Protocol Cover Page

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Protocol Version: 7.0

Title: An Open Label Window of Opportunity Phase II Study of the FAK Inhibitor Defactinib (VS-6063) in Participants with Surgical Resectable Malignant Pleural Mesothelioma

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Local Protocol #: 13-296
Coordinating Center: DFCI/BWH

Title: An Open Label Window of Opportunity Phase II Study of the FAK Inhibitor Defactinib (VS-6063) in Participants with Surgical Resectable Malignant Pleural Mesothelioma.

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Head of Hematology and Oncology Development
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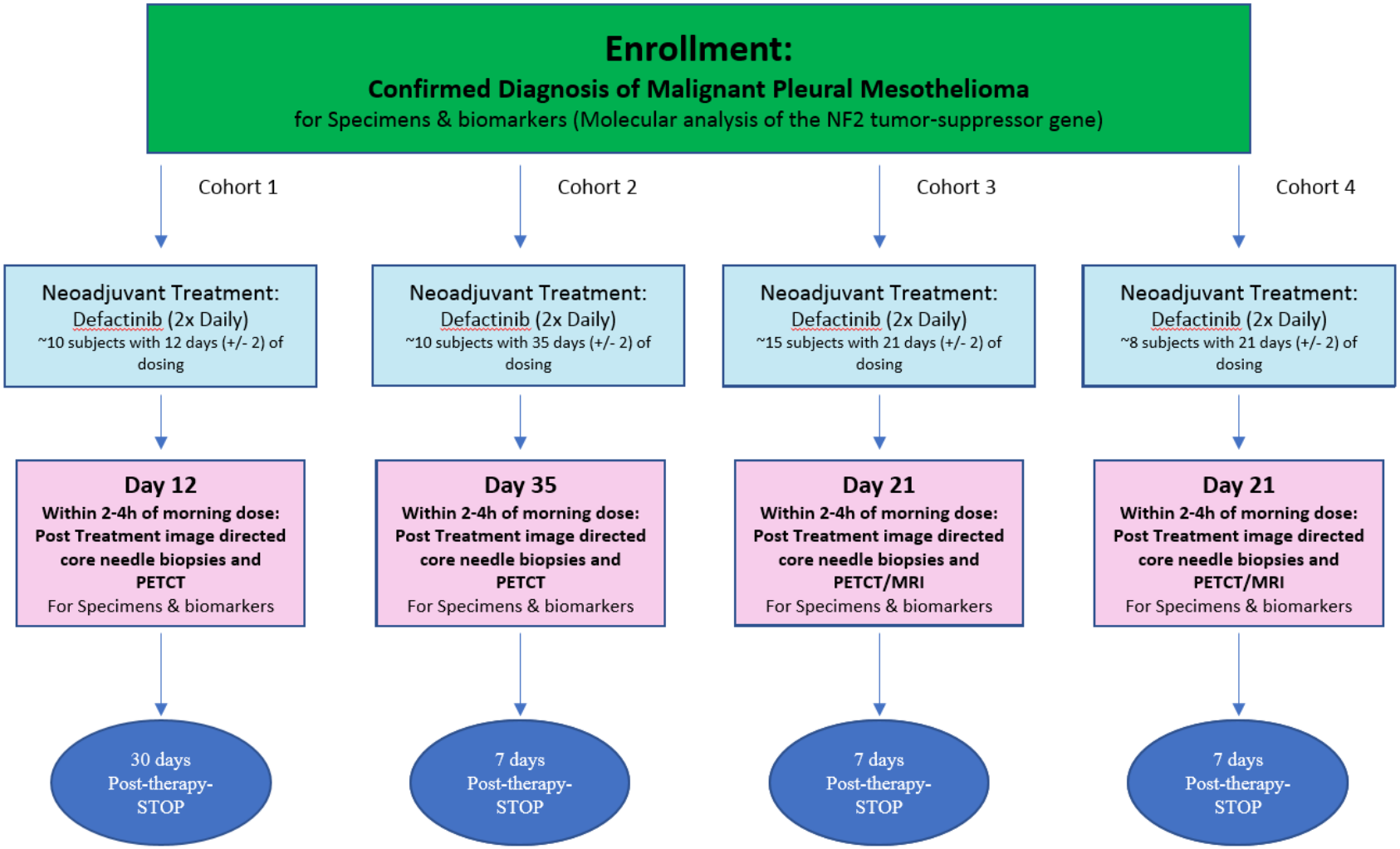
Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Protocol VS-6063-203 Version 7.0 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with current International Conference on Harmonization (ICH) guidance, Good Clinical Practice (GCP) guidance, the Declaration of Helsinki

Name of Clinical Investigator: _____

Investigator Signature	Date


Enrollment:
Confirmed Diagnosis of Malignant Pleural Mesothelioma
for Specimens & biomarkers (Molecular analysis of the NF2 tumor-suppressor gene)
Cohort 1
Cohort 2
Cohort 3
Cohort 4
Neoadjuvant Treatment: Defactinib (2x Daily) ~10 subjects with 12 days (+/- 2) of dosing
Neoadjuvant Treatment: Defactinib (2x Daily) ~10 subjects with 35 days (+/- 2) of dosing
Neoadjuvant Treatment: Defactinib (2x Daily) ~15 subjects with 21 days (+/- 2) of dosing
Neoadjuvant Treatment: Defactinib (2x Daily) ~8 subjects with 21 days (+/- 2) of dosing
Day 12
Within 2-4h of morning dose: Post Treatment image directed core needle biopsies and PETCT
For Specimens & biomarkers
Day 35
Within 2-4h of morning dose: Post Treatment image directed core needle biopsies and PETCT
For Specimens & biomarkers
Day 21
Within 2-4h of morning dose: Post Treatment image directed core needle biopsies and PETCT/MRI
For Specimens & biomarkers
Day 21
Within 2-4h of morning dose: Post Treatment image directed core needle biopsies and PETCT/MRI
For Specimens & biomarkers
30 days Post-therapy- STOP
7 days Post-therapy- STOP
7 days Post-therapy- STOP
7 days Post-therapy- STOP

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine transaminase (SGPT)
ANC	Absolute neutrophil count
AST	aspartate transaminase (SGOT)
ATP	adenosine-5'-triphosphate
AUC	area under the curve
BID	twice daily
BOR	best overall response
BP	blood pressure
BSC	best supportive care
CI	confidence interval
C_{ave}	average plasma concentration in steady state
C_{eff}	efficacious concentration
C_{max}	peak plasma concentration
CP	conditional power
CR	complete response
CRO	contract research organization
CRF	case report form
CSC	cancer stem cell
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DOR	duration of response
DLT	dose limiting toxicity
DSMB	Data and Safety Monitoring Committee
EC_{50}	half maximal effective concentration
ECG	Electrocardiogram
ECM	extracellular matrix
FAK	focal adhesion kinase
FDA	Food and Drug Administration
FIH	first in human
GCP	Good Clinical Practice
GI	gastrointestinal
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ITT	intent to treat
IWRS	interactive Web Response System
Merlin	moesin-ezrin-radixin-like protein

MPM	malignant pleural mesothelioma
MTD	maximum tolerated dose
NCI	National Cancer Institute
NF2	neurofibromatosis type 2 gene
NOAEL	no observed adverse effect level
ORR	objective response rate
OS	overall survival
PD	progressive disease
PR	partial response
PK	pharmacokinetic
PFS	progression-free survival
Pyk2	proline-rlch tyrosine kinase-2
PP	per protocol
QoL	quality of Life
QTc	corrected QT interval
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SOC	system organ class
SOP	standard operating procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment emergent adverse event
$t_{1/2}$	terminal half-life
T_{max}	time of peak plasma concentration
TTP	time to progression
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

The reality is that Malignant Pleural Mesothelioma (MPM) treatment in the US is variable and based on regional preferences, varying expertise, physician choice and patient preference. The Brigham and Women's Hospital's International Mesothelioma Program (IMP) has been one of the largest international centers for surgical treatment for MPM in the world. Hundreds of patients come here every year to be considered for surgical therapy. As a consequence, the IMP leadership has developed a clinical and research program focusing on improving care for MPM patients including collaborative clinical care, research infrastructure and all types of support including a house to provide accommodations to patients treated here. The majority of patients who come to the BWH are eligible for surgical resection. This patient population is largely chemotherapy naïve and has good functional status. As part of the IMP, large funds have been invested in tumor collection and annotation as well as in refining staging and pre-treatment stratification. As new biological agents with promise for response in MPM come on line, the IMP has been engaging to examine these drugs to better the lot of patients. We hypothesize that the most rational manner to develop therapeutic strategies for patients with MPM is to take promising drugs and use them in short course in patients who come here for surgical evaluation. These patients generally have as part of their staging, pleural biopsies and multiple staging tests as part of standard approach and in parallel with consented tissue acquisition for research.

The proposal herein is to offer these patients enrollment in brief phase II trials to evaluate promising drugs for 12-35 days as defined in specific cohorts, in biomarker driven studies, determine their response, define the predictive biomarker for response, and then after an adequate period to clear the drug and any potential side effects, offer them surgery for which they have come to the BWH in the first place. This specific protocol is to study a promising drug which is a FAK inhibitor in this fashion.

The drug proposed in this protocol, defactinib (VS-6063) was demonstrated to be a potent and selective ATP-competitive, reversible inhibitor of recombinant human Focal Adhesion Kinase (FAK) and proline-rich tyrosine kinase-2 (Pyk2) in biochemical and cell based assays. This drug, defactinib, is an orally bioavailable, small-molecule FAK inhibitor with potential anti-angiogenic and antineoplastic activities. The FAK pathway is a critical regulator of the survival of cancer stem cells, which are an underlying cause of cancer recurrence and metastasis [1]. Therefore, defactinib can prevent the integrin-mediated activation of several downstream signal transduction pathways, including ERK, JNK/MAPK and PI3K/Akt (most of which have been implicated in mesothelioma), thus inhibiting tumor cell migration, proliferation and survival.

2. OBJECTIVES

Aim 1:
The purpose of this study is to determine biomarker responses to the Focal Adhesion Kinase (FAK) inhibitor, defactinib (VS-6063, formerly PF-04554878) in Malignant Pleural Mesothelioma (MPM). This study is a biomarker driven study, and the primary endpoint in this Phase II trial is biological response to defactinib, including tumor and other surrogate tissue (Platelet Rich Plasma, PRP) phospho-FAK (pFAK) inhibition, change in cancer stem cells, tumor immune cells, and the tumor microenvironment. Ultimately, the goal is to define the

biomarker best suited to predict the response to defactinib which is expected to result in therapeutic response.

Aim 2:
To quantify the toxicity of the investigational drug administered as neoadjuvant prior to conventional MPM multi modality therapy to chemotherapy naïve patients. As this trial is positioned to be offered for patients eligible and interested in surgical treatment for MPM, many may undergo surgery after induction therapy. This surgery and subsequent treatment may consist of excisional surgery by Extrapleural Pneumonectomy (EPP) or Pleurectomy Decortication (P/DC) followed by intra operative intra thoracic/intra peritoneal heated chemotherapy and adjuvant treatment as necessary. However, some patients may not undergo surgery and may opt for chemotherapy or other therapies. The endpoint will be to determine how many patients at day 30-35 are still eligible to undergo surgery should they choose to.

Aim 3:
To procure samples to evaluate the pharmacokinetics of the investigational drug by measuring plasma concentrations of defactinib and potential metabolites. The established recommended daily dose of defactinib is 400 mg PO BID. This drug has been dosed as high as 750 mg PO BID without reaching the MTD.

Aim 4:
To evaluate radiographic and metabolic response to the defactinib by comparing the pre-treatment PET CT to a PET CT performed at the end of therapy. We will measure tumor volume and FDG activities in the pre and post treatment studies. The PET CT will also guide the post-treatment biopsy by demonstrating the locations of tumor activity and bulk.

Study Design

This is an open label neoadjuvant study in subjects with malignant pleural mesothelioma who are eligible for extirpative surgery based on functional, pathologic and clinical parameters. Patients eligible for this study can have either epithelial or non epithelial histology, negative mediastinal lymph nodes (by PET-CT or mediastinoscopy) and at least 100 cc tumor volume by chest PET-CT. They should not have contralateral or metastatic disease (defined as evidence of cancer outside the ipsilateral chest cavity) at staging as defined by PET-CT or biopsy. The objectives of this Phase II clinical trial are to assess the ability of the Focal Adhesion Kinase (FAK) inhibitor, defactinib, to modulate key biological markers and mesothelioma cell populations, to define the pharmacodynamic in this population, to investigate tumor response by PET CT, to define the best predictive biomarker for response, to determine whether patients undergoing this therapy can remain candidates for surgical treatment and to describe any associated adverse reactions (toxicities) in this patient population.

Defactinib will be administered at 400 mg twice daily for 12 (cohort 1), 35 (cohort 2), 21 (cohort 3) +/- 2 days, or at 100 mg twice daily for 21 (cohort 4) +/- 2 days with up to 43 participants. Each participant will already have a pre-study drug biopsy as an entry criteria which will be accomplished during the routine work up of any mesothelioma patient at BWH/DFCI and then as part of the trial undergo a post treatment biopsy on Day 12 (cohort 1), Day 35 (cohort 2), Day 21

(cohort 3) or Day 21 (cohort 4) of treatment. After at least 10, 33, or 19 days of defactinib administration, the post treatment biopsy will be collected within 2-4 hours post the last dose of study drug. This will be obtained via core needle biopsy that is imaged-guided. Specifically, the patient will undergo a PET CT in Radiology or the AMIGO suite at BWH. The scan will be used to define areas consistent with tumor best suited for biopsy. The biopsy will be planned using guidance of the CT and/or Ultrasound at the same time and location and be undertaken by a team composed of a thoracic surgeon and radiologist. At least 4 cores will be obtained, to be analyzed by both the sponsor and Dr. Bueno's lab.

