal to, 2 times their nadir value on 2 occasions, at least 1 week apart.
- Patients with normal CA-125 before treatment must show evidence of a CA-125 greater than, or equal to, 2 times the upper limit of normal on 2 occasions, at least 1 week apart.

13.1.3.5 Tumor progression detected through pelvic examination occurs if any new or expanding lesion is measurable (visible or palpable) by the physician. Progression events detected through CA-125 measurement or pelvic examination are qualifying events, but have to be confirmed through CT imaging.

13.1.3.6 Independent study radiologists will review and confirm any diagnosis of tumor progression based on CT imaging. Time of first confirmed detection of tumor mass by CT will be documented, as well as tumor size and location. Standardized operating procedures for laboratory tests, pelvic examinations and CT imaging will be provided. Standardized RECIST criteria for the diagnosis of tumor progression based on CT will be used to analyze CT images.

13.1.4 Progression-Free Survival. Progression-free survival (PFS) is defined as the duration of time from start of study treatment until objective tumor progression or death.

13.1.5 Time to Progression. Time to progression is defined as the duration of time from start of study treatment until objective tumor progression.

13.1.6 Overall Survival. Overall survival is defined as the duration of time from start of study treatment to death.

13.1.7 Quality of Life. Quality of Life will be assessed by the Trial Outcome Index of the Functional Assessment of Cancer Therapy – Ovary (FACT-O) survey, which provides a summary score based on a total 112 points possible. These questionnaires focus on topics particularly important to ovarian cancer patients (e.g., chronic pain, fatigue, abdominal symptoms and functional status), with higher scores indicating a better quality of life. The surveys will be filled out prior to chemotherapy cycles 1, 3, 6 (and after every third subsequent cycle), as well as at 3, 6, 12, and 24 month follow-up appointments following completion of chemotherapy.

14.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Progression of the cancer under study or events which are unequivocally due to disease progression should not be reported as an AE during the study (unless it is considered to be drug related by the investigator).

14.1.1 Adverse Event Monitoring. Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins after initiation of study treatment and ends 28 days following the last administration of study treatment or start of new anti-cancer therapy, whichever is earlier.

All patients experiencing an adverse event, regardless of its relationship to study drug [or at least possibly related to the drug], will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

14.1.2 Severity. All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

14.1.3 Seriousness. A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. **Results in death.**
   If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. **Is life-threatening.**
   The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. **Requires in-patient hospitalization or prolongation of existing hospitalization.**
   Note: Hospitalization (including hospitalization for an elective procedure) for a pre-existing condition which has not worsened does not constitute a serious adverse event.
4. **Results in persistent or significant disability or incapacity.**
5. **Is a congenital anomaly/birth defect.**
6. **Is an important medical event.**
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.
   For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

14.1.4 Relationship. Attribution categories for adverse events in relationship to protocol therapy are as follows:

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

14.1.5 Prior experience. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol or the current Investigator’s Brochure.

14.1.6 Adverse Event Outcome Categorization. Outcome of an AE/SAE may be classified as resolved, resolved with sequelae, unresolved or unresolved at time of death.

14.1.7 Clinical Laboratory Adverse Events. Outcome of an AE/SAE may be classified as resolved, resolved with sequelae, unresolved or unresolved at time of death.

A clinical laboratory AE is any laboratory value that is considered clinically significant by the Investigator and has caused a medical intervention or accompanied by clinical symptoms. Laboratory abnormalities that have not required medical intervention should not be recorded as AEs and will be captured and reported in the Laboratory section of the clinical study report. If a medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE (e.g., anemia with treatment required and blood transfusion recorded as a procedure, hyperglycemia with treatment required and change in insulin dose recorded on concomitant medications).

The Investigator should decide, based upon the AE criteria and the clinical condition of the patient, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

If, at the end of the treatment phase with the study drug, there are pathological laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (i.e., concomitant disease) is found for the pathological laboratory values

14.1.8 Overdose. No information on treatment of overdose of VS-6063 is currently available. Overdoses will not be considered serious adverse events. It will be treated as a serious adverse event if the outcome of the overdose meets seriousness criteria (fatal outcome, hospitalization, prolongation of existing hospitalization or important medical event per Investigator). In the event of an over dosage, the PI and Sponsor should be immediately notified. The subject should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional standards of care.

