COLUMBIA UNIVERSITY MEDICAL CENTER

A Phase II Trial of Sitravatinib (MGCD516), a Multi-receptor Tyrosine Kinase Inhibitor, in Advanced Liposarcoma and Other Soft Tissue Sarcomas

Herbert Irving Comprehensive Cancer Center Protocol
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TITLE: A phase II trial of Sitravatinib (MGCD516), a multi-receptor tyrosine kinase inhibitor, in advanced liposarcoma and other soft tissue sarcomas

Coordinating Center:	Columbia University Medical Center
Sponsor-Investigator:	Benjamin Izar, MD 650 W. 168th Street BB17-1706D New York NY 10032 Email address: bi2175@cumc.columbia.edu
Statistician:	Shing M. Lee, PhD 722 West 168th Street 6th Floor, Room 645 New York, NY 10032 Telephone: 212-342-1266 Email address: sml2114@columbia.edu

Funding Source:	Mirati Therapeutics 9393 Towne Center Drive, Suite 200 San Diego, CA 92121 Telephone: 858-332-3410
Study Agent:	MGCD516

Affiliate Institutions:

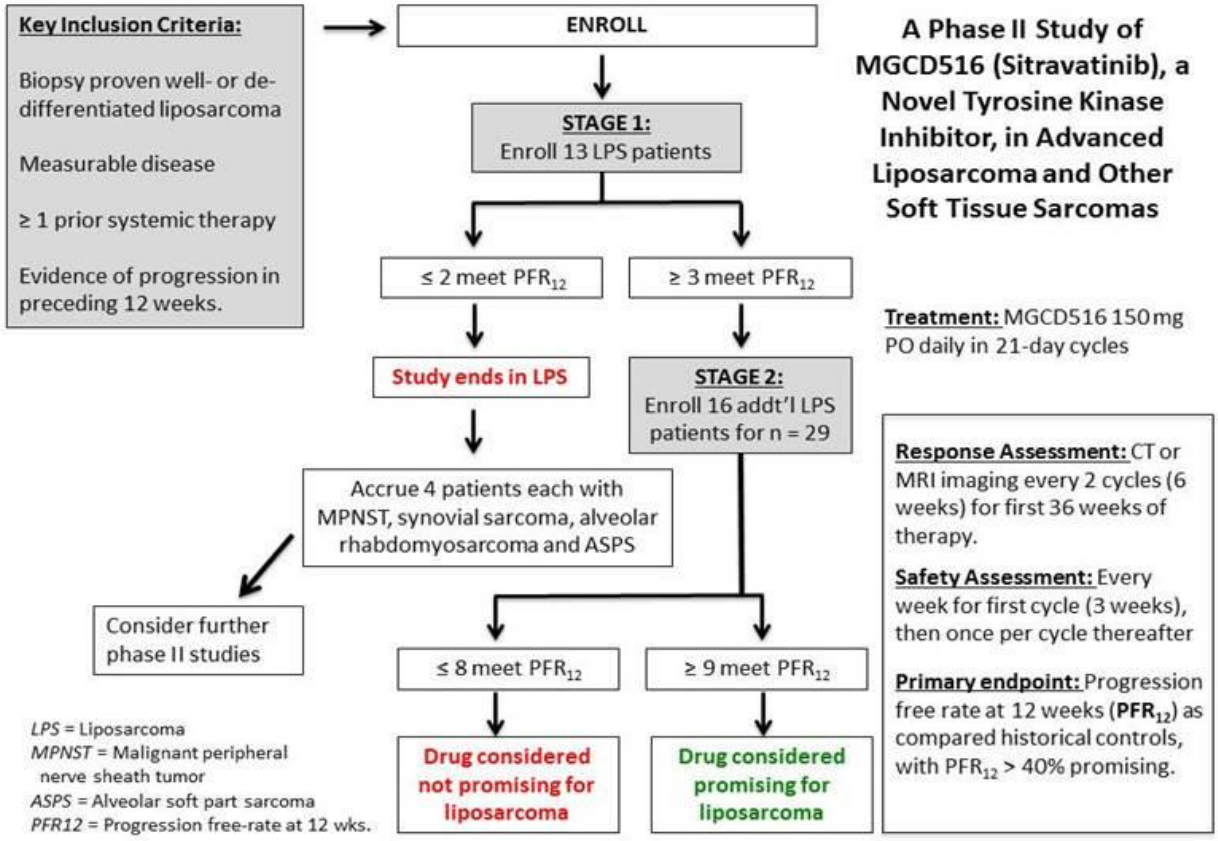
Site Principal Investigator and Contact Information:
Massachusetts General Hospital **Principal Investigator:** Edwin Choy, MD, PhD Hematology/Oncology 55 Fruit Street Boston MA, 02114-2696 **Phone 1:** 617-724-4000 **Fax:** 617-643-1915 Email address: echoy@partners.org
Washington University in St. Louis **Principal Investigator:** Brian Van Tine, MD, PhD Medical Oncology, Barnes and Jewish Hospital 660 S. Euclid Ave. St. Louis, MO 63110 **Phone 1:** 314-747-3096 Email address: bvantine@wustl.edu