To assess the pharmacokinetics of defactinib in this patient population, plasma concentrations of the study drug will be determined over a 24 hour period beginning on Day 11 of the study. A single plasma sample will also be collected on Day 12 (+/- 2 days), within 30 minutes of the second biopsy (Cohort 1 patients only). Additional samples will be collected on Day 35 and 42 in cohort 2 and Day 21 and 28 in cohort 3 and cohort 4 subjects. Exposures of VS-6063 in the tumor biopsy may be examined.

The definitive surgery will occur no earlier than 30 (cohort 1) or 7 (cohort 2, 3 and 4) days after the last dose of study drug to minimize any risk to the patient from potential surgery. It is expected that the drug will completely clear the patient within 7 days of cessation of therapy based on the terminal $t_{½}$ following a single dose averaged about 9 hours across all treatment groups in the FIH Phase I study. The safety of defactinib will be assessed continually until 30 (cohort 1) or 7 (cohort 2, 3 and 4) days post last dose of study drug. All treatment related AEs should be followed until resolution, stabilization, or for 30 days, whichever is least. Any SAE occurring after the reporting period must be reported as soon as possible, but no later than 24 hours, if a causal relationship to the investigational drug is suspected. Death must always be reported when it occurs during the 30-day reporting period irrespective of intervening treatment.

2.1 Primary Objectives

The primary objectives of this Phase II trial are to assess biomarker responses in patient derived tumor and other surrogate tissues, including but not limited to inhibition of phospho-FAK, alterations in markers of cell cycle and apoptosis, changes in cancer stem cells, tumor immune cells, and the tumor microenvironment. Specifically, we will assess percent pFAK inhibition in a tumor specimen as the primary objective. Specimens will also be profiled genetically and immunologically to discover potential predictive biomarkers.

2.2 Secondary Objectives

a. To evaluate the safety of defactinib in subjects with malignant mesothelioma.

b. To evaluate the pharmacokinetics of defactinib in plasma of subjects with malignant mesothelioma.

c. To evaluate tumor response by PET/CT

3. BACKGROUND

3.1 Study Disease

Malignant pleural mesothelioma (MPM) is a rare thoracic tumor that develops from transformed cells originating in the pleural mesothelium and is associated with asbestos dust and fibers exposure [1]. MPM progresses primarily by local extension to involve the ipsilateral lung and mediastinal structures causing death by such locoregional extension. Malignant pleural mesothelioma is often unresectable at diagnosis, is refractory to most conventional therapies including cytotoxic agents and is frequently complicated by pleural effusion [2]. Clinical behavior of the malignancy is affected by the continuous mesothelium surface of the pleural cavity that enable local metastasis via exfoliated cells, invasion to underlying tissue and other organs within the pleural cavity [3]. Prognostic scoring systems from our mesothelioma center at BWH, the EORTC and CALGB have shown that the most important predictors of poor prognosis for patients with MPM are: poor performance status; patient's age; tumor stage, male gender; low hemoglobin; high platelet count; high white blood cell count; high lactate dehydrogenase (LDH) and the histological subtype [4,5,6]. Our group has also validated these parameters and are in the process of submitting a manuscript proposing pre-operative staging.

The management of the disease by single modality treatment did not achieve higher results than supportive care [7]. Complete responses to systemic treatment are rarely observed and the common responses are of short duration. Presently available chemotherapy regimens achieved a response rate of 30–40%, a median progression free of 6 months and an overall survival of 12 months [8,9]. The epithelioid histology responds better to treatment and has a survival advantage over nonepithelioid sarcomatoid histology [10,11]. Radiation therapy alone is also ineffective.

The current treatment paradigm for any solid tumors in the absence of metastatic disease is first to remove all macroscopic disease with surgical resection [12] and then to eradicate residual microscopic disease and prevent the development of micrometastatic recurrence with adjuvant local and systemic treatment with chemotherapy and radiation therapy. Successful application of this treatment strategy depends on both appropriate patient selection of those with favorable conditions for resection and on the efficacy of additional modalities used to control microscopic disease. Surgeons, oncologists and radiation oncologists at the BWH and DFCI pioneered the use of surgery for mesothelioma and developed new techniques to accomplish surgical extirpation. We also established the benchmark in terms of expected outcome as well as research protocols adding multimodality therapies to the treatment of this disease. Extrapleural pneumonectomy is an aggressive treatment option which removes all tumor. Pleurectomy and decortication (PD) is indicated for patients with earlier disease where the lung can be spared resection. EPP based multimodality therapy for MPM in surgical candidates with resectable tumors has been associated with increase in median survival and with approximately 20% of selected number of patients experiencing long-term survival [5,13,14].

Despite initial success for most patients, early recurrence and a short disease free interval are observed in over 50% of the patients with MPM [14]. The most common sites of recurrence are the contralateral hemithorax, abdomen, ipsilateral hemithorax, and distant regions. The median survival from time of recurrence to death is about 3 months [14]. However, there are patients who represent approximately 20% of the cohort who benefit long term survival after surgical therapy for MPM.

Due to the fact that the overall prognosis from MPM is usually dismal, many different approaches have been proposed and different centers treat patients in radically different manners. Certainly, a number of first line chemotherapy options exist. In addition to surgery followed by chemotherapy and radiotherapy as practiced at our centers, other centers recommend neoadjuvant therapy with a variety of agents followed by restaging and surgery as well as the addition to surgery of other innovative techniques including immunotherapy, heated intra-pleural chemotherapy and photodynamic therapy.

Furthermore, there is the understanding now that it is important to stratify patients upfront to protocol-driven care. We have led this strategy at BWH/DFCI by defining a pre-treatment evaluation of both the patient's cardiorespiratory status as well as the oncologic status using lymph node staging, defining the subtype of the cancer, measuring serum markers and testing for a prognostic gene expression-based test developed here.

To conclude the prognosis for MPM remains poor although there have been some modest improvements in survival from newer chemotherapies and multimodality treatments [11,13,14]. However, this improvement has occurred longer than 12 years ago and no other agents has shown improvement to-date. Surgery has shown improved survival in a selected subset of patients. However, additional therapy is required to extend survival. **It must be clarified that Mesothelioma is almost universally a fatal illness for which we do not yet have adequate therapy. The mortality overall remains at 95-99%. Urgent new therapies are required and hope is focused on biologically driven compounds.**

The rationale for this study is based on the fact that tumor biology appears to be a major determinant of extended survival [15]. Therefore tailored treatment based on patient's individual tumor biology, as is currently studied in Breast Cancer [16,17], will most likely contribute to the existing treatment of Malignant Pleural Mesothelioma. This protocol is to study a biological drug with a promising target in mesothelioma and is supported by pre-clinical studies.

Study Agent

Defactinib was demonstrated to be a potent and selective ATP-competitive, reversible inhibitor of recombinant human Focal Adhesion Kinase (FAK) and proline-rich tyrosine kinase-2 (Pyk2) in biochemical and cell based assays.

The drug defactinib is an orally bioavailable, small-molecule FAK inhibitor with potential antiangiogenic and antineoplastic activities.

FAK pathway is a critical regulator of the survival of cancer stem cells, which are an underlying cause of cancer recurrence and metastasis [1]. Therefore, defactinib can prevent the integrin-mediated activation of several downstream signal transduction pathways, including ERK, JNK/MAPK and PI3K/Akt (most of which have been implicated in mesothelioma), thus inhibiting tumor cell migration, proliferation and survival.

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. Defactinib also demonstrated antitumor efficacy in three human tumor xenograft models in nude mice including glioma, colon, and pancreatic carcinoma models. In these studies, oral administration of defactinib resulted in significant growth inhibition or regression of established tumors at well-tolerated dose levels. In addition, studies investigating the dose- and time-dependent inhibition of FAK activity following oral administration of defactinib provided insight towards the relationship of inhibition of FAK to antitumor efficacy and the PK/PD relationship for this compound. The PK/PD relationship and subsequent target efficacious plasma concentration was determined by measuring defactinib in plasma samples isolated from the same individual mice in which target inhibition data was generated. Collectively, the combination of studies to assess the relationship between defactinib exposure in plasma, inhibition of FAK activity and tumor growth established several conclusions relevant to the evaluation of clinical efficacy [Presented at ASCO 2011 by S.F. Jones. Phase I study of VS-6063, a second-generation focal adhesion kinase (FAK) inhibitor, in patients with advanced solid tumors. 2011 ASCO Annual Meeting Abstract No: 3002]. Namely that the drug is relatively safe with the MTD not reached at 700 BID dosing and that biochemical effects are seen very rapidly.

The main purpose of the trial proposed herein is to evaluate the activity of defactinib for future trials in MPM patients.

Focal Adhesion Kinase (FAK)

FAK protein is a member of the non-receptor protein tyrosine kinases (PTKs) subfamily that was first described in the early 90s [2]. FAK protein is encoded by the Protein Tyrosine Kinases PTK2 gene located on the long (q) arm of chromosome 8 [3, 4] and is expressed in sub-membranous structures called focal adhesions (FAs) involved in cellular adhesion and spreading processes.

Obstructing FAK may prevent the integrin-mediated activation of several downstream signal transduction pathways, including ERK, JNK/MAPK and PI3K/Akt, thus inhibiting tumor cell migration, proliferation and survival. The tyrosine kinase FAK is a signal transducer for integrins that is up-regulated in many tumor cell types and is involved in tumor cell invasion, migration and proliferation. [1]

The FAK is activated by several stimuli including integrins, cellular substances, receptors, and various pathological conditions. Increased FAK expression and activity has been observed in a variety of solid human tumors and is frequently correlates with metastatic disease and poor prognosis [11]. In Breast Cancer, FAK is important for progression and invasion and is necessary for the dynamic turnover of focal adhesions [12]. It has been shown that when FAK was blocked, breast cancer cells became less metastatic due to decreased mobility [11,12].

Src family kinases (SFK)

A variety of PTK families have been identified in mammalian cells. The Src family kinases (SFK) are non-receptor (cytoplasmic) tyrosine kinases comprising nine known kinases members: blk, c-fgr, fyn, hck, lck, lyn, c-src, c-yes and yrk [5], of which three, c-src, fyn and c-yes are widely expressed. Members of this kinase family have several common features: 1) unique N-terminal domains, 2) attachment to cellular membranes through a myristylated N-terminus, and 3) homologous SH2, SH3, and catalytic domains, phosphotyrosines and proline-rich regions, by which, postactivation, interacts with various proteins [6,7,8]. The nonreceptor PTK c-Src is probably the most important enzyme interacting with FAK. It is characterized by the ability to bind and interact with phosphortyrosine residues of other molecules, such as c-Met and FAK, through its SH2 domain [6,7]. The FAK/Src complex regulates various basic cellular functions and the behavior of terminally differentiated, post-mitotic cell types, such as cellular proliferation and growth, protection from apoptosis, adhesion, spreading, invasion, and migration. [9,10]. The FAK/Src complex binds and phosphorylates many downstream molecules such as p130Cas, Grb2, and PI3K, transducing signals down for many different pathways [9]. FAK/Src complex is activated in many tumor cells and generates signals leading to tumor growth and metastasis [10].

Epithelial-mesenchyme transition (EMT) in Human Cancer

Epithelial-mesenchyme transition (EMT) is an epithelial plasticity characterized by long-lasting morphological and molecular changes in epithelial cells as a result of differentiation towards a mesenchymal cell type [13].

EMT was first recognized as a feature of embryogenesis, which is vital for morphogenesis during embryonic development as is the case of mesoderm formation, neural tube formation and the myocardium induce endothelial transformation into prevalvular mesenchyme [14]. Several oncogenic pathways like peptide growth factors; Src, Ras, Ets, Integrin, Wnt/beta-catenin and Notch may induce EMT. In addition, initiation of metastasis involves invasion, which has many phenotypic similarities to EMT including a loss of cell-cell adhesion mediated by E-cadherin repression and an increase in cell mobility. It has been shown that EMT can generate cells with properties of stem cells. Those stem-like cells express markers associated with EMT and inducing phenotypes associated with cancer stem cells [15]. The epithelial-mesenchymal transition that generates cells with properties of stem cells was reported in varies human organs: uterus, breast, lung, gastro-intestinal tract, pleura and ovary [16-21].

Therefore, EMT may play a role in transforming normal cells to malignant ones and in metastasis. The morphological patterns of malignant mesothelioma may be the outcome of different steps in an epithelial–mesenchymal transition process resulting in mesothelioma histological classification of epithelioid (mostly composed of epithelial-shaped cells), sarcomatoid (mostly composed of spindle-shaped cells), or biphasic (composed of both types of cell) [22].

EMT and Drug Resistance

In advanced disease or diseases like pancreatic carcinoma where often curative surgery is not feasible, chemotherapy could be theoretically an attractive option in managing the disease [23]. However, a major problem preventing chemotherapy success is drug resistance, which is often acquired during treatment [24]. Recent studies have shown that EMT is associated with drug resistance and cancer cell metastasis [25]. Three observations support this notion: (i) Cells which have undergone EMT tend to be more resistant to drugs; (ii) When cells are cultured in the presence of a certain drug, specific drug-resistant cells will have a selective advantage; these cells will often have undergone EMT; (iii) Targeting EMT pathways not only leads to a decrease in invasive potential, but also to an increase in drug sensitivity [23]. When pancreatic cancer cells were cultured in serially increasing concentrations of gemcitabine, they gained up to 50-fold increase in drug resistance and they also showed hallmarks of EMT [26]. Gene expression profiling of pancreatic cancer cell lines revealed that cells resistant or sensitive to three chemotherapeutic agents (gemcitabine, 5-fluorouracil, and cisplatin) formed two distinct groups, with features of EMT in the drug-resistant group [27]. Our group reported chemoresistance in Mesothelioma specimens, both *in vitro* [28] and *in vivo* [29]. A significant proportion of mesothelioma tumors exhibited extreme/intermediate resistance to cisplatin, gemcitabine, or vinorelbine. Chemoresistance to cisplatin (27%), gemcitabine (31%), or vinorelbine (59%) and 11% had extreme/intermediate resistance to all 3 drugs [28].

EMT therefore has impact on both the neoplastic progression and patient survival, as well as the on resistance of cancers to therapeutics such as taxol, vincristine, oxaliplatin, EGF-R targeted therapy and radiotherapy. New therapeutic combinations using genotoxic agents and/or EMT signaling inhibitors expected to circumvent the chemotherapeutic resistance of cancers characterized by transient or sustained EMT signatures [30].