14.1.9 Reporting Requirements for Adverse Events - Expedited Reporting.

A. The **Principal Investigator** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

B. The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

C. The **FDA** and **UCSD Institutional Biosafety Committee (IBC)** must be notified according to the following timelines:

- within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

14.1.10 Routine Reporting Requirements.

A. The **UCSD HRPP** must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.

B. The **FDA and UCSD IBC** must be notified of all non-serious adverse events annually at the time of the annual report.

15.0 AGENT INFORMATION

15.1.1 VS-6063. Please refer to the Verastem Investigator's Brochure for more comprehensive information.

15.1.2 Mechanism of action/Product description: VS-6063 (defactinib) is an inhibitor of FAK and Pyk2, which is being investigated for the treatment of advanced solid tumors including malignant pleural mesothelioma (MPM), ovarian cancer and non-small cell lung cancer (NSCLC). Defactinib was found to be a potent and selective ATP-competitive, reversible inhibitor of recombinant human FAK and Pyk2 kinase in biochemical and cell based assays. A comprehensive evaluation of selectivity against a large panel of other kinases in enzyme assays demonstrated that defactinib was highly selective for FAK and Pyk2 kinases strongly suggesting that its predominant pharmacologic activity is mediated by inhibition of FAK and Pyk2 kinases.

15.1.3 Formulation: Defactinib is being provided as a white to pale-colored powder in an immediate release tablet. The dosage strength provided will be 200-mg tablets. The formulation components include microcrystalline cellulose, lactose monohydrate, sodium starch glycolate and magnesium stearate. The study drug is packaged in bottles labeled with pill strength and other information as per local regulatory requirements.

15.1.4 Storage: All packages of oral VS-6063 tablets provided by Verastem will be labeled with an expiration date. Unopened packages are stable to the date indicated on the package when stored between 15 and 25°C (59 and 77°F).

15.1.5 Administration:

- Take defactinib with a meal. Take it with a full glass of water (approximately 8 ounces or 230 mL). Swallow the tablet(s) whole.
- If a scheduled dose of study drug is missed and less than 6 hours have passed since the scheduled dosing time, immediately take the missed dose. If more than 6 hours have passed since the scheduled dosing time, do not take the missed dose. Wait and take the next regularly scheduled dose.

15.1.6 Adverse effects: Overall, defactinib has been found to be well tolerated in clinical studies, with mostly grade 1 or 2 adverse events. The overall adverse event and laboratory profile has been clinically manageable with the majority of adverse events resolving after cessation of treatment. These include increased bilirubin (not associated with increases in AST or ALT, nausea, blood pressure changes, and potential drug interactions (such as warfarin). Consult the package insert for the most current and complete information.

15.1.7 Supplier: All VS-6063 medication will be supplied from the drug company, Verastem Inc., free of charge.

15.1.8 Return and Retention of Study Drug. Remaining drug is to be destroyed, according to Moores Cancer Center Investigational Drug Services destruction policy.

15.1.9 Drug Accountability/Subject Compliance.

- All study drug must be accounted for by using the NCI Drug Accountability Form during the course of this study. The pharmacist or qualified research staff member will maintain inventory records. The records will include details of materials received, date dispensed, patient identification number and initials of patient receiving the dose.
- Records of study medications used, dosages administered, and intervals between visits will be kept during the study. Patients will be asked to fill out a pill diary and bring with them for review after each cycle of study treatment.
- Each day, record date and time the tablets were taken on the diary card. If a dose is missed, include the reason the dose was not taken.
- Drug accountability will be noted at the completion of the trial. Patients will be asked to return all unused medication at the end of the study.

16.0 CARBOPLATIN

16.1.1 Formulation: Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL, or 600mg/60mL of carboplatin.

16.1.2 Storage: Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F). Excursions from 15 to 30°C (59 to 86°F) are permitted. Protect from light. Carboplatin multi dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

16.1.3 Preparation: Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C / 77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution. Institutional pharmacy policy may allow refrigeration and longer storage.

*NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must NOT be used for the preparation or administration of carboplatin.