Protocol Synopsis

Title	A phase II trial of MGCD516, a multi-receptor tyrosine kinase inhibitor, in advanced liposarcoma and other soft tissue sarcomas
Short Title	MGCD516 in advanced liposarcoma and other soft tissue sarcomas
Protocol Number	AAAQ8661
Phase	Phase II
Methodology	Open-label, single-arm, Simon 2-stage
Study Duration	60 months (estimated)
Study Center(s)	Multi-center, 3 sites.
Objectives	This study will assess the efficacy of the oral, small molecule, multi-receptor tyrosine kinase (RTK) inhibitor MGCD516 in patients with unresectable or metastatic well-differentiated and de-differentiated liposarcoma by evaluating the progression free rate at 12 weeks as compared historical controls. Secondary objectives include assessment of overall response rate, overall survival, progression free survival and safety parameters. One correlative objective will measure changes in total and phospho-protein expression of MGCD516 RTK targets between baseline and on-treatment tumor biopsies using reverse phase protein array technology in a subset of liposarcoma patients. Another correlative objective will use next generation sequencing to assess liposarcoma pre-treatment tumor specimens for genetic changes in MGCD516 targets and evaluate the effect of such changes on drug efficacy. If the study fails to show evidence of efficacy during stage 1 (liposarcoma patients), a set of other sarcoma subtypes suggested sensitive by preclinical studies will be evaluated for preliminary signs of efficacy.
Number of Subjects	29 patients
Diagnosis and Main Inclusion Criteria	Eligible patients for stage I include those 18 years or older with histologically confirmed, unresectable or metastatic well-differentiated or de-differentiated liposarcoma with measurable disease by RECIST criteria who have received one prior line of systemic therapy and have demonstrated evidence of disease progression prior to enrollment. If the study does not meet its endpoint in the 13 liposarcoma patients during stage I of the Simon 2-stage design, an additional 16 patients will be enrolled, composed of 4 patients each with malignant peripheral nerve sheath tumor, synovial sarcoma, alveolar rhabdomyosarcoma and alveolar soft part sarcoma to evaluate for potential signs of efficacy in those subtypes.
Study Product, Dose, Route, Regimen	MGCD516 120 mg orally daily in continuous 21 day cycles

Duration of administration	Continuous, 21-day cycles
Reference therapy	Not applicable
Statistical Methodology	The primary endpoint is the progression free rate (PFR) at 12 weeks. This corresponds to the number of patients who are alive and without evidence of disease progression at 12 weeks out of all evaluable patients. On the basis of historical controls (see section 15), a PFR greater than 40% at 12 weeks is associated with active second line agents in sarcoma and considered promising, whereas a PFR less than 20% at 12 weeks is associated with inactive agents and considered not promising. We will use a Simon optimal 2-stage design. The study will enroll 13 liposarcoma patients in the first stage. If 3 or more liposarcoma patients meet the endpoint in the first stage, the study will be expanded to a total of 29 liposarcoma patients. If a total of 9 or more liposarcoma patients demonstrate the PFR endpoint, the agent will be considered promising in liposarcoma and worthy of further study. This design provides for a type 1 error of 0.10 and type 2 error of 0.14. The study design has a power of 85% to detect a difference between a PFR of 20% versus 40% at 12 weeks. If the study does not meet its endpoint in liposarcoma patients during stage I, an additional 16 patients will be enrolled, composed of 4 each of MPNST, synovial sarcoma, alveolar rhabdomyosarcoma and alveolar soft part sarcoma as exploratory cohorts to evaluate for potential signs of efficacy in those subtypes to inform further clinical study.