FAK and Mesothelioma

There is accumulating evidence supporting the role of FAK up-regulation on the neoplastic transformation of different types of cells [31] and increased FAK expression/activity is frequently correlated with highly malignant or metastatic tumors having a poor prognosis like MPM [31].

a. Merlin is a tumor suppressor frequently inactivated in malignant mesothelioma (at least 40% of cases) (MM)(neurofibromatosis type 2 NF2 gene product). Merlin inactivation is a critical step in mesothelioma pathogenesis and is related with up-regulation of FAK activity [32]. Merlin negative breast cancer cells are most sensitive to FAK Inhibition and Merlin negative mesothelioma cell lines are especially sensitive to FAK Inhibition. (AK Inhibitor VS-4718 Preferentially Attenuates Growth of Malignant Mesotheliomas with NF2 Mutation: Role of Cancer Stem Cells. Shapiro IM, Kolev VN et al, Poster presented at IMIG 2012, Boston: http://www.verastem.com/attachments/VSTM_iMig_poster_2012.pdf)

b. Mesothelin is a glycoprotein expressed on normal mesothelial cells and is over-expressed in several histologic types of tumors including pancreatic adenocarcinomas and MPM. Silencing Mesothelin induces a significant decrease in activation (phosphorylation) of ERK1 and phospho-AKT and the expression of β- catenin, a known EMT marker, was reduced [33].

c. Membrane chondroitin sulphate proteoglycan 4 (CSPG4), has been successfully targeted in melanoma and breast cancer, and was found highly expressed in Malignant Mesothelioma, but not in normal mesothelium [34]. CSPG4 was expressed on 75% of MM cell lines and in 61% of MM biopsies, with minimal expression in surrounding healthy cells. Mesothelioma cell adhesion is mediated by CSPG4 and inhibited by CSPG4 mAb-based immunotherapy resulting in decreased phosphorylation of focal adhesion kinase (FAK), AKT and reducing apoptosis [34].

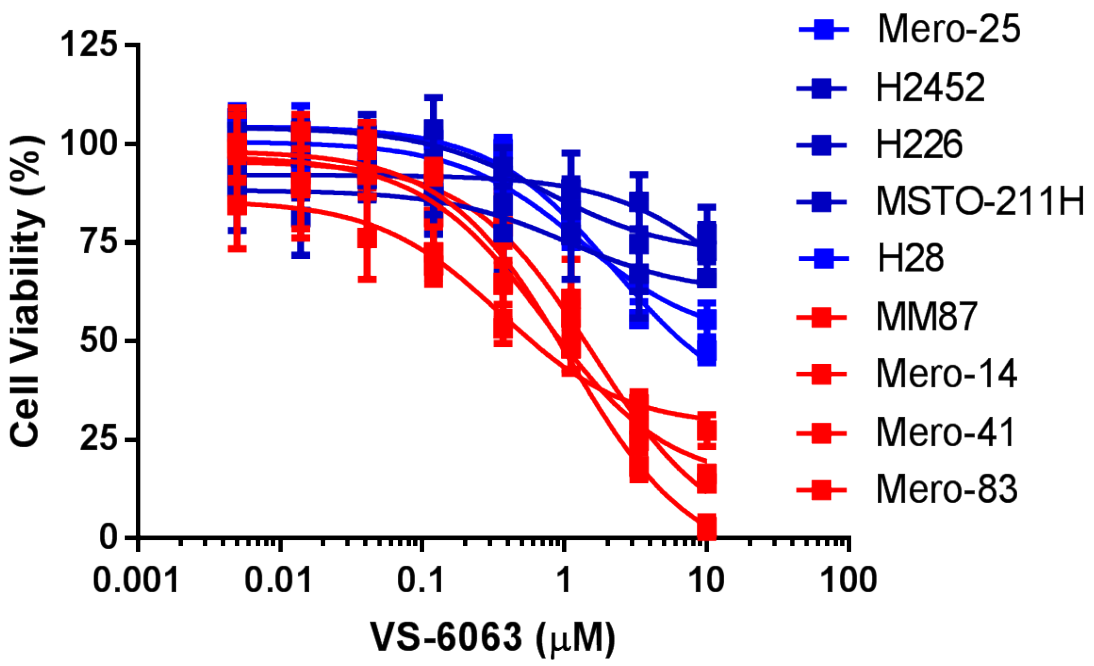
Pre-clinical work by Verastem and by our BWH research group

A significant number of experiments at many levels has been recently completed first at Verastem and then at BWH in collaboration with Verastem.

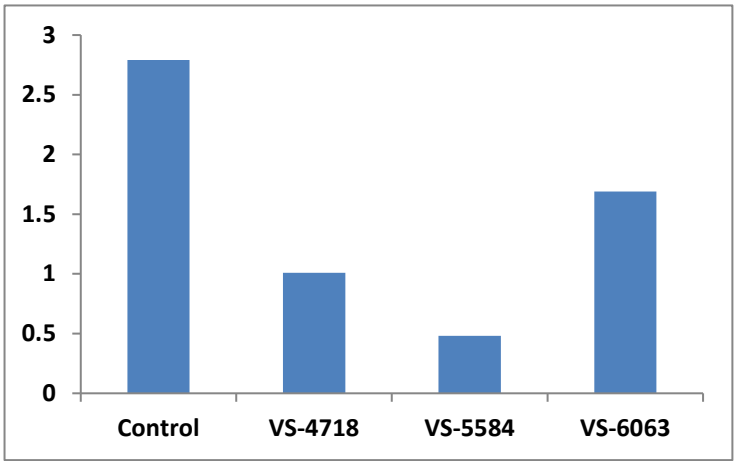
There are many preclinical data supporting this trial. NF2 mutations which affect the Merlin protein levels have been demonstrated previously in mesothelioma. Furthermore, we recently conducted a deep sequencing study of 100 mesothelioma tumors (unpublished and confidential). We found that at least 40% of the cases had NF2 mutations which included chromosomal loss, reduced copy number, point mutations and loss by other novel mechanisms. The other two major recurrent mutations were in Bap1 and P53 with minimal overlap.

We also performed extensive analysis of hundreds of mesotheliomas linked to clinical outcomes for chromosomal deletions using FFPE specimens and tissue microarrays, NF2 deletions, Merlin levels and related proteins. We found that 54% of the tumors had chromosome 22 loss (where NF2 is located), 1% had NF2 deletions, and 50% had low Merlin levels. The overall merlin levels were even lower in non-epithelial mesothelioma tumors which have worse prognosis in general and truly have no reliable therapy.

The FAK inhibitor drug defactinib was developed to treat triple negative breast cancer based on stem cell sensitivities. When explored with cell lines of all tumors it was shown to be particularly effective with mesothelioma and ovarian cell lines which are related malignancies. The figures below show in red the sensitivities of mesothelioma cell lines with low Merlin level and the decreased sensitivities to the drug with high Merlin levels. Merlin is known by many other studies to be an important interrelated pathway in mesothelioma so this effect makes biological sense. The protein levels were measured by a Western Blot.



We also created CSC in mesothelioma using fresh tumors from surgery and showed good response to the study drug as seen in the below figure.



The preclinical work described above suggests that this drug defactinib and other FAK inhibitors have good response in cases with low expression of Merlin. However, the cutoff is unknown and not every mesothelioma with low Merlin has a good response and vice versa, necessitating a broad study of mesothelioma patients.

3.2 Rationale

3.2.1 Defactinib in solid tumors

Defactinib was demonstrated 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.

3.2.2 Clinical Summary of defactinib, second generation FAK/Pyk2 inhibitor

Phase I safety, pharmacokinetics, and pharmacodynamics trial of the focal adhesion kinase (FAK) inhibitor defactinib was conducted at 2 sites including DFCI, Boston (protocol 08-383). This phase 1 dose escalation study of defactinib given as continuous oral dosing in 21-day cycles in patients with solid tumors had several endpoints include safety, pharmacokinetics (PK), and response by RECIST. The enrollment included patients with advanced non-hematologic malignancies, including patients with malignancies appropriate for serial biopsy. Screening consisted of medical history, physical examination ECOG performance status, blood draws, a pregnancy test for female patients of childbearing potential tumor imaging. Treatment consisted of defactinib pills continued until progression of disease, unacceptable toxicity, or patient request.

In this study 46 patients received doses ranging from 12.5 mg to 750 mg BID on a fasted schedule. The most frequently reported treatment-emergent adverse events were nausea (19/46 [41.3%] subjects) followed by fatigue (18/46 [39.1%] subjects), vomiting (15/46 [32.6%] subjects) and unconjugated hyperbilirubinemia (15/46 [32.6%] subjects). Adverse events were generally Grade 1/2 in severity. A total of 5 subjects were reported with DLTs, 1 subject had a DLT of headache (in the 200 mg BID fasting cohort); 1 subject had a DLT of fatigue (in the 425 mg BID fed cohort) and 3 subjects had a DLT of hyperbilirubinemia (1 in the 300 mg BID fasting cohort, 1 in the 425 mg BID fasting cohort and 1 in the 425 mg fed cohort). In all cases of hyperbilirubinemia, AST and ALT were within normal limits. No treatment related serious adverse events were reported.

Overall, 16 subjects had 17 cases of abnormal blood bilirubin. In all cases, AST and ALT were within normal limits. Reports of hyperbilirubinemia were asymptomatic and reversible (on or off drug) with no evidence of other liver function abnormalities or hemolysis.

A total of 9 (19.6%) subjects had a maximum increase from baseline ≥30 mmHg in supine systolic blood pressure and 9 (19.6%) subjects had a maximum increase from baseline ≥30 mmHg in standing systolic blood pressure. A total of 8 (17.4%) subjects had maximum increase from baseline ≥20 mmHg in supine diastolic blood pressure and 5 (10.9%) subjects had maximum increase from baseline ≥20 mmHg in standing diastolic

blood pressure.

No subjects experienced an increase in QTc interval from baseline ≥60 msec.

PK analysis supports the BID-dosing regimen and shows that doses above 100 mg BID lead to exposures above the minimal efficacious concentration predicted preclinically. Increasing the dose beyond 425 mg BID did not increase drug exposure. Following single oral doses of defactinib under fasted conditions (at doses ranging from 12.5 mg to 750 mg), defactinib was rapidly absorbed and maximum serum defactinib concentrations were generally achieved 1 to 2 hours post dose. Mean terminal elimination half-life was approximately 9 hours across the dose groups. Hepatic metabolism was predicted to be the major clearance pathway for VS 6063 in humans. See Section 4.3 for possible drug-drug interactions with substrates for CYP3A4 and CYP2C9.

Stable disease was achieved in 16 of 37 subjects (43%) treated at doses ≥100 mg BID. Stable disease was not achieved at doses <100 mg BID (N=9). Of note, eight subjects enrolled in this study had ovarian cancer which is biologically similar to mesothelioma. Of these subjects, four subjects achieved stable disease (three for ≥6 months) and the duration of stable disease with VS-6063 was equal to or exceeded that reported with prior therapy.

Phase II, randomized, double blind, placebo controlled study in subjects with malignant pleural mesothelioma (protocol VS-6063-202) was conducted at ~75 sites across 16 countries and enrolled 344 subjects. Prior to entry and randomization to the study, tumor moesin-ezrin-radixin-like protein (Merlin) status for each subject was determined by immunohistochemistry performed at a central laboratory. Subjects were randomized in a 1:1 ratio to receive oral VS-6063 400 mg twice daily (BID) or matched placebo. Randomization was stratified by tumor Merlin status (high versus low). The study was terminated due to futility, following a Data Safety Monitoring Board (DSMB) recommendation from a pre-planned interim analysis. The study was not stopped due to any safety concerns with the study drug. The results of the analysis demonstrated that VS-6063 was generally well tolerated, but that there was not a sufficient level of efficacy in this patient setting (maintenance setting in malignant pleural mesothelioma subjects with stable disease after >/= 4 cycles of pemetrexed/platinum chemotherapy) to warrant continuation of the study.

Study VS-6063-103 compared a modified prototype formulation (new formulation) with the current clinical formulation (reference) of defactinib and evaluated the effect of food (high fat) on both formulations. The study was conducted in 24 healthy volunteer male subjects who received a single dose of 200 mg reference formulation of defactinib and single dose of 100 mg new formulation defactinib. There was a statistically significant food effect for the reference formulation of defactinib. Exposure increased by approximately 2 to 3-fold following dosing of defactinib reference formulation tablet in the fed state compared to the fasted state. The geometric mean ratio (GMR) and 90% CIs for AUC(0-t), AUC(0-inf) and Cmax of 273.36 (215.19%, 347.26%), 457.73 (275.75%, 759.79%), and 192.52 (146.67%, 252.71%), respectively. The time taken to reach maximum plasma concentrations of defactinib was 2 to 4 times longer in the fed state

than in the fasted state, indicating a food effect on the rate of absorption. An approximate 4-fold increase in exposure was observed following dosing of defactinib new formulation tablet in the fasted state in comparison to the reference formulation tablet in the fasted state. The GMR and 90% CIs for AUC(0-t), AUC(0-inf) and Cmax of 433.05 (366.77%, 511.32%), 617.39 (387.20%, 984.42%) and 421.33 (348.42, 509.51), respectively. In conclusion, the 100 mg new formulation gave exposure potentially similar to 400 mg reference formulation when dosed to healthy volunteers as a single dose in fasted state. VS-6063 was well tolerated when administered in both fasted and fed states as a 200 mg reference formulation tablet and as a 100 mg new formulation tablet. There were no deaths, serious adverse events (SAEs) or severe AEs reported during the study, and no subject was withdrawn as a result of an AE.

Based on both preclinical and clinical data the recommended Phase 2 dose schedule is 400 mg BID (current clinical formulation). Given the specific timeline of the protocol and the need for a week-day only availability of the PET/CT and biopsy, we will only start patient treatments on Monday, Tuesday, or Wednesday. Based on the results of the VS-6063-103 study described above, the new 100 mg defactinib formulation will be evaluated in Cohort 4 of this study.