16.1.4 Adverse Effects: Consult the package insert for the most current and complete information.

16.1.5 Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

17.0 PACLITAXEL

17.1.1 Formulation: Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi-dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile nonpyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

17.1.2 Storage: Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

17.1.3 Stability: Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

17.1.4 Preparation/administration: Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

- NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylenelined administration sets.
- Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

17.1.5 Premedication: All patients should be pre-medicated with corticosteroids, diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to paclitaxel should not be re-challenged with the drug.

17.1.6 Adverse Effects: Consult the package insert for the most current and complete information.

17.1.7 Supplier: Commercially available both from Bristol-Myers Squibb as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

18.0 STATISTICS

18.1.1 Study Design and Study Endpoints. This is a prospective, multi-center, open-label, phase 1/2 trial with an initial safety lead-in period followed by a single treatment arm design. In Phase 1, the primary endpoint is the toxicity of the drug combination (carboplatin, paclitaxel, and VS-6063) to determine the recommended Phase 2 dose. In Phase 2, the primary endpoint is objective response rate (ORR). Secondary objectives include progression-free survival (PFS), overall survival (OS), quality of life outcomes, and measurement of FAK phosphorylation and cancer stem cell biomarkers.

During Phase 1 of the study, an independent safety assessment committee will meet at least once to evaluate the safety and tolerability of the investigational drug combination. The committee will meet after at least 6 patients have been enrolled and have completed 2 cycles of treatment (VS-6063 plus carboplatin/paclitaxel). The safety committee will discuss any adverse events and recommend procedures for Phase 2 of the study (start patient enrollment or modify study treatment plan). No patients will be enrolled in Phase 2 of the study until approved by the safety assessment committee.

18.1.2 Statistical Design: Sample Size and Accrual. In Phase 1, the rate of dose limiting toxicities (DLTs) and the tolerability of the drug combination will be assessed in a 3 + 3 study design. There will be a maximum of 12 patients enrolled in Phase 1 as specified in the dose escalation decision in Section 10.1.3.

18.1.3 Power and sample size calculation for Phase 2: A Simon's optimal two-stage design[34] will be used in the second phase of this trial. Up to 72 subjects will be accrued and treated with VS-6063 plus paclitaxel and carboplatin. The primary endpoint is the best objective response rate (ORR) initially determined by12 months according to the RECIST 1.1 criteria.

Historical control for our patients' response rate (unacceptable response rate) is set to be 20%. If the response rate in this study is ≤20%, we will consider the treatment as not meeting the threshold of further consideration. We will test the null hypothesis H0: p≤20% against the alternative hypothesis H1: p=35%, where p is the ORR. The two-stage design proposed below will have 80% power to reject the null hypothesis at 5% significance level. The study design is described in detail as follows:

18.1.3.1 Stage 1: 22 subjects will be treated; if needed, accrual will be held until the response results for these subjects are known. The trial will be terminated at Stage 1 if 5 or fewer of the 22 subjects have a defined response; otherwise it will continue to Stage 2.

18.1.3.2 Stage 2: 50 more patients will be accrued. We will reject the therapy if, among all the 72 (=22+50) subjects, the number of patients who have response is ≤19; if ≥20 patients have a response, the treatment will be claimed to be successful, and we will conclude that at the 5% significance level that the study treatment is associated with an ORR more than 35%. The final observed ORR will be summarized as proportion with 95% confidence intervals adjusted for the design's adaptiveness[34].

Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 73.3%. Sample size calculation did not incorporate the safety endpoint. Statistics for safety outcomes will be presented descriptively.

18.1.4 Progression Free Survival and Overall Survival: We will consider the rate of progression-free survival (PFS) from start of study treatment at 12 months and at 18 months. Based on past GOG studies, we assume a PFS of 32% at 12 months and 20% at 18 months in this patient population (historical control). With a total of 72 patients, the study is sufficiently powered (80%) to detect the PFS of 48.1% at 12 months and 34.5% at 18 months for the new intervention. We will also consider the overall survival (OS) defined as from start of study treatment to time of death.

18.1.5 Evaluable Subjects and Subject Replacement: Only those patients who are deemed "ineligible" or who receive no therapy will be eliminated from the analysis. All patients who receive any therapy will be evaluated for both treatment safety and toxicity. In Phase 1, if the patient withdraws from investigational treatment for a reason that is definitely unrelated to toxicity of the study agent (e.g. drop out or disease progression) before the 2-cycle evaluation period, replacement patients may be enrolled.