Protocol Schema



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1. INTRODUCTION AND RATIONALE

This document is a protocol for a human research study. This study is to be conducted according to US and International standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Medical Center institutional research policies and procedures.

1.1 Sarcoma and receptor tyrosine kinases.

Sarcomas comprise a heterogeneous group of uncommon solid tumors of mesenchymal origin, of which more than 50 subtypes have been defined. In 2015, approximately 11,930 people will be diagnosed with sarcoma, and 4,870 will die of the malignancy[1]

The most common subtypes of soft tissue sarcoma include gastrointestinal stromal tumor (GIST), liposarcoma, leiomyosarcoma, synovial sarcoma and malignant peripheral nerve sheath tumor (MPNST). The more common bone tumors include osteosarcoma, chondrosarcoma and the Ewing's family of tumors. The primary management for most localized sarcomas is surgical resection when feasible. Unfortunately, therapeutic options for patients with metastatic or unresectable disease remain limited. The various subtypes of sarcoma differ greatly in their clinical and molecular characteristics as well as response to traditional cytotoxic agents and radiotherapy. Outcomes are generally poor in advanced disease, with doxorubicin or the combination of gemcitabine and docetaxel eliciting objective responses in about 25% of patients, with median overall survival from the diagnosis of metastatic disease limited to 12 to 18 months[2]. The recent approval of trabectedin for advanced liposarcoma and leiomyosarcoma[3], and pazopanib for advanced non-adipocytic sarcomas[4], has resulted in modest improvements in progression free survival for these disease subtypes with no demonstrated benefit in overall survival. Molecular characterization of certain subtypes of sarcoma has permitted some progress in targeted systemic therapy, most notably with the discovery of activating KIT mutations in GIST, and amplification of CDK4 and MDM2 in well-differentiated/de-differentiated liposarcomas[5]. However, for the majority of patients with advanced sarcomas, outcomes remain disappointing, and new approaches are urgently needed.

Complex organisms rely on cell-cell communication, largely conveyed by small proteins termed growth factors, to convey critical messages, including those related to growth, division, survival, motility and changes in cell shape. Receptor tyrosine kinases (RTKs) play the critical role in transducing these extracellular signals into the cell where they elicit an array of biologic responses. The prototypical RTK includes an N terminal domain extending into the extracellular space which functions in ligand binding. The middle segment of the RTK protein contains a transmembrane domain composed of hydrophobic amino acids. The C-terminal domain extends into the cytoplasm and contains the RTK's tyrosine kinase activity, which phosphorylates tyrosine residues on various cytoplasmic proteins, resulting in activation of various signaling pathways and downstream processes. Most RTKs function as heterodimers or homodimers, with dimerization often induced by extracellular ligand binding. The cytoplasmic kinase domains then phosphorylate each other resulting in a change in the conformation of the catalytic cleft, allowing substrates to bind.

RTKs may be dysregulated by gene amplification, point mutations, increased transcription or

translation, autocrine growth factor secretion from neoplastic cells and by other means. These dysregulated RTKs have been shown to play an important role in tumor development across nearly all cancer types through their effects on cell growth, differentiation, migration, angiogenesis and apoptosis, among other phenotypes on which cancer cells depend. RTK-targeted therapies, both small molecular inhibitors and antibodies, have proven efficacious in the clinic for numerous cancers, as evidenced by regulatory approval of a growing list of such agents, including imatinib, sorafenib, sunitinib, pazopanib, regorafeninb, trastuzumab, cetuximab, erlotinib and gefitinib, among others. The efficacy of these RTK-based therapies in human cancer have been thoroughly reviewed elsewheref[6]. In some cases, a tyrosine kinase inhibitor has been indicated for use in a disease subset with a defined genetic abnormality in that RTK, such as crizotinib for ALK-translocated non-small cell lung cancer or imatinib in KIT-mutant GIST. In other cases, the agent was studied and approved in a broader disease subpopulation, such as pazopanib for non-adipogenic soft tissue sarcomas, without a predefined genetic alteration, but with upregulation of RTKs and downstream pathways associated with drug target.