3.3 Making the Case for personalized treatment by MPM Molecular diagnostic and predictive test

3.3.1 Patient and Tumor Variation

Given the wide range of survival among MPM patients with similar tumors and treatment and the wide range of chemoresistance, there is a keen need for directing drugs to molecular pathways that characterize the disease in subsets of patients will improve treatment efficacy [3,22].

Though most of the MPM patients have poor survival, a subset of patients who underwent multimodality therapy with an aggressive surgical approach yield disease-free for over 3 years [5,6]. Among 636 patients who underwent extrapleural pneumonectomy at Brigham and Women's Hospital, 117 (18%) survived at least 3 years following surgery. The median survival of the 117 patients who survived 3-years was 59 months.

On the other hand, the prevalence of in vitro chemotherapeutic drug resistance in MPM is substantial. In a cohort of 203 MPM specimens resected at out center [4], a significant proportion of tumors had drug resistance to cisplatin, gemcitabine, or vinorelbine or even extreme resistance to all 3 drugs as measured in primary cell cultures. No significant differences in chemoresistance were found in tumors of patients who had received neoadjuvant chemotherapy compared with those who had not [4] and these findings support the need for new agents and this trial plan.

As far as clinical trials for drugs, CALGB has conducted over 18 multi-center drug trials for mesothelioma without a single positive trial. In fact, the only positive drug trial is from over 10 years ago showing a 2 months benefit in survival (10 to 12 months) for the

combination of Alimta and Cisplatin. This is still the standard of care. There is an urgent need for new drugs, particularly biological drugs for this cancer and we propose that our population is the best for it.

This study is proposed with a promising drug which is biologically designed based on mutations that are present in over 50% of patients with mesothelioma. We propose a short course to look at response and have available tissue before and after to hone in and define the best patient population. This is somewhat similar to I SPY 2 in breast cancer and is a new paradigm for clinical trial. We believe that in this very lethal disease it is justifiable. There is always potential harm to patients in any clinical trial, but we believe that a short course will demonstrate those who may benefit and they will have access to the drug should and when they recur.

As to the risk of a biopsy, we can address that risk because we have open an accruing study to do fine needles and core biopsy for mesothelioma patients for diagnosis and prognosis (04-349) for which we performed needle biopsies under image guidance on approximately 133 patients to date with no complications. The benefit of the biopsy is that it will rapidly inform us of the response and provide an opportunity to develop integral biomarkers for this drug.

3.3.2 MPM basic and Translational Research at BWH/DFCI

Our group has pioneered genomic and predictive studies in MPM using our resources of the tumor bank. We have developed diagnostic and prognostic tests based on gene expression analysis and have established expertise in developing biomarkers at the RNA and DNA levels. In addition, we have described the first transcriptome and genome sequencing projects in MPM.

We have also looked at the NF2 gene in MPM and find that there are some nucleotide altering mutations or NF2 loss in nearly 60% of the cases. We have recently discovered evidence for novel mechanisms of NF2 inhibition is a subset of MPM which can be possibly utilized to alter NF2 wt tumors into NF2 negative tumors (confidential preliminary results). Therefore, establishing which types of mutations may be associated with response in MPM becomes important.

Recent pathway analysis done in our lab showed that co-regulation networks related to the cross talk between MPM and its micro-environment, in particular involving the adhesion molecules, integrins, and cytokines, as well as progression related to genes related to EMT might have an important role in MPM (De Rienzo et al. Clin Cancer Res In Press). This is consistent with the expected role of the study drug. Our experience is presented to demonstrate our capabilities to study and develop biomarkers for this drug.

3.3.3 Tailoring drugs to MPM molecular pathways

By using microarray platform and sequence analysis for the specimens before and after the neoadjuvant treatment of defactinib and comparing them to the outcome we will be

able to better characterize the role played by these genes in MPM. We will also perform DNA sequencing on these specimens to relate specific NF2 mutations and look for other mutations in the DNA and RNA of pre-operative specimens for additional clues to novel biomarkers associated with response. Directing drugs to molecular pathways that characterize the disease in subsets of patients will most definitely improve treatment efficacy. This clinical trial will follow-up patients with newly diagnosed locally advanced MPM to test the effect of this investigational drug. The trial will use the information from each participant who completes the study treatment to help decide treatment for future patients.

3.3.4 Current clinical experience with defactinib

The Sponsor (Verastem) is currently conducting multiple clinical trials with defactinib. Patients participating in this study who are perceived to have received clinical benefit from defactinib administration will be eligible to participate in ongoing studies providing other entry criteria are met.

4. PARTICIPANTS SELECTION

4.1 Inclusion Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

4.1.1 Participant must have histologically confirmed malignant pleural mesothelioma at BWH that is not metastatic or unresectable.

4.1.2 Participants should be evaluated by a surgeon and a medical oncologist.

4.1.3 Participants are eligible to undergo excisional surgery such as extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/DC) or any other mesothelioma surgery.

4.1.4 Localized disease. The malignancy is confined to one affected hemithorax. Mediastinal N2 lymph nodes via cervical mediastinoscopy or endobronchial ultrasound (EBUS) are allowed.

4.1.5 Completed preoperative evaluation including: chest MRI, pulmonary function tests, echocardiogram (ejection fraction >30% for P/DC), and PET-CT within 45 days prior to registration.

4.1.6 Grossly normal pulmonary, cardiac function, renal, hepatic, hematologic and performance functions:

a. ECOG 0-1 or Karnofsky >80%

b. Normal contralateral pulmonary function as evidenced by a chest radiograph that fails to show acute infiltrates and a minimum postoperative predicted FEV1 of 0.8L or % predicted FEV-1 of greater than 35%.

c. Renal and hepatic function (serum Creatinine level less than upper limit of normal, SGOT (AST) of < 80 IU/L and total bilirubin of < 1.9 mg/dL) within 7 days of registration.

d. Hematology: Pre-operative WBC of > 4 K/uL, hemoglobin > 8 mg/dl and platelet count of > 80 K/mm3 within 7 days of registration.

4.1.7 Male or non-pregnant female (based on pregnancy test within 2 weeks of initial drug administration for premenopausal women).

4.1.8 Age ≥ 18 years of age.

4.1.9 This protocol requires patient's tissue to be collected and stored at BWH tumor bank prior to enrollment. If patient was diagnosed outside BWH and we do not have his/her tissue, a pleural biopsy for frozen tissue collection is required. Currently all patients with mesothelioma are offered the opportunity to enroll in 98-063 that allows consented storage of discarded tissue in the BWH tumor bank (enclosed).

4.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

4.2.1 Participants who have had chemotherapy or radiotherapy any time prior to entering the study or at any prior time for mesothelioma. Patients receiving chemotherapy type drugs for benign conditions can participate in this trial (e.g. methotraxate for arthritis).

4.2.2 History of upper gastrointestinal bleeding, ulceration, or perforation within 12 months prior to the first dose of study drug.

4.2.3 Known history of Gilbert's Syndrome or any current hyperbilirubinemia of any cause.

4.2.4 Known history of stroke or cerebrovascular accident within 6 months prior to the first dose of study drug.

4.2.5 Subjects with known infection with human immunodeficiency virus (HIV) or Acquired Immune Deficiency Syndrome (AIDS) (testing not required).

4.2.6 Subjects with confirmed Hepatitis A, B or C (testing not required).

4.2.7 Subjects with other cancers who have not been continuously disease-free for at least 3 years. Exceptions: subjects with prior history of in situ cancer that has been cured (e.g. cervical) or adequately treated basal or squamous cell skin cancer are eligible. Men under observation for local prostate cancer (defined as T1a-c, NO, MO Gleason grade ≤6, PSA <10 or T2a, NO, MO Gleason grade ≤6, PSA <10) are also eligible if they have had stable disease for at least 1 year.

4.2.8 Use of an investigational drug within 28 days or 5 half-lives (whichever is shorter) prior to the first dose of study drug. A minimum of 10 days between termination of the investigational drug and administration of the study treatment is required. In addition, any drug-related toxicity except alopecia should have recovered to grade 1 or less.

4.2.9 Pregnant or breastfeeding. The effects of defactinib on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control, or abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Men on this study must also agree to use adequate contraception (barrier method of birth control) when sexually involved with women of child-bearing potential.

4.2.10 Uncontrolled or severe cardiovascular disease, including myocardial infarct or unstable angina within 6 months prior to study treatment, New York Heart Association (NYHA) Class II or greater congestive heart failure, serious arrhythmias requiring medication for treatment, clinically significant pericardial disease, or cardiac amyloidosis

4.2.11 Known history of malignant hypertension

4.2.12 Uncontrolled intercurrent illness including symptomatic congestive heart failure, cardiac arrhythmia, or psychiatric illness/social situations which in the opinion of the study investigators would be associated with undue risk of participation in the study.

4.3 Prohibited Concomitant Treatment

Patients who are receiving anticoagulants (Coumadin, Plavix etc.) who cannot safely come off these drugs for at least a week prior to biopsy.

In vitro studies have shown that defactinib inhibits CYP2C9 and CYP3A4 in human liver microsomes. Extrapolation to expected human exposure indicates the potential for inhibition or induction of CYP enzymes is low. However, as the clinical significance of these potential interactions has not been formally assessed, it is recommended that compounds that are substrates for CYP2C9 and CYP3A4 are used with caution in concomitant administration with

defactinib may increase their exposure. A list of examples of 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 CYP3A4 or CYP2C9 should be avoided if possible or used with caution. A list of examples of inducers of CYP2C9 and CYP3A4 can be found in Appendix C.

4.4 Inclusion of Women, Minorities and Other Underrepresented Populations

4.4.1 This study is recruiting minorities, women and underrepresented population. Translational/Language services will be used as needed.

4.4.2 The vast majority of mesothelioma patients are over 18 years of age and the median age at presentation is 70 making the exclusion of children not relevant.

5. REGISTRATION PROCEDURES

5.1 General Guidelines for DF/HCC and DF/PCC Institutions

Patients seen at DFCI or BWH Surgery clinic and have the diagnosis of MPM will be approached by the treating physician to participate in this study. They will be evaluated by a study surgeon to determine if they meet eligibility for surgery and by a study medical oncologist to determine if they are deemed eligible to receive drug therapy.

Institutions will register eligible participants with the DF/HCC Clinical Trials Management System (CTMS) OnCore. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

Applicable DF/HCC policy (REGIST-101) must be followed.

6. TREATMENT PLAN

Oral Treatment will be administered on an outpatient basis. Potential risks as well as dose modifications for agent defactinib are described in Section 7 (Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

We will register and enroll participants with confirmed diagnosis of Malignant Pleural Mesothelioma at Brigham and Women's Hospital and DFCI. Please see the detailed eligibility list in Section 4.1. All participants will have specimens and blood work, including a biomarker profile (molecular analysis including the tumor suppressor gene NF2) procured at BWH. Participants presenting from outside facilities without available specimens and biomarkers profile will undergo a pretreatment biopsy and blood analysis.

Defactinib will be administered at 400 mg twice daily for 12 +/- 2 days through the Day 12 morning dose in cohort 1, for 35 +/- 2 days through the Day 35 morning dose in cohort 2, for 21 +/- 2 days through the Day 21 morning dose in cohort 3 and at 100 mg (new formulation) twice daily for 21 +/- 2 days through the Day 21 morning dose in cohort 4 for a total of ~43 participants. Each participant will undergo both a pre and post treatment biopsy. The pretreatment biopsy will be collected prior to the first dose of defactinib and the post treatment biopsy will be collected within 2-4 hours post the last dose of study drug on Day 12 (+/- 2 days) in cohort 1, Day 35 (+/- 2 days) in cohort 2 and Day 21 (+/- 2 days) in cohort 3 and 4. Neoadjuvant treatment will be monitored with blood analysis at baseline, Day 12 (+/- 2 days), Day 35 (+/- 2 days) in cohort 2, Day 21 (+/- 2 days) in cohort 3 and 4, and the end of study visit (4 weeks post-treatment in cohort 1 or 1 week post-treatment in cohort 2, 3 and 4). For subjects with ongoing laboratory adverse events **related** to defactinib, weekly laboratory assessments are required through resolution (including: CBC, CMP, and PT/INR).

The follow up and biopsies will be performed at BWH site using PET/CT guidance either at AMIGO or another radiology site.

On Day 11 (+/- 2 days) of the study, serial plasma samples will be collected (via IV catheter if possible) for defactinib pharmacokinetic analysis and to evaluate the presence of its potential metabolites. Additional samples will be collected on Day 35 and Day 42 in cohort 2 and on Day 21 and 28 in cohort 3 and 4 subjects. Note: Initiation of PK sampling must occur the preceding Day 12 (cohort 1), Day 35 (cohort 2), or Day 21 (cohort 3 and 4) biopsy collection. Blood samples should be collected according to the time points listed below by the BWH Clinical Trials Center staff:

Table 1. Pharmacokinetic Sampling Time points

Sample	Study Day	PK Sampling Time Points
1	11	Pre-dose (within 30 minutes of dosing with defactinib)
2	11	15 min (± 5 min) after dosing with defactinib
3	11	30 min (± 5 min) after dosing with defactinib

Sample	Study Day	PK Sampling Time Points
4	11	1 hour (± 10 min) after dosing with defactinib
5	11	2 hours (± 10 min) after dosing with defactinib
6	11	4 hours (± 10 min) after dosing with defactinib
7	11	8 hours (± 1 hour) after dosing with defactinib
8	12	24 hours (± 2 hours) after dosing with defactinib prior to any Day 12 defactinib administration
9	12	2-4 hours (± 10 min) after dosing with defactinib within 30 min (± 10 min) of biopsy (cohort 1 only)
10*	35	24 hours (± 3 hours) after Day 34 morning defactinib dose, prior to any Day 35 defactinib administration
11*	35	2-4 hours (± 10 min) after dosing with defactinib within 30 min (± 10 min) of biopsy
12	42	End of Study visit
10**	21	24 hours (± 3 hours) after Day 20 morning defactinib dose, prior to any Day 21 defactinib administration
11**	21	2-4 hours (± 10 min) after dosing with defactinib within 30 min (± 10 min) of biopsy
12**	28	End of Study visit

*cohort 2 subjects only
**cohort 3 and 4 subjects only

On Day 12, Day 35, or Day 21 (+/- 2 days), cohort 1, 2 or 3 and 4 respectively, post treatment core biopsies for specimens and biomarkers will be performed. This will be performed under PET/CT in the BWH's AMIGO suite or another radiology suite. The PET CT will allow (a) guidance into metabolically active tumor; (b) assessment of the overall response based on overall appearance of the PET and (c) assessment of the tumor volume to be compared to pre-treatment CT for evaluation for response to therapy. The biopsy should be obtained within 2-4 hours post the last dose of study drug. Study drug can be held and administered at the clinical site to ensure biopsy is obtained with the preferred window. The trial and data collection ends 30 days post treatment (Cohort 1) or 7 days post treatment, (Cohorts 2, 3 or 4). Treatment related adverse events and serious adverse events will be followed until resolution as defined in Section 2 and Section 12.4.1.