- Only the patients enrolled in Phase 2 will be evaluated for efficacy. If applicable, "Intention-to-treat" analyses will be performed for an efficacy endpoint. To be specific, if the efficacy endpoints for a subject cannot be assessed (for example, a subject drops out early prior to the assessment dates), it will be considered to be an event that does not respond to the study therapy (e.g., disease progression for the primary outcome) for the calculation of response rate.

18.1.6 Data Analyses Plans. Primary Analyses.

18.1.6.1 For Phase 1, incidence of adverse events will be summarized by event type, grade and body system, and the recommended does for Phase 2 will be made.

18.1.6.2 For Phase 2, we will report the point estimate of the primary endpoint objective tumor response rate with its 95% confidence interval. The objective response rate will be compared with the response rate reported from a historical control using the one-sample normal test of proportions. The final observed ORR will be summarized as proportion with 95% confidence intervals adjusted for the design's adaptiveness[34].

18.1.7 Data Analyses Plans. Secondary Analyses.

18.1.7.1 Progression-free survival will be analyzed using Kaplan-Meier estimates based on data from start of treatment to one of the following events: 1) detection of tumor mass by CA-125 or pelvic examination and validation by CT scan; 2) death from any cause. Patients without event will be censored at last follow-up.

18.1.7.2 Overall survival will be assessed at two and five years of surveillance, based on recorded patient information. Survival probability at 24 months and 60 months will serve as a surrogate measure to determine overall survival.

19.0 STUDY MANAGEMENT

19.1.1 Conflict of Interest. Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

19.1.2 Institutional Review Board (IRB) Approval and Consent. The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

19.1.3 Required Documentation. Before the study can be initiated at any site, the following documentation must be provided to the UCSD Moores Cancer Center Clinical Trials Office.

- A copy of the official IRB approval letter for the protocol and informed consent.
- A copy of the IRB-approved consent form.
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study.

- Form FDA 1572 appropriately filled out and signed with appropriate documentation. (NOTE: this is required if UCSD holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification numbers and institution lab normal values.
- Executed clinical research contract.

19.1.4 Registration Procedures. All patients must be registered with the UCSD Moores Cancer Center Clinical Trials Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the UCSD Study Coordinator. To register a patient, call 858-246-2892 Monday through Friday, 8:00AM-4:30PM. Study sites other than UCSD must fax informed consent documentation, completed eligibility checklist, and all source documentation for eligibility confirmation to the UCSD Clinical Trials Office (Fax: 858-822-5360). Once eligibility is confirmed, patient will be given a unique sequential study number.

19.1.5 Subject Data Protection. In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

19.1.6 Data and Safety Monitoring/Auditing. In addition to adverse event monitoring and clinical oversight by the principal investigator and co-investigators, quality assurance of the study will be performed by the UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be dependent upon the number of patients enrolled and the complexity of the study.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Frequency and severity of AEs will be discussed at Data and Safety Monitoring Board (DSMB) meetings scheduled six months after initiation of the study, or when 50% of enrolled patients pass the third cycle of chemotherapy, whichever comes first. Further DSMB meetings will be scheduled semi-annually, or earlier if the number of AEs exceeds the institutional norms for standard chemotherapy regimens. Data reported will include the following:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the dates of patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) a response evaluation for evaluable patients when available
6) a summary of any recent literature that may affect the ethics of the study.

19.1.7 Adherence to the Protocol. Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB.

19.1.8 Amendments to the Protocol. Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRBs FDA and IBC for approval prior to implementation.

19.1.9 Record Retention. Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

19.1.10 Obligations of Investigators. The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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21.0 APPENDICES

Appendix A. Calculation of Carboplatin Dose

1) The Cockcroft-Gault formula will be used
2) Conversion of IDMS creatinine levels to “non-IDMS” values will not be permitted.
3) The carboplatin calculation tool is available on the GOG website (Web Menu, Tools).