There is substantial evidence to implicate numerous RTKs in sarcomagenesis. The most prominent example of aberrant RTK activity in sarcomagenesis is reflected by activating mutations in the KIT gene in GISTs. KIT binds its ligand stem cell factor and exerts important downstream effects on the development of a variety of cell types, including gut motility cells, from which GISTs are thought to arise. Mutations in KIT result in constitutive, ligand independent activation of the RTK and downstream signaling. GISTs are responsive to the KIT inhibitor imatinib. In the initial phase II study of this agent in advanced GIST, 53% of patients demonstrated objective tumor shrinkage[7] and, following the introduction of imatinib, median overall survival in advanced GIST improved from 11 to 57 months[8]. Patients progressing on imatinib benefit when treated with the multi-targeted RTK inhibitor sunitinib, which acts on vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor alpha (PDGFRa), c-KIT and FLT3[9].

The RTKs VEGFR and PDGFR play an important role in angiogenesis, and are often dysregulated by tumors to enhance vascular supply and ameliorate conditions of hypoxia. Moreover, PDGFR plays an important role in normal cells of mesenchymal origin. A number of studies have documented VEGF and VEGFR overexpression in various sarcomas and expression often correlates with clinical outcomes[10]. Bevacizumab, a monoclonal antibody against VEGFR, has received regulatory approval for its activity in various settings, including advanced colon and lung cancers. Solitary fibrous tumor, previously termed hemangiopericytoma, is an uncommon soft tissue sarcoma that characteristically demonstrates prominent ectatic blood vessels and is traditionally resistant to cytotoxic chemotherapy. A phase II study of the combination of bevacizumab and temozolomide demonstrated favorable results in this sarcoma subtype, with a median progression free survival of 10 months, highly favorable as compared historical controls and chemotherapy[11]. Pazopanib is an orally available small molecule inhibitor of VEGFR and PDGFR among other RTKs. This agent was studied in a phase III trial of patients with various advanced soft tissue sarcomas, excluding adipocytic sarcomas and GIST, demonstrating progression on at least one prior regimen. The drug demonstrated an improvement in progression free survival as compared placebo, leading to its FDA approval[12].

Aside from VEGFR and PDGFR, numerous RTKs have been implicated in tumorigenesis across

the various soft tissue and bone sarcomas, including IGF1-R, MET, Axl, RET and others. The role of RTKs in sarcoma has been reviewed in detail elsewhere[13]. In numerous cases, overexpression of these various RTKs correlates with worsened clinical outcomes. In undifferentiated pleomorphic sarcoma, for example, overexpression of MET has been observed in up to 40% of tumors and dysregulation of the downstream targets MEK and AKT is associated with worse survival[14]. Using expression profiling and tissue microarray validation linked to patient clinical data, expression of RET, IGF-1 and IGF-2 was found to correlate with clinical outcomes in myxoid liposarcoma.[15] Phosphorylated forms of KIT and PDGFRb are overexpressed in synovial sarcoma[16]. The role of IGF-1R in bone tumors, such as osteosarcoma and Ewing sarcoma, has been supported by various in vitro and in vivo models[17]. Axl has recently been shown to be overexpressed in Ewing sarcoma where this RTK plays a role in cell viability and migration[18]. Furthermore, Axl, EphB2, FGFR2 and RET were recently implicated in osteosarcoma pathogenesis in addition to established roles for PDGFR and VEGFR.[19] In clear cell sarcoma, the EWS-ATF1 fusion gene has been shown to activate transcription of MET, and MET inhibition has shown important clinical effects in preclinical models[20].

One recent study attempted to identify a role for driver receptor tyrosine kinases in sarcoma cell lines and xenografts using a novel phosphoproteomics strategy[21]. Phosphotyrosine peptide immunoprecipitation was followed by LC MS/MS to identify phosphorylated tyrosine kinases in a collection of sarcoma cell lines including osteosarcoma (MNNG, U2OS, MG63, Saos2), rhabdomyosarcoma (RD18, A204), leiomyosarcoma (SK-LMS1), fibrosarcoma (HT1080), and Ewing's sarcoma (RD-ES and A673). In this analysis, numerous phosphorylated receptor tyrosine kinases were identified including EGFR, several Eph and FGFR receptors, IGF-1R, KIT, MET and PDGFRa, among others, with expression levels confirmed by Western blot. A panel of existing TKIs was then used against particular cell lines based on the phosphoproteomics results and siRNA techniques were used to demonstrate the driver role for the proposed kinases. Using this approach, PDGFRa was implicated in rhabdomyosarcomas, MET in osteosarcomas, and IGF-1R in Ewing's sarcoma.