PRP biomarkers will be investigated at baseline prior to the first dose of defactinib and within 2-4 hours post last dose on Day 12 (cohort 1), on Day 35 (cohort 2), or on Day 21 (cohort 3). Additional plasma biomarker samples will be collected on Day 12 and 42 for cohort 2 and Day 12 and 28 for cohort 3 and 4. Peripheral blood biomarkers from whole blood will be investigated for cohort 3 and 4 patients only at baseline prior to the first dose of Defactinib and within 2-4 hours post last dose on Day 21.

An overall treatment period is approximately 4 to 6 weeks: in the absence of treatment delays.

- The treatment cycle will be 12, 21 or 35 +/- 2 days when defactinib is administered P.O. 400 mg BID or 100 mg BID.
- Image directed core biopsy will be performed within 2-4 hours post the last dose of defactinib on Day 12, 35 or 21 (+/- 2 days), cohort 1, 2, 3 and 4 respectively.
- Definitive Surgery if appropriate will occur 30 (cohort 1) or > 7 (cohort 2, 3 and 4) days after the last defactinib dose and not within this trial.

Participants will be considered to have completed the trial 30 (cohort 1) or 7 (cohort 2, 3 and 4) days post the last dose of study drug.

Current adjuvant treatment for Malignant Pleural Mesothelioma includes chemotherapy and radiation therapy and will be discussed with the participant's Oncologist.

Table 2. Treatment Description

Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
defactinib	Fasting	400 mg	PO	BID	12 +/- 2 days (cohort 1)
defactinib	Fasting	400 mg	PO	BID	35 +/- 2 days (cohort 2)
defactinib	Immediately after meals with a full glass of water	400 mg	PO	BID	21 +/- 2 days (cohort 3)
defactinib*	Fasting	100 mg	PO	BID	21 +/- 2 days (cohort 4)

*New formulation

6.1 Pre-treatment Criteria

Screening evaluations are to be completed prior to the start of protocol therapy (see Section 10 Study Calendar for a complete list of evaluations).

- Tissue biopsies
- Medical History
- Physical Examination
- Complete blood count: WBC of > 4 K/uL, hemoglobin > 8 mg/dl and platelet count of > 80 K/mm3, PT and INR
- Serum chemistry (including: Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium). Serum Creatinine level less than 2, SGOT (AST) of < 80 IU/L and total bilirubin of < 1.9 mg/dL
- Blood for biomarker studies, including flow cytometry analysis and determination of phosphoFAK.

- Chest PET/CT scan, chest MRI, pulmonary function tests, and echocardiogram (ejection fraction >30% for P/DC).
- Normal contralateral pulmonary function with a chest radiograph that fails to show acute infiltrates and a minimum postoperative predicted FEV1 of 0.8L or % predicted FEV-1 of greater than 35%.
- Negative pregnancy test (in women of childbearing potential) by serum.

6.2 Administration of Defactinib

6.2.1 Defactinib Dosing Information

Defactinib will be administered at 400mg twice daily for 12 +/- 2 days in cohort 1, for 35 +/- 2 days in cohort 2 or for 21 +/- 2 days in cohort 3. Defactinib (new formulation) will be administered at 100 mg twice daily for 21 +/- 2 days in cohort 4 for a total of ~43 participants in all cohorts. The day 12 for cohort 1 subjects, day 35 for cohort 2 subjects or day 21 for cohort 3 and 4 subjects (+/- 2) morning dose will be the final dose respectively. The drug will be supplied for oral dosing as either 200 mg tablets for cohorts 1, 2 and 3 or 100 mg tablets for cohort 4.

6.2.2 Defactinib Dosing Instructions for Study Participants

The following instructions should be reviewed with the participant and a written copy of the instructions provided to the participant:

- Take defactinib tablets by mouth twice each day with the second dose about 12 hours after the first dose. For cohort 1, 2 and 4 subjects, take the tablets with a full glass of water (approximately 8 ounces) either one hour before or two hours after a meal. For cohort 3 subjects, take the tablets with a full glass of water (approximately 8 ounces) immediately after a meal. Swallow the tablets whole.

- In the event of emesis occurring after trial medication ingestion, the participant should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Participants should record the time of the emesis in their dosing diary.

- Each day record date and time the tablets were taken on the drug diary. If a dose is missed, include the reason the dose was not taken.

- Return the drug diary to your study doctor at each visit.

- Return opened and unopened bottles in which the tablets were dispensed.

- Adherence with the study treatment regimen must be assessed at each visit by checking the returned drug supply and reviewing the drug diary.

6.2.3 Compliance

Participant compliance will be assessed by pill counts performed at the end of the cycle as well as by review of the participant's drug diary.

6.2.4 Missed or Vomited Doses

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. In the event that a patient fails to take the trial medication within 6 hours of the designated dosing time, that dose should be omitted. The patient should record any missed doses and resume dosing at next scheduled time with prescribed dose.

In the event of emesis occurring after trial medication ingestion, the patient should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patients should record the time of the emesis. Under no circumstance should a patient repeat a dose or the dosing schedule.

6.2.5 Overdose and Medication Error Instructions

For this study, overdose is defined as a daily dose of defactinib, higher than the prescribed daily dose. In the event of an overdose or medication error, the Sponsor should be contacted immediately to discuss the details and formulate a clinical management plan. Documentation must be included in the dosing log.

No information regarding overdose of defactinib in humans is available. No specific antidotes exist for the treatment of defactinib overdose.

In the event of an overdose, the subject should be immediately admitted and monitored for possible signs of toxicity. As there is no specific antidote for overdose of defactinib, general supportive care should be provided. An overdose will only be considered SAEs criteria as defined in Section 12.1.4.

6.3 Surgery

Definitive Surgery will occur after 30 days (cohort 1) or >7 days (cohort 2, 3 and 4) from the last defactinib dose. If surgery is elected it will not be part of this study. Definitive Surgery includes but is not limited to extrapleural pneumonectomy or pleurectomy/decortication, with or without adjuvant therapy.

To alleviate the concern of potential delay in surgery due to this trial we examined the timeline of surgery in our center. During the past 3 years, 194 patients underwent surgery for resection of mesothelioma at BWH. Of these 27 had positive lymph nodes and 22 received neoadjuvant therapy prior to resection. In the ones immediately resected, the wait between staging and surgery was mean 36 days and median 28 days. The

argument that from day one of trial till day 42 after trial will substantially delay patient care is not very persuasive given these data thus.

6.3.1 Follow-Up

The study will include a follow-up period of 30 (cohort 1) or 7 days (cohort 2, 3 and 4) post final drug administration. Cohort 1 participants will be evaluated weekly during the follow-up period. Assessments will include adverse event and collection of concomitant medications. For subjects with ongoing laboratory adverse events related to defactinib, weekly laboratory assessments are required (CBC including platelet count and differential, PT and INR, and a serum chemistry (including: Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium). Cohort 1 subjects will complete an end of study visit 30 days post-treatment and cohort 2, 3 and 4 subjects will complete the visit 7 days post-treatment. Assessments will include a physical exam, ECOG status, laboratory assessments, adverse events and collection of concomitant medications. In addition, an ECG (in triplicate) and two plasma samples (PK and Biomarkers) will be collected in cohorts 2, 3 and 4 along with whole blood collection for flow cytometry in cohort 3 and 4 subjects only.

6.4 General Concomitant Medication and Supportive Care Guidelines

Concomitant use of any other anti-cancer treatment is not allowed during the study to avoid confounding the assessment of trial medication.

6.5 Duration of Therapy

The duration of drug therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, oral treatment may continue for 12 (cohort 1), 35 (cohort 2), or 21 (cohort 3 and 4) +/- 2 days unless one of the following occurs prior to completion of planned therapy:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator

6.6 Duration of Follow Up

Participants will be followed for 30 (cohort 1) or 7 +2 (cohort 2, 3 and 4) days after the last dose of the drug.

Participants removed from study for unacceptable adverse events will be followed until resolution, stabilization, or for 30 days (whichever is least) of the adverse event.

6.7 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 6.5 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator Dr. Raphael Bueno.

7. TOXICITY MANAGEMENT AND DOSING DELAYS/DOSE MODIFICATIONS

Toxicity assessments will be done using the CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).
In the setting of any toxicities of grade 2 or less, drug is continued at the current dose and schedule, and symptom management is provided as applicable.

For toxicities > grade 2, other than hyperbilirubinemia (see Section 7.1), that are not adequately managed by supported therapy, drug is discontinued and the subject will be removed from the study and replaced. The patients will be followed to the end of the trial but will not restart the drug.

All adverse events experienced by participants will be collected from the time of the first dose until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

For a list of adverse events and potential risks associated with VS-6063, please refer to the Investigator's Brochure.

7.1 Other Potential Risks

Increased Bilirubin

Overall, 15 subjects (32.6%) reported hyperbilirubinemia. In all these cases, aspartate aminotransferase and alanine aminotransferase were within normal limits. This unconjugated hyperbilirubinemia was generally asymptomatic and reversible with dosing holiday or continued treatment.

If the increase in bilirubin is grade ≤ 3 and is not associated with an increase in AST or ALT, continue treatment. Cohort 2, 3 and 4 subjects with elevated bilirubin will be re-tested weekly until resolution or return to baseline. If the bilirubin increases to ≥ grade 2 and is associated with a ≥ grade 2 increase in AST and/or ALT, permanently discontinue study drug.

Blood Pressure

Minor, generally asymptomatic increases in blood pressure were observed in a single agent Phase I study of defactinib. Subjects experiencing recurrent, persistent, or symptomatic increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits, should be initiated on antihypertensive therapy according to institutional policies. Study drug does not need to be interrupted if hypertension can be controlled.

For subjects with persistent systolic BP >= 160 mm Hg or diastolic BP >= 100 mm Hg despite optimal antihypertensive therapy, study drug should be discontinued and the patient removed from the study.

Genitorurinary

Based on extrapolations from nonclinical toxicities, potential manifestations in humans may also include impaired fertility.

Appropriate monitoring in humans includes serial liver function testing, routine blood biochemical, hematological parameters, urinalyses, vital signs, and ECG.

7.2 Toxicity Management

If a participant experiences toxicities, the Investigator has the option of suspending treatment until resolution. Subjects failing to receive the 12 (cohort 1), 35 (cohort 2), or 21 (cohort 3 and 4) days +/-2 days of defactinib will be replaced. Subjects may be replaced at the Investigators discretion following discussions with the Sponsor.

7.3 Supportive Care

Supportive care (e.g., analgesics, antiemetics, antidiarrheal agents, antidepressants) may be administered prophylactically after the first dose or therapeutically at the Investigator's discretion.

8. DRUG FORMULATION AND ADMINISTRATION

8.1 Agent Defactinib (VS-6303)

Treatment Description					
Agent	**Pre-medications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Defactinib (VS-6063)	Fasting	400 mg	PO	BID	12 +/- 2 days (cohort 1)
Defactinib (VS-6063)	Fasting	400 mg	PO	BID	35 +/- 2 days (cohort 2)

Defactinib (VS-6063)	Immediately after meals with a full glass of water	400 mg	PO	BID	21 +/- 2 days (cohort 3)
Defactinib * (VS-6063)	Fasting	100 mg	PO	BID	21 +/- 2 days (cohort 4)

***New formulation of defactinib**

8.2 Description

Defactinib (in the form of: N-methyl-4-({4-[({3-methyl(methylsulfonyl)aminopyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride) is an orally bioavailable, small-molecule focal adhesion kinase (FAK) inhibitor with potential antiangiogenic and antineoplastic activities. The molecular formula is C20H22ClF3N8O3S with a Molecular Weight of 545.97 Daltons.

Defactinib is rapidly absorbed under fasted conditions (at doses ranging from 12.5 mg to 750 mg). Maximum serum defactinib concentrations are achieved within 1 to 2 hours post dose. Peak and total exposure (Cmax and AUC) increased with increasing dose from 12.5 mg to 425 mg BID; however, doses above 425 mg BID did not result in significant increases in exposure. Hepatic metabolism is expected to be the major pathway of elimination with a half life of approximately 9hrs following a single oral dose in man.

8.3 Form

Defactinib will be supplied as 200 mg immediate release tablets for oral dosing (cohort 1, 2 and 3). Tablets will be oval with a white to off-white appearance. Defactinib (new formulation) will be supplied as 100 mg tablets for oral dosing (cohort 4). Tablets will be oval with a white to off-white appearance and VS1 embossed on one side.
The study drug will be packaged in bottles labeled with pill strength and other information as per local regulatory requirements.

8.4 Storage and Stability

The drug product has been demonstrated to be stable when stored in the defined container closure (HDPE bottles). The labeled storage condition for the drug product is “Store between 15 and 25°C (59 and 77°F)”. Bottles labeled with pill strength and other information as per local regulatory requirements.

8.5 Compatibility

N/A

8.6 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of defactinib per internal standard operating procedure.

8.7 Availability

Defactinib is an investigational agent and will be supplied free-of-charge from Verastem.