Carboplatin Dosing:
1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.
2) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.
3) Carboplatin doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.
4) At the time of dose modification, if the patient’s age had changed (the patient has had a birthday), the site can use the current age.
5) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using **a minimum value of 0.7 mg/dl.** For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR + 25)
NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.
Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg
For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:
Creatinine Clearance (mL/min) = [140-Age (years)] x Weight (kg) x 0.85
72 x serum creatinine (mg/dl)

Notes:
1) Weight in kilograms (kg):
a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.
d. Adjusted weight calculation:
Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) + 45.5
Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).
At the time of a dose modification for toxicity:

If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

APPENDIX B: EXAMPLES[1] OF SUBSTRATES OF CYP2C9 AND CYP3A4

Substrates of CYP2C9	Substrates of CYP3A4
Celecoxib Phenytoin Tolbutamide Warfarin	Alprazolam Astemizole Buspirone Calcium Channel Blockers Carbamazepine Cisapride Cyclosporine Doxorubicin Erythromycin Etoposide Felodipine Fentanyl HIV protease inhibitors Ifosphamide Lovastatin (not prevastatin) Midazolam Nifedipine Pimozide Quinidine Quinine Simvastatin Tacrolimus Terfenadine Triazolam

[1]Note that this is not an exhaustive list. Additional information on drugs and possible interactions can be found at http://www.drugs.com.

APPENDIX C: EXAMPLES[1] OF STRONG INHIBITORS AND INDUCERS OF CYP2C9 AND CYP3A4

Inhibitors of CYP2C9	Inhibitors of CYP3A4
fluconazole miconazole amentoflavone (constituent of Ginkgo biloba and St. John's Wort) sulfaphenazole valproic acid	boceprevir clarithromycin conivaptan grapefruit juice indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole
Inducers of CYP2C9	**Inducers of CYP3A4**
rifampicin secobarbital	carbamazepine phenytoin oxcarbazepine phenobarbital St. John's wort rifampicin rifabutin efavirenz nevirapine pioglitazone troglitazone modafinil

[1]Note that this is not an exhaustive list. Additional information on drugs and possible interactions can be found at http://www.drugs.com.

Appendix D. FACT-O Quality of Life Questionnaire (Version 4, November 2007)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4

GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4

GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some- what**	**Quite a bit**	**Very much**

O1	I have swelling in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4

Appendix E. GOG Performance Status

GOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead.

Appendix F. Pill Diary

VS-6063 (defactinib) In Combination with Carboplatin/ Paclitaxel Subject Dosing Card & Instructions

Top portion to be completed by study staff

Twice a Day

Subject #: _____ **Cycle #:** _____ **Dose:** _____ **mg** **Date:** _____

Take ____capsules from the 200 mg bottle every morning and evening for 28 days

Instructions:

Record the date and times that you take your study medication below
Record the total number of capsules taken in the morning and evening in the boxes below

If you are LESS THAN 6 hours late in taking your morning or evening dose, the dose should be taken immediately
If you are MORE THAN 6 hours late in taking your morning or evening dose, the dose should be skipped. Wait and take the next regularly scheduled dose

Bring any unused capsules, capsule bottles and your completed dosing card to your next appointment
Please call your study doctor if unsure about any of the instructions above.

Please carefully review the chart on the last page for medications and foods that CANNOT be taken while on study drug.

Week 1:

Instructions	Day 1 morning dose	Day 2 morning dose	Day 3 morning dose	Day 4 morning dose	Day 5 morning dose	Day 6 morning dose	Day 7 morning dose
Date (dd/mon/yr)	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___
Time (hr:min)	____:____ AM	____:____ AM	____:____ AM	____:____ AM	____:____ AM	____:____ AM	____:____ AM
Total # of Capsules Taken							
Instructions	**Day 1 evening dose**	**Day 2 evening dose**	**Day 3 evening dose**	**Day 4 evening dose**	**Day 5 evening dose**	**Day 6 evening dose**	**Day 7 evening dose**
Time (hr:min)	____:____ PM	____:____ PM	____:____ PM	____:____ PM	____:____ PM	____:____ PM	____:____ PM
Total # of Capsules Taken							

Date, time and # of capsules to be completed by subject

VS-6063 (defactinib) Dosing Card_16Mar17

VS-6063 (defactinib) In Combination with Carboplatin/ Paclitaxel Subject Dosing Card & Instructions

Week 2:

Instructions	Day 8 morning dose	Day 9 morning dose	Day 10 morning dose	Day 11 morning dose	Day 12 morning dose	Day 13 morning dose	Day 14 morning dose
Date (dd/mon/yr)	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___
Time (hr:min)	____:____ AM	____:____ AM	____:____ AM	____:____ AM	____:____ AM	____:____ AM	____:____ AM
Total # of Capsules Taken							
Instructions	**Day 8 evening dose**	**Day 9 evening dose**	**Day 10 evening dose**	**Day 11 evening dose**	**Day 12 evening dose**	**Day 13 evening dose**	**Day 14 evening dose**
Time (hr:min)	____:____ PM	____:____ PM	____:____ PM	____:____ PM	____:____ PM	____:____ PM	____:____ PM
Total # of Capsules Taken							

Week 3:

Instructions	Day 15 morning dose	Day 16 morning dose	Day 17 morning dose	Day 18 morning dose	Day 19 morning dose	Day 20 morning dose	Day 21 morning dose
Date (dd/mon/yr)	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___
Time (hr:min)	____:____ AM	____:____ AM	____:____ AM	____:____ AM	____:____ AM	____:____ AM	____:____ AM
Total # of Capsules Taken							
Instructions	**Day 15 evening dose**	**Day 16 evening dose**	**Day 17 evening dose**	**Day 18 evening dose**	**Day 19 evening dose**	**Day 20 evening dose**	**Day 21 evening dose**
Time (hr:min)	____:____ PM	____:____ PM	____:____ PM	____:____ PM	____:____ PM	____:____ PM	____:____ PM
Total # of Capsules Taken							

VS-6063 (defactinib) Dosing Card_16Mar17

VS-6063 (defactinib) In Combination with Carboplatin/Paclitaxel Subject Dosing Card & Instructions

Week 4:

Instructions	Day 22 morning dose	Day 23 morning dose	Day 24 morning dose	Day 25 morning dose	Day 26 morning dose	Day 27 morning dose	Day 28 morning dose
Date (dd/mon/yr)	___/____/___	___/____/___	___/____/___	___/____/___	___/____/___	___/____/___	___/____/___
Time (hr:min)	_____:_____ AM	_____:_____ AM	_____:_____ AM	_____:_____ AM	_____:_____ AM	_____:_____ AM	_____:_____ AM
Total # of Capsules Taken							
Instructions	**Day 22 evening dose**	**Day 23 evening dose**	**Day 24 evening dose**	**Day 25 evening dose**	**Day 26 evening dose**	**Day 27 evening dose**	**Day 28 evening dose**
Time (hr:min)	_____:_____ PM	_____:_____ PM	_____:_____ PM	_____:_____ PM	_____:_____ PM	_____:_____ PM	_____:_____ PM
Total # of Capsules Taken							

Verified by Study Personnel:
Site staff to sign here: _____ **Date:** _____

Print Name/Signature **Day, Month, Year**

VS-6063 (defactinib) Dosing Card_16Mar17

Prohibited Medications:
Do NOT consume while on VS-6063

Antibiotics	**clarithromycin, telithromycin, rifampin, rifampicin, rifabutin**
Anti-virals	**boceprevir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, telaprevir, nevirapine, efavirenz**
Anti-fungals	**itraconazole, ketoconazole, nefazodone, posaconazole, voriconazole, fluconazole, miconazole, sulfaphenazole**
Anti-epileptics	**carbamazepine, phenytoin, oxcarbazepine, valproic acid, secobarbital**
Diabetes	**pioglitazone, troglitazone**
Other:	**grapefruit juice, conivaptan, mibefradil, modafinil, St. John's wort, glucocorticoids, Ginkgo biloba**

VS-6063 (defactinib) Dosing Card_16Mar17

Appendix G. Response Evaluation Criteria in Solid Tumors (RECIST)

Tumor assessments will be made according to the schedule of assessments. Response and progression will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines [Eisenhauer et al. 2009].

1 Definitions

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

1.1 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Conventional CT. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

1.3 Response Criteria

1.3.1 Evaluation of target lesions

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

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

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

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

1.3.2 Evaluation of non-target lesions

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

1.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

1.3.4 Duration of overall response

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

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

1.3.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.