8.8 Administration

Defactinib is to be taken twice daily orally continuously for 12 +/- 2 days in cohort 1, for 35 +/- 2 days in cohort 2 or for 21+/- 2 days in cohort 3 and 4. The final dose will be administered the morning of the scheduled biopsy on Day 12 (+/- 2) in cohort 1, Day 35 (+/- 2) in cohort 2 or Day 21 +/- 2 days in cohort 3 and 4. See Section 6.2 for additional information.

The patient will get a bottle of pills. Each bottle will contain tablets of a single formulation. The tablets will be repackaged to the patient as a 14-day supply for cohort 1 subjects, a 35 day supply for cohort 2 subjects or a 21 day supply for cohort 3 and 4 subjects. Study drug is stored at room temperature.

8.9 Ordering

Defactinib will be supplied by Verastem or its designee.
The agent may be requested by contacting Verastem directly at:

Drug Orders
Verastem, Inc.
117 Kendrick St, Suite 500, Needham, MA 02494
[redacted]

8.10 Accountability

The Investigator or an approved representative (e.g. Pharmacist) will ensure that defactinib is stored in a secured area under recommended storage conditions and in accordance with applicable regulatory requirements. The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product. Verastem may supply drug accountability forms that must be used or may approve use of standard institutional forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities.

The individual who dispensed the drug must sign the forms, and copies will be provided to Verastem. At the end of the trial, Verastem will provide instructions as to disposition of any unused investigational product. If Verastem authorizes destruction at the trial site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Verastem. Destruction must be adequately documented.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocol Development for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

8.11 Destruction and Return

At the end of the study, unused supplies of defactinib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

9. BIOMARKER STUDIES

9.1 Biomarker and Pharmacodynamic Sampling

Tumor biopsy samples for pharmacodynamic biomarker analysis will be taken at baseline (prior to the first dose of defactinib, and at the end of the 12, 35-day, or 21 defactinib treatment course in cohort 1, cohort 2, or cohort 3 and 4 respectively). At least 4 core needle biopsies will be obtained and each collection will include two Fine Needle Aspirates, one tumor Core Needle Biopsy to be fresh frozen, one tumor Core Needle Biopsy to be FFPE processed. Fine Needle Aspirates will be collected for tumor immune cell measurements by flow cytometry. Core Needle Biopsies are to be collected from the same needle site following the Fine Needle Aspirate. Additional core needle biopsies will be collected and kept frozen and/or FFPE in Dr. Bueno's lab for experiments.

In the event that the tumor biopsy cannot be collected on Day 12 (cohort 1), 35 (cohort 2), or 21 (cohort 3 and 4), subjects should continue dosing with defactinib until the 2nd biopsy is collected (a +/- 2 day visit window is allowed for this visit). On the last day of the defactinib run-in, the morning dose of defactinib should be administered in-clinic, up to 4 hours before the 2nd tumor biopsy is collected.

Blood samples will be collected for Biomarker analysis and PK. Separate blood tubes will be collected for Platelet Rich Plasma (PRP) and plasma at baseline prior to the first dose of defactinib and within 2-4 hours post the last dose on Day 12 (cohort 1), Day 35 (cohort 2) or Day 21 (cohort 3 and 4 for plasma only). In cohort 2, additional plasma biomarker samples will be collected pre-dose on Day 12 and at the end of study on Day 42 and on Day 12 and at the end of study on Day 28 for cohort 3 and 4.

In cohort 3 and 4 only, flow cytometry biomarkers will be investigated from whole blood collected at baseline prior to the first dose of defactinib and within 2-4 hours post the last dose on Day 21 and at end of study.

Comprehensive information on tissue processing, handling, storage and sample shipments for PK, Biomarker and core biopsies can be found in the Laboratory Manuals.

9.2 Biomarker and Pharmacodynamic Endpoints

Pharmacodynamic and predictive response biomarkers intended to demonstrate inhibition of the molecular target and determination of the mechanism of action will be assessed in in the tumor biopsies whole blood, plasma, and PRP. Key markers may include phospho-FAK, as well as specific markers for immunomodulation, cell cycle inhibition, apoptosis and cancer stem cells. Key immune cell markers will include but are not limited to CD8, CD4, ICOS, PDL1, PDL2, PD1, CD25, FOXP3, and marker panels for MDSCs. Immune marker comparisons between tumor and blood will be evaluated. Cancer stem cell biomarkers such as ALDH1, CD44, CD133, SOX2, and Integrins may be investigated.

Blood-based Biomarkers of response will be evaluated including chemokines, cytokines, growth and differentiation factors. Additional biomarkers may be identified and measured as appropriate.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1-week prior to start of protocol therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within $\pm$ 2 days of the protocol-specified date, unless otherwise noted.

Table 3: Schedule of Assessments Cohort 1

	Pre-study	Day 1 (-2d)	Day 8	Day 11 (+/- 2)	Day 12 (+/- 2)	Follow-up Week 1[g]	Follow-up Week 2[g]	Follow-up Week 3[g]	Follow-up Week 4[h]
Study Agent		----------BID throughout ---------							
Biopsy /PRP Biomarker Collection	X[d]				X[d]				
Informed Consent	X								
History	X								
Concurrent Medications [a]	X	X	X	X	X	X	X	X	X
Physical Exam/Vital Signs (Ht, Wt, BSA)	X				X				X
Performance Status	X				X				X
Pulmonary Function test	X								
CBC w/ diff, plts	X	X			X				X
PT/INR	X	X			X				X
Serum chemistry [b]	X	X			X				X
PK Assessments				X[f]	X[f]				
ECG	X				X				
Adverse Event Evaluation[c]		X	X	X	X	X	X	X	X
Tumor Measurement [e]	X				X				
Radiologic Evaluation[e]	X				X[e]				
Pregnancy test	X								
Off-study									X[i]

a: Concurrent medications will be self-reported by participant throughout duration of study
b: Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
c: Adverse event evaluation will be recorded as they are encountered by clinician or self-reported by participant.
d: Biopsy and PRP biomarker samples obtained prior to the initiation of oral therapy and within 2-4 hours of the last dose of defactinib.
e: Evaluations should occur within 8 weeks of Day 1 and after completion of the 12 day (+/- 2 days) oral therapy treatment.

f: Refer to protocol Section 6 for serial PK sampling table.
g: Weekly laboratory assessments (CBC, Chemistry, PT/INR) required for ongoing toxicities related to defactinib
h. All week 4 follow-up assessments completed 30 days after the last dose of study drug.
i: Off study after all week 4 follow-up assessments completed.

Table 4: Schedule of Assessments Cohort 2

	Pre-study	Day 1 (-2d)	Day 8	Day 11 (+/- 2)	Day 12 (+/- 2)	Day 35 (+/- 2)	End of Study[h]
Study Agent		----------BID throughout ---------					
Biopsy / PRP Collection	X[f]					X[f]	
Plasma Collection	X[f]				X[g]		X[g]
Informed Consent	X						
History	X						
Concurrent Medications [a]	X	X	X	X	X	X	X
Physical Exam/Vital Signs (Ht, Wt, BSA)	X				X	X	X
Performance Status	X				X	X	X
Pulmonary Function test/ECHO[b]	X						
CBC w/ diff, plts	X	X			X	X	X
PT/INR	X	X			X	X	X
Serum chemistry [c]	X	X			X[h]	X	X
PK Assessments				X[i]	X[i]	X[i]	X[i]
ECG	X				X	X	X
Adverse Event Evaluation[d]		X	X	X	X	X	X
Tumor Measurement [e]	X					X	
Radiologic Evaluation[e]	X					X[e]	
Pregnancy test	X						
Off-study							X[j]

a: Concurrent medications will be self-reported by participant throughout duration of study.
b: Evaluations should occur within 45 days of Day 1 and must be repeated within 1 week of Day 1 if results were abnormal and clinically significant or for any new clinically significant abnormalities per Investigator assessment.
c. Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
d: Adverse event evaluation will be recorded as they are encountered by clinician or self-reported by participant.
e: Evaluations should occur within 8 weeks of Day 1and after completion of the Day 35 (+/- 2 day) oral therapy treatment.
f: Biopsy, PRP biomarker samples obtained prior to the initiation of oral therapy and within 2-4 hours of the morning Day 35 dose.
g. Plasma biomarker samples obtained prior to initiation of oral therapy, prior to the morning dose of defactinib on Day 12 and the End of Study Visit (Day 42).
h. Weekly retesting of Bilirubin, ALT, and AST is required for subjects with increased bilirubin (Grade 1-2 per CTCAE V4.0) on Day 12. Local laboratory testing is permitted.
i: Refer to protocol section 6 for serial PK sampling table.
j. End of Study assessments completed 7 days after the last dose of study drug.

Table 5: Schedule of Assessments Cohort 3 and 4

	Pre-study	Day 1 (-3d)	Day 8	Day 11 (+/- 2)	Day 12 (+/- 2)	Day 21 (+/- 2)	End of Study[j]
Study Agent Cohort 3		Orally, immediately after a meal BID throughout ---------					
Study Agent Cohort 4		----------BID THROUGHOUT----------					
Tumor Fine Needle Aspirate and Core Needle Biopsy[k]	X					X	
Platelet Rich Plasma Collection (Cohort 3 only)	X[f]					X[f]	
Plasma Collection	X[g]				X[g]		X[g]
Whole Blood Collection[l]	X[f]					X[f]	X
Informed Consent	X						
History	X						
Concurrent Medications [a]	X	X	X	X	X	X	X
Physical Exam/Vital Signs (Ht, Wt, BSA)	X				X	X	X
Performance Status	X				X	X	X
Pulmonary Function test/ECHO[b]	X						
CBC w/ diff, plts	X	X			X	X	X
PT/INR	X	X			X	X	X
Serum chemistry [c]	X	X			X[h]	X	X
PK Assessments				X[i]	X[i]	X[i]	X[i]
ECG	X				X	X	X
Adverse Event Evaluation[d]		X	X	X	X	X	X
Tumor Measurement [e]	X					X	
Radiologic Evaluation, PET-CT & MRI [e]	X					X[e]	
Serum Pregnancy test	X						
Off-study							X[j]

a: Concurrent medications will be self-reported by participant throughout duration of study.
b: Evaluations should occur within 45 days of Day 1 and must be repeated within 1 week of Day 1 if results were abnormal and clinically significant or for any new clinically significant abnormalities per Investigator assessment.
c. Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
d: Adverse event evaluation will be recorded as they are encountered by clinician or self-reported by participant.
e: Evaluations should occur within 45 days of Day 1and after completion of the Day 21 (+/- 2 day) oral therapy treatment.(PET-CT and MRI)
f: Biopsy, PRP and whole blood collection samples obtained prior to the initiation of oral therapy and within 2-4 hours after the last dose (Day 21 ± 2 days) **(PRP collection in Cohort 3 only)**.
g. Plasma biomarker samples obtained prior to initiation of oral therapy, prior to the morning dose of defactinib on Day 12 and the End of Study Visit (Day 28).
h. Weekly retesting of Bilirubin, ALT, and AST is required for subjects with increased bilirubin (Grade 1-2 per CTCAE V4.0) on Day 12. Local laboratory testing is permitted.
i: Refer to protocol section 6 for serial PK sampling table.
j. End of Study assessments completed 7 days after the last dose of study drug.
k. Tumor biopsy by Fine Needle Aspirate and Core Needle Biopsy at Pre-study and **post** the morning dose Day 21.
l. Whole Blood collection for Flow cytometry analysis

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by measuring the Tumor Volume.

11.1 Antitumor Effect– Solid Tumors – Radiology and Biomarkers

For the purposes of this study, participants should be evaluated for response prior to Day 1 oral treatment and again after the end of the oral treatment. Response and progression will be evaluated using the modified RECIST criteria for mesothelioma as established by Byrne and Nowak (Modified RECIST criteria for assessment of response in malignant pleural mesothelioma, Ann Oncol 2004) to evaluate response using the PET CT obtained at approximate day 12 (+/- 2 days) for subjects in cohort 1 and at the end of study treatment for subjects in cohort 2, Day 35 (+/- 2) and for subjects in cohort 3 and 4, Day 21 (+/- 2). For cohort 3 and 4 subjects only, this will also include a MRI.

11.2 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

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

11.3 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter >10 millimeters (mm) using conventional techniques (CT, PET/CT) or >10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Lesions must be accurately measured in 1 dimension with a minimum size of 10 mm by CT (slice thickness no greater than 5 mm), 20 mm by CT scan. Nodes must have a short axis $\geq$ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

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.

11.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 8 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 when both methods have been used to assess the anti-tumor effect of a treatment.

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (L.K. Shankar, J.M. Hoffman, S. Bacharach, M.M. Graham, J. Karp, A.A. Lammertsma, S. Larson, D.A. Mankoff, B.A. Siegel, A. Van den Abbeele, J. Yap, D. Sullivan. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in participants in National Cancer Institute Trials. J Nucl Med, 47(6):901-903, 2006). Participants should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Participants should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult participants. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent participant preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized.

MRI. MRIs should be acquired according to RECIST criteria prior to start of oral treatment and after last day of oral treatment and according to other institutional MRI research procedures/policies.

11.5 Response Criteria

11.5.1 Evaluation of Target Lesions:

This is a brief trial driven by imaging and biomarkers. We will use the modified RECIST criteria for mesothelioma as established by Byrne and Nowak (Modified RECIST criteria for assessment of response in malignant pleural mesothelioma, Ann Oncol 2004 to evaluate response using the PET CT obtained at the end of therapy.

11.5.2 Definitions

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

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

Progressive Disease (PD):
At least a 20% increase in the volume of target lesions, taking as reference the baseline measurements. Or, new measurable lesions are detected.

Stable Disease (SD):
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Unknown (UN):
Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

11.5.3 Evaluation of Biomarkers

The primary objective of this trial is to measure biomarker response to the treatment. We will measure inhibition of phospho-FAK, alterations in markers of tumor immune populations, tumor microenvironment, cell cycle and apoptosis, and additional changes in cancer stem cells in the pre and post treatment specimens. Ultimately, these patients with response based on RECIST criteria, PET and pathological features (degree of tumor necrosis and viable tumor in the post-treatment biopsy) will be compared with non-responders on the basis of profiling as discussed in a previous section to define the best biomarker for response. All samples will be evaluated with genomic analytical platforms such as sequencing and other profiling tools to determine potential predictive biomarkers.

12. ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Definitions

12.1.1 Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (AE) is any unfavorable and unintended sign, symptom or disease temporarily associated with the use of a drug and does not imply any judgment about causality.

12.1.2 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

12.1.3 Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

12.1.4 Serious adverse event (SAE)

An adverse event or suspected adverse event is considered serious if, in the view of the investigator or sponsor, it results in any of the following outcomes::

- Death
- A life-threatening event. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Inpatient hospitalization or prolongation of existing hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect; or
- An important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission

- Respite care

12.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

12.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current Reference Safety Information section in the Investigator's Brochure.

12.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current Reference Safety Information section of the Investigator's Brochure.

12.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned 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 treat.

12.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.
A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

12.3 Reporting Requirements

The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the sponsor.

Each investigative site will be responsible for reporting SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report SAEs to the study sponsor and/or others as described below.

The study sponsor or designee will notify investigators of all suspected, unexpected serious adverse reactions (SUSAR; 7 / 15 Day Safety Reports) that occur during any clinical studies that are using the investigative compound. Each investigator is responsible for reviewing each SUSAR and is responsible for notifying his/her IRB of these external SUSARs.

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must also be reported. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the investigational drug is suspected.

In addition, the following AEs, including serious and non-serious events, meeting the criteria below, will be recorded on the toxicity CRF and are to be reported to the Sponsor and the DFCI IRB per the Adverse Event Reporting Policy:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last dose of study drug.

12.4 Serious Adverse Event Reporting

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 12.1.1 and Section 12.1.2) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

Investigators will submit reports of all SAEs, regardless of attribution, to Verastem's designated Pharmacovigilance representative within 24 hours of learning of the events. For initial SAE reports, investigators should record all case details that can be gathered within 24 hours on the study specific SAE form and faxed or emailed immediately upon completion to Verastem's Drug Safety:

by FAX to PAREXEL Safety: [redacted]
or
by email to [redacted]

The participating investigator must provide follow-up information on the SAE as soon as additional information becomes available and must report the follow up information to Verastem within 24 hours of becoming aware of the follow up. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

12.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events, and non-serious events as outlined in section 12.3, directly to the DFCI Office for Human Research Studies (OHRS).

12.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

12.7 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from the time the subject signs the informed consent, throughout the study, and within 30 days of the last study intervention should be **followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up**. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12.8 Pregnancy

The effects of defactinib on conception, pregnancy, and lactation are unknown. Pregnancies occurring in patients or partners of male patients during the study treatment period are considered immediately reportable events. If a pregnancy occurs in a patient, study treatment must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling and the pregnancy reported to the Sponsor within 24 hours of the investigator's knowledge of the pregnancy.

13. DATA AND SAFETY MONITORING

13.1 Data Reporting

13.1.1 Method

The study staff will collect, manage, and monitor data for this study. Research staff will assist with project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized subject record. Case Report Forms (CRF's) will be developed and updated by the Clinical Trials Research Informatics Office (CTRIO). These data forms will be sent to the Principal Investigator for his review and will be computerized and monitored for completeness and accuracy. Reports are provided as needed to the Study Team.

13.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the Office of Data Quality (ODQ) is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation

Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

13.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

14. REGULATORY CONSIDERATIONS

14.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other

necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

14.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

14.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki.
  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws

- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

  It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

14.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

14.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

15. STATISTICAL CONSIDERATIONS

15.1 Study Design/Endpoints

This is an open label neoadjuvant study in subjects with malignant pleural mesothelioma. Defactinib will be administered at 400 mg twice daily for 12+/- 2 days in cohort 1, for 35+/- 2 days in cohort 2, for 21+/- 2 days in cohort 3, or at 100 mg twice daily (new formulation) for 21+/- 2 days in cohort 4. For each patient, a pre-treatment biopsy will be collected prior to the first dose of defactinib and a post-treatment biopsy will be collected within 2-4 hours post the last dose on Day 12 (+/-2 days) in cohort 1, on Day 35 (+/-2 days) in cohort 2 or on Day 21 (+/-2 days) in cohort 3 and 4.

15.2 Primary Objective

The primary aim is to assess the biomarker responses to a FAK inhibitor in tumor and surrogate tissues obtained from pre and post treatment biopsies, including inhibition of phospho-FAK, alterations in markers of cell cycle, immunomodulation, and apoptosis as well as changes in cancer stem cells.

A useful biomarker must demonstrate very high activity in the molecularly targeted group while providing no information on other patients, thus a biomarker response rate of 10%

may be specified as an upper bound in the non-target group. The power available to detect a difference in biomarker response depends on the total number of pre- and post-treatment biopsy pairs as well as the underlying frequency among untreated specimens. Assuming paired biopsies were obtained from 80% of patients, 83% power is achieved to detect a biomarker response rate of 55% in a molecular subgroup if the biomarker frequency were as high as 50%. In contrast, 81% power is attained to detect a biomarker response rate of 80% in a molecular subgroup if the biomarker frequency were as low as 10%. A one-sided test is used at 0.10 level, as biomarker responses are expected only in molecular subgroups along the targeted pathways of defactinib. Due to longer exposure, cohorts 2 and 3 may show larger differences in biomarker change between pre- and post-treatment biopsies. Thus, the three cohorts will be summarized separately as well as pooled based on the appropriateness of the biomarker data.

Biomarker responses will be analyzed between histologic subtypes and by the extent of disease based on our published criteria. On the other hand, the other analyses will be considered exploratory due to limited power, as epitheliod tumors are the dominant histology and a majority of patients are classified with poor prognosis.

15.3 Sample Size/Accrual Rate

Patients may be replaced if they were terminated from the protocol due to failure to receive at least approximately 80% of the planned treatment within the 12, 21 or 35-day indicated period. The protocol will replace treated patients who do not proceed to the second biopsy post-treatment. In order to account for cases without paired biopsies as well as assay failures, the target accrual is a total of up to 43 patients.

15.4 Analysis of Secondary Endpoints

a. The safety of defactinib will be assessed until 30 (cohort 1) or 7 (cohort 2, 3 and 4) days following the last dose of defactinib or until definitive surgery, whichever occurs first. Adverse events will be graded by the CTCAE 4.0 and summarized according to the worst grade observed since the first treatment dose. The rates of specific toxicities will be reported with 95% exact confidence intervals based on the exact binomial distribution separately by cohort as well as across all treated patients.

b. Plasma concentrations of defactinib will be determined over a 24-hour period on Day 11 for pharmacokinetic analysis. Cohorts 1 and 2 will be pooled for pharmacokinetic analysis. Cohorts 4 pharmacokinetic analysis will be done separately. The additional Day 35 and 42 samples in cohort 2 and the Day 21 and 28 samples in cohort 3 and 4 will be summarized separately. The observed (e.g. peak and trough concentrations) and derived (e.g. AUC, clearance, elimination half-life) parameters will be characterized by average and variation summaries in the patient population. Samples collected may also be tested for potential defactinib metabolites.

c. Tumor response will be assessed by the PET-CT performed in conjunction with the post-treatment core biopsy according to the criteria in Section 11.1. The response rate

will be reported for with 95% exact confidence intervals based on the exact binomial distribution separately by cohort as well as across all treated patients.

15.5 Reporting and Exclusions

15.5.1 Evaluation of toxicity. All participants will be evaluable for toxicity from the time of their first treatment dose.

16. PUBLICATION PLAN

The results should be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of data collection.

17. REFERENCES

Section 3.1:

[1] Peto J, Seidman H, Selikoff IJ. Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. Br J Cancer. 1982 Jan;45(1):124-35.
[2] Castagneto B, Zai S, Mutti L, Lazzaro A, Ridolfi R, Piccolini E, Ardizzoni A, Fumagalli L, Valsuani G, Botta M. Palliative and therapeutic activity of IL-2 immunotherapy in unresectable malignant pleural mesothelioma with pleural effusion: Results of a phase II study on 31 consecutive patients. Lung Cancer. 2001 Feb-Mar;31(2-3):303-10.
[3] Baldini EH, Recht A, Strauss GM, DeCamp MM Jr, Swanson SJ, Liptay MJ, Mentzer SJ, Sugarbaker DJ. Patterns of failure after trimodality therapy for malignant pleural mesothelioma. Ann Thorac Surg. 1997 Feb;63(2):334-8.
[4] Steele JP, Klabatsa A, Fennell DA, Palläska A, Sheaff MT, Evans MT, Shamash J, Rudd RM. Prognostic factors in mesothelioma. Lung Cancer. 2005 Jul;49 Suppl 1:S49-52
[5] Wolf AS, Richards WG, Tilleman TR, Chirieac L, Hurwitz S, Bueno R, Sugarbaker DJ. Characteristics of malignant pleural mesothelioma in women. Ann Thorac Surg. 2010 Sep;90(3):949-56; discussion 956.
[6] Metintas M, Metintas S, Ucgun I, Gibbs AR, Harmanci E, Alatas F, Erginel S, Tel N, Pasaoglu O. Prognostic factors in diffuse malignant pleural mesothelioma: effects of pretreatment clinical and laboratory characteristics. Respir Med. 2001 Oct;95(10):829-35.
and:Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the cancer and leukemia group B. Chest. 1998 Mar;113(3):723-3.
and:Borasio P, Berruti A, Billé A, Lausi P, Levra MG, Giardino R, Ardissone F. Malignant pleural mesothelioma: clinicopathologic and survival characteristics in a consecutive series of 394 patients. Eur J Cardiothorac Surg. 2008 Feb;33(2):307-13.
[7] Merritt N, Blewett CJ, Miller JD, Bennett WF, Young JE, Urschel JD. Survival after conservative (palliative) management of pleural malignant mesothelioma. J Surg Oncol 2001;78:171—4.
[8] Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, Niyikiza C, Paoletti P. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636—44.
[9] Van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase II study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organization for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol 2005;23(28):6881–8.
[10] Sugarbaker DJ, Wolf AS, Chirieac LR, Godleski JJ, Tilleman TR, Jaklitsch MT, Bueno R, Richards WG. Clinical and pathological features of three-year survivors of malignant pleural mesothelioma following extrapleural pneumonectomy. Eur J Cardiothorac Surg. 2011 Aug;40(2):298-303.
[11] Pasello G, Ceresoli GL, Favaretto A. An overview of neoadjuvant chemotherapy in the multimodality treatment of malignant pleural mesothelioma. Cancer Treat Rev. 2012 Mar 27.
[12] Sugarbaker DJ. Macroscopic complete resection: the goal of primary surgery in multimodality therapy for pleural mesothelioma. J Thorac Oncol. 2006 Feb;1(2):175-6.
[13] Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM, Corson

JM, DeCamp Jr MM, Swanson SJ, Bueno R, Lukanich JM, Baldini EH, Mentzer SJ. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1999;117:54—63 [discussion 63—55].
[14] Tilleman TR, Richards WG, Zellos L, Johnson BE, Jaklitsch MT, Mueller J, Yeap BY, Mujoomdar AA, Ducko CT, Bueno R, Sugarbaker DJ. Extrapleural pneumonectomy followed by intracavitary intraoperative hyperthermic cisplatin with pharmacologic cytoprotection for treatment of malignant pleural mesothelioma: a phase II prospective study. J Thorac Cardiovasc Surg. 2009 Aug;138(2):405-11.
[15] Sugarbaker DJ, Wolf AS, Chirieac LR, Godleski JJ, Tilleman TR, Jaklitsch MT, Bueno R, Richards WG. Clinical and pathological features of three-year survivors of malignant pleural mesothelioma following extrapleural pneumonectomy. Eur J Cardiothorac Surg. 2011 Aug;40(2):298-303. Epub 2011 Feb 9.
[16] Richards WG. Recent advances in mesothelioma staging. Semin Thorac Cardiovasc Surg 2009;21:105—10.
[17] Esserman LJ, Berry DA, Cheang MC, Yau C, Perou CM, Carey L, DeMichele A, Gray JW, Conway-Dorsey K, Lenburg ME, Buxton MB, Davis SE, van't Veer LJ, Hudis C, Chin K, Wolf D, Krontiras H, Montgomery L, Tripathy D, Lehman C, Liu MC, Olopade OI, Rugo HS, Carpenter JT, Livasy C, Dressler L, Chhieng D, Singh B, Mies C, Rabban J, Chen YY, Giri D, Au A, Hylton N; I-SPY 1 TRIAL Investigators. Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). Breast Cancer Res Treat. 2012 Apr;132(3):1049-62. Epub 2011 Dec 25.
[18] Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther. 2009 Jul;86(1):97-100. Epub 2009 May 13.

Section 3.2:

[1] National Cancer Institute Website: http://www.cancer.gov/drugdictionary?cdrid=626159
[2] Guan JL, Shalloway D. Regulation of focal adhesion-associated protein tyrosine kinase by both cellular adhesion and oncogenic transformation. Nature. 1992;358:690-692.
[3] André E, Becker-André M. Expression of an N-terminally truncated form of human focal adhesion kinase in brain. Biochem Biophys Res Commun. 1993 Jan 15;190(1):140-7.
[4] Zachary I. Focal adhesion kinase. Int J Biochem Cell Biol. 1997;29:929-934.
[5] Kefalas P, Brown TR, Brickell PM. Signaling by the p60c-src family of protein-tyrosine kinases. Int J Biochem Cell Biol. 1995 Jun;27(6):551-63.
[6] Cary LA, Guan JL. Focal adhesion kinase in integrin-mediated signaling. Front Biosci. 1999;Jan 15;4:D102-13.
[7] Xing Z, Chen HC, Nowlen JK, et al. Direct interaction of v-Src with the focal adhesion kinase mediated by the Src SH2 domain. Mol Biol Cell. 1994;5:413-421.
[8] BD Biosciences; Non-Receptor PTK Sampler Kit 611664 Catalog: http://www.ebiotrade.com/buyf/productsf/BD%20Pharmingen/611664.pdf
[9] Chatzizacharias NA, Giaginis C, Zizi-Serbetzoglou D, Kouraklis GP, Karatzas G, Theocharis SE. Evaluation of the clinical significance of focal adhesion kinase and SRC expression in human pancreatic ductal adenocarcinoma. Pancreas. 2010 Aug;39(6):930-6.

[10] Schlaepfer DD, Hauck CR, Stieg DJ. Signaling through focal adhesion kinase. Prog Biophys Mol Biol. 1999;71:435-478.
AndMitra SK, Schlaepfer DD. Integrin-regulated FAK-Src signaling in normal and cancer cells. Curr Opin Cell Biol. 2006 Oct;18(5):516-23. Epub 2006 Aug 17. Review.
[11] Kong X, Li G, Yuan Y, He Y, Wu X, Zhang W, Wu Z, Chen T, Wu W, Lobie PE, Zhu T. MicroRNA-7 inhibits epithelial-to-mesenchymal transition and metastasis of breast cancer cells via targeting FAK expression. PLoS One. 2012;7(8):e41523.
[12] Chan KT, Cortesio CL, Huttenlocher A. FAK alters invadopodia and focal adhesion composition and dynamics to regulate breast cancer invasion. J Cell Biol. 2009 Apr 20;185(2):357-70. Epub 2009 Apr 13.
[13] Van Marck VL, Bracke ME. Epithelial-Mesenchymal Transitions in Human Cancer. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience; 2000.
[14] Mjaatvedt CH, Markwald RR. Induction of an epithelial-mesenchymal transition by an in vivo adheron-like complex. Dev Biol. 1989 Nov;136(1):118-28. Erratum in: Dev Biol 1990 Jan;137(1):217.
[15] Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, Brooks M, Reinhard F, Zhang CC, Shipitsin M, Campbell LL, Polyak K, Brisken C, Yang J, Weinberg RA. The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell. 2008 May 16;133(4):704-15.
[16]Kong D, Li Y, Wang Z, Sarkar FH. Cancer Stem Cells and Epithelial-to-Mesenchymal Transition (EMT)-Phenotypic Cells: Are They Cousins or Twins? Cancers (Basel). 2011 Feb 21;3(1):716-729.
[17] Sirvent A, Benistant C, Roche S. Oncogenic signaling by tyrosine kinases of the SRC family in advanced colorectal cancer. Am J Cancer Res. 2012;2(4):357-71. Epub 2012 Jun 28.
[18] Auersperg N, Wong AST, Choi K-C. et al. Ovarian surface epithelium: biology, endocrinology, and pathology. Endocr Rev. 2001;22:255–288.
[19] Kouso H, Yano T, Maruyama R, Shikada Y, Okamoto T, Haro A, Kakeji Y, Maehara Y. Differences in the expression of epithelial-mesenchymal transition related molecules between primary tumors and pulmonary metastatic tumors in colorectal cancer. Surg Today. 2012 Oct 7. [Epub ahead of print]
[20] Leong AS-Y, Stevens MW, Mukherjee TM. Malignant mesothelioma: cytologic diagnosis with histologic, immunohistochemical, and ultrastructural correlation. Semin Diagn Pathol. 1992;9:141–150.
[21] Kouso H, Yano T, Maruyama R, Shikada Y, Okamoto T, Haro A, Kakeji Y, Maehara Y. Differences in the expression of epithelial-mesenchymal transition related molecules between primary tumors and pulmonary metastatic tumors in colorectal cancer. Surg Today. 2012 Oct 7. [Epub ahead of print]
[22] Fassina A, Cappellesso R, Guzzardo V, Dalla Via L, Piccolo S, Ventura L, Fassan M. Epithelial-mesenchymal transition in malignant mesothelioma. Mod Pathol. 2012 Jan;25(1):86-99. doi: 10.1038/modpathol.2011.144. Epub 2011 Oct 7.
[23] Sarkar, F.H.; Li, Y.; Wang, Z.; Kong, D. Pancreatic cancer stem cells and EMT in drug resistance and metastasis. Minerva Chir 2009, 64, 489-500.
[24] Harald J. Maier HJ, Wirth T , Beug H . Epithelial-Mesenchymal Transition in Pancreatic Carcinoma. Cancers 2010, 2, 2058-2083; doi:10.3390/cancers2042058
[25] Cheng GZ, Chan J, Wang Q, Zhang W, Sun CD, Wang LH. Twist transcriptionally up-regulates AKT2 in breast cancer cells leading to increased migration, invasion, and resistance

to paclitaxel. Cancer Res 2007;67:1979–87.
[26] Shah, A.N.; Summy, J.M.; Zhang, J.; Park, S.I.; Parikh, N.U.; Gallick, G.E. Development and characterization of gemcitabine-resistant pancreatic tumor cells. Ann. Surg. Oncol. 2007, 14, 3629-3637.
[27] Arumugam, T.; Ramachandran, V.; Fournier, K.F.; Wang, H.; Marquis, L.; Abbruzzese, J.L.; Gallick, G.E.; Logsdon, C.D.; McConkey, D.J.; Choi, W. Epithelial to mesenchymal transition contributes to drug resistance in pancreatic cancer. Cancer Res. 2009, 69, 5820-5828.
[28] Mujoomdar AA, Tilleman TR, Richards WG, Bueno R, Sugarbaker DJ. Prevalence of in vitro chemotherapeutic drug resistance in primary malignant pleural mesothelioma: Result in a cohort of 203 resection specimens. J Thorac Cardiovasc Surg. 2010 May 29.
[29] Hartman ML, Esposito JM, Yeap BY, Sugarbaker DJ. Combined treatment with cisplatin and sirolimus to enhance cell death in human mesothelioma. J Thorac Cardiovasc Surg. 2010 May;139(5):1233-40. Epub 2009 Oct 22.
[30] Sabbah M, Emami S, Redeuilh G, Julien S, Prévost G, Zimber A, Ouelaa R, Bracke M, De Wever O, Gespach C. Molecular signature and therapeutic perspective of the epithelial-to-mesenchymal transitions in epithelial cancers. Drug Resist Updat. 2008 Aug-Oct;11(4-5):123-51. Epub 2008 Aug 20. Review.
[31] McLean GW, Carragher NO, Avizienyte E, Evans J, Brunton VG, Frame MC. The role of focal-adhesion kinase in cancer - a new therapeutic opportunity. Nat Rev Cancer. 2005 Jul;5(7):505-15. Review.
[32] Poulikakos PI, Xiao GH, Gallagher R, Jablonski S, Jhanwar SC, Testa JR. Re expression of the tumor suppressor NF2/merlin inhibits invasiveness in mesothelioma cells and negatively regulates FAK. Oncogene. 2006 Sep 28;25(44):5960-8.
[33] Wang K, Bodempudi V, Liu Z, Borrego-Diaz E, Yamoutpoor F, Meyer A, Woo RA, Pan W, Dudek AZ, Olyaee MS, Esfandyari T, Farassati F. Inhibition of mesothelin as a novel strategy for targeting cancer cells. PLoS One. 2012;7(4):e33214. Epub 2012 Apr 2.
[34] Rivera Z, Ferrone S, Wang X, Jube S, Yang H, Pass HI, Kanodia S, Gaudino G, Carbone M. CSPG4 as a Target of Antibody-Based Immunotherapy for Malignant Mesothelioma. Clin Cancer Res. 2012 Oct 1;18(19):5352-63.

Section 3.3:

[1] Siu L, Burris H, Mileshkin L, et al. A phase 1 clinical, pharmacokinetic (PK) and pharmacodynamic (PD) evaluation of PF-00562271 targeting focal adhesion kinase (FAK) in patients with advanced solid tumors, *J Clin Oncol* 26: 2008 (May 20 supplement); abstract 3534.
[2] Suzanne Field Jones. Phase I study of PF-04554878, a second-generation focal adhesion kinase (FAK) inhibitor, in patients with advanced solid tumors.2011 ASCO Annual Meeting Abstract No: 3002.
[3] Bueno R. Making the case for molecular staging of malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg. 2009 Summer;21(2):188-93. Review.
[4] Mujoomdar AA, Tilleman TR, Richards WG, Bueno R, Sugarbaker DJ. Prevalence of in vitro chemotherapeutic drug resistance in primary malignant pleural mesothelioma: result in a cohort of 203 resection specimens. J Thorac Cardiovasc Surg. 2010 Aug;140(2):352-5.
[5] D.J. Sugarbaker, R.M. Flores, M.T. Jaklitsch et al. Resection margins, extrapleural nodal

status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: Results in 183 patients. J Thorac Cardiovasc Surg, 117 (1999), pp. 54–63 , discussion, 63-65
[6] D.J. Sugarbaker, M.J. Liptay Therapeutic approaches in malignant mesothelioma. J. Aisner, R. Arriagada, M.R. Green (Eds.) et al., Comprehensive Textbook of Thoracic Oncology, Williams and Wilkins, Baltimore, MD (1996), pp. 786–798
[7] Wolf AS, Richards WG, Tilleman TR, Chirieac L, Hurwitz S, Bueno R, Sugarbaker DJ. Characteristics of malignant pleural mesothelioma in women. Ann Thorac Surg. 2010 Sep;90(3):949-56; discussion 956.
[8] G.J.Gordon,R.V.Jensen,L.L.Hsiao,S.R.Gullans,J.E.Blumenstock,W.G.Richards,M.T. Jaklitsch, D.J. Sugarbaker, R. Bueno, Using gene expression ratios to predict outcome among patients with mesothelioma, J. Natl. Cancer Inst. 95 (2003) 598–605.
[9]. G.J.Gordon,G.N.Rockwell,R.V.Jensen,J.G.Rheinwald,J.N.Glickman,J.P.Aronson, B.J. Pottorf, M.D. Nitz, W.G. Richards, D.J. Sugarbaker, R. Bueno, Identification of novel candidate oncogenes and tumor suppressors in malignant pleural mesothelioma using large-scale transcriptional profiling, Am. J. Pathol. 166 (2005) 1827–1840.
[10]. L. Dong, R.V. Jensen, R.A. De, G.J. Gordon, Y. Xu, D.J. Sugarbaker, R. Bueno, Differentially expressed alternatively spliced genes in malignant pleural mesothelioma identified using massively parallel transcriptome sequencing, BMC Med. Genet. 10 (2009) 149.
[11]. G.J. Gordon, L. Dong, B.Y. Yeap, W.G. Richards, J.N. Glickman, H. Edenfield, M. Mani, R. Colquitt, G. Maulik, O.B. Van, D.J. Sugarbaker, R. Bueno, Four-gene expression ratio test for survival in patients undergoing surgery for mesothelioma, J. Natl. Cancer Inst. 101 (2009) 678–686.
[12] Gordon GJ, Jensen RV, Hsiao LL, et al: Translation of microarray data into clinically relevant cancer diagnostic tests using gene expression ratios in lung cancer and mesothelioma. Cancer Res 62:4963-4967, 2002.
[13] Gordon GJ, Deters LA, Nitz MD, et al: Differential diagnosis of solitary lung nodules with gene expression ratios. J Thorac Cardiovasc Surg 132:621-627, 2006
[14] Gordon GJ, Richards WG, Sugarbaker DJ, et al: A prognostic test for adenocarcinoma of the lung from gene expression profiling data. Cancer Epidemiol Biomarkers Prev 12:905-910, 2003 41.
[15] Ma XJ, Wang Z, Ryan PD, et al: A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. Cancer Cells 5:607-616, 2004 [16] Ankerst DP, Groskopf J, Day JR, et al: Predicting prostate cancer risk through incorporation of prostate cancer gene 3. J Urol 180:1303- 1308, 2008, discussion, 1308 [17] Deras IL, Aubin SM, Blase A, et al: 3: A molecular urine assay for predicting prostate biopsy outcome. J Urol 179:1587-1592, 2008.
[18] Gordon GJ, Rockwell GN, Godfrey PA, et al: Validation of genomics- based prognostic tests in malignant pleural mesothelioma. Clin Cancer Res 11:4406-4414, 2005.
[19] Bueno R, Gordon GJ. Genetics of malignant pleural mesothelioma: molecular markers and biologic targets. Thorac Surg Clin. 2004 Nov;14(4):461-8. Review.
[20] Melaiu O, Cristaudo A, Melissari E, Di Russo M, Bonotti A, Bruno R, Foddis R, Gemignani F, Pellegrini S, Landi S. A review of transcriptome studies combined with data mining reveals novel potential markers of malignant pleural mesothelioma. Mutat Res. 2012 Apr-Jun;750(2):132-40. Epub 2011 Dec 15. Review.

[21] De Rienzo A, Dong L, Yeap BY, Jensen RV, Richards WG, Gordon GJ, Sugarbaker DJ, Bueno R. Fine-needle aspiration biopsies for gene expression ratio-based diagnostic and prognostic tests in malignant pleural mesothelioma. Clin Cancer Res. 2011 Jan 15;17(2):310-6. Epub 2010 Nov 18.
[22] Esserman LJ, Berry DA, Cheang MC, Yau C, Perou CM, Carey L, DeMichele A, Gray JW, Conway-Dorsey K, Lenburg ME, Buxton MB, Davis SE, van't Veer LJ, Hudis C, Chin K, Wolf D, Krontiras H, Montgomery L, Tripathy D, Lehman C, Liu MC, Olopade OI, Rugo HS, Carpenter JT, Livasy C, Dressler L, Chhieng D, Singh B, Mies C, Rabban J, Chen YY, Giri D, Au A, Hylton N; I-SPY 1 TRIAL Investigators. Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). Breast Cancer Res Treat. 2012 Apr;132(3):1049-62. Epub 2011 Dec 25.
[23] Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ.
I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther. 2009 Jul;86(1):97-100. Epub 2009 May 13.

18. APPENDICES

Appendix A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B: Examples 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 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	ritonavir indinavir nelfinavir saquinavir clarithromycin telithromycin chloramphenicol ketoconazole itraconazole nefazodone
Inducers of CYP2C9	**Inducers of CYP3A4**
rifampicin secobarbital	carbamazepine phenytoin oxcarbazepine phenobarbital St. John's wort rifampicin rifabutin efavirenz nevirapine pioglitazone troglitazone glucocorticoids 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.