Nonetheless, antibodies and small molecule inhibitors of RTKs have not always been successful in clinical trials in sarcoma. In a single center study of 36 patients with advanced soft tissue or bone sarcoma treated with the anti-EGFR monoclonal antibody cetuximab, progression-free survival (PFS) was poor, even in the subgroup of patients demonstrating EGFR overexpression by immunohistochemistry, where 4-month PFS was just 4%[22]. In a multi-arm phase II study cohorted by disease subtype and using a Simon two-stage design, clinical activity of sorafenib was suggested only in angiosarcomas, with minimal evidence of activity in other sarcoma subtypes[23]. The use of anti-IGF-1R agents, including the monoclonal antibodies cixutumumab and R1507, have also demonstrated unimpressive results[24].

Explanations for these modest results likely include the activation of compensatory pathways to overcome inhibition by a narrowly targeted RTK inhibitor and failure to select for a subgroup of tumor types most likely to respond to the targeted agent. This experience suggests that a more broadly targeted agent demonstrating clinically relevant inhibition of a selected group of RTKs strongly implicated in tumorigenesis may be more clinically effective, and also reinforces the need for correlative studies to understand mechanisms of drug action and resistance.

1.2 MGCD516, a novel small molecular RTK inhibitor

MGCD516 is an orally available, potent, small molecule inhibitor of a group of related tyrosine kinases including MET, Axl, VEGFR, PDGFR, KIT, FLT3, Trk, RET, DDR2 and a subset of Eph receptors. These tyrosine kinases are known to play important roles in tumor growth, survival, invasion and angiogenesis. Activation of signaling through some of these RTKs may represent resistance mechanisms following inhibition of others, as has been suggested for MET in the case of VEGFR.

In biochemical kinase assays, MGCD516 was shown to potently inhibit the catalytic activity of these RTKs, with IC_{50} values between 0.5 and 76 nanomolar. Activity was confirmed in RTK-dependent cell-based assays with IC_{50} ranging from less than 10 to 181 nanomolar. MGCD516 also demonstrated clinical activity against several clinically relevant MET mutants. The drug did not show significant inhibitory activity of intracellular tyrosine kinases or serine threonine kinases.

The anti-tumor efficacy of MGCD516 was studied in 17 human tumor xenograft models in human cancer types with dysregulation of receptor tyrosine kinases. The drug showed tumor growth regression or inhibition as compared vehicle control in all of these models evaluated at doses ranging from 1.25 to 20 mg/kg/day, with all dose levels well tolerated. Drug efficacy ranged from partial growth inhibition to robust cytoreduction. At the 20 mg/kg/day dose, near complete tumor growth inhibition was seen in several models, several of which had underlying genetic alterations in at least one of the drug's targets. Anti-tumor efficacy and frank regression were also observed at lower dose levels.

1.3 Preclinical rationale for MGCD516 in sarcoma

The efficacy of MGCD516 in sarcoma has been thoroughly evaluated in the preclinical setting in the laboratory of Dr. Gary Schwartz[25]. These preclinical studies first aimed to identify RTKs highly expressed in common sarcoma subtypes, followed by an evaluation of MGCD516 both in vitro and in vivo. In an initial analysis, basal expression of a set of receptor tyrosine kinases was assessed by Western immunoblotting in a subset of sarcoma cell lines. These sarcoma cell lines included osteosarcoma (Saos2), Ewing sarcoma (A673, CHP100), dedifferentiated liposarcoma (DDLS, LS141), malignant peripheral nerve sheath tumor (MPNST) and synovial sarcoma (SYO-1).

A range of RTKs were tested for basal expression and included Axl, PDGFR, IGF-1R, FGFR2, KIT, Eph, VEGFR, RET and MET, among others. Basal expression levels are shown in figure 1A across the cell types. Based on basal expression patterns, five cell lines were chosen for further study based on their expression of the most RTKs: A673, DDLS, LS141, MPNST and Saos2. All of these five cell lines showed expression of EphA1, EphB4 and VEGFR1, but expression of the other tested RTKs varied by cell line. For example, DDLS, LS141 and Saos2 appeared to showed relatively high levels of IGF-1R expression, MPNST showed significant levels of PDGFRa. LS141, and to a lesser extent, A673 and MPNST, expressed PDGFRb.

Basal phosphorylation was then studied using a phospho-RTK proteome profiler kit. Results are shown in figure 1B. A673, LS141 and Saos2 showed high levels of phosphorylated IGF1-R.

Two cell lines, DDLS and MPNST, showed high basal phosphorylated MET. DDLS, LS141 and MPNST showed evidence of phosphorylated EGFR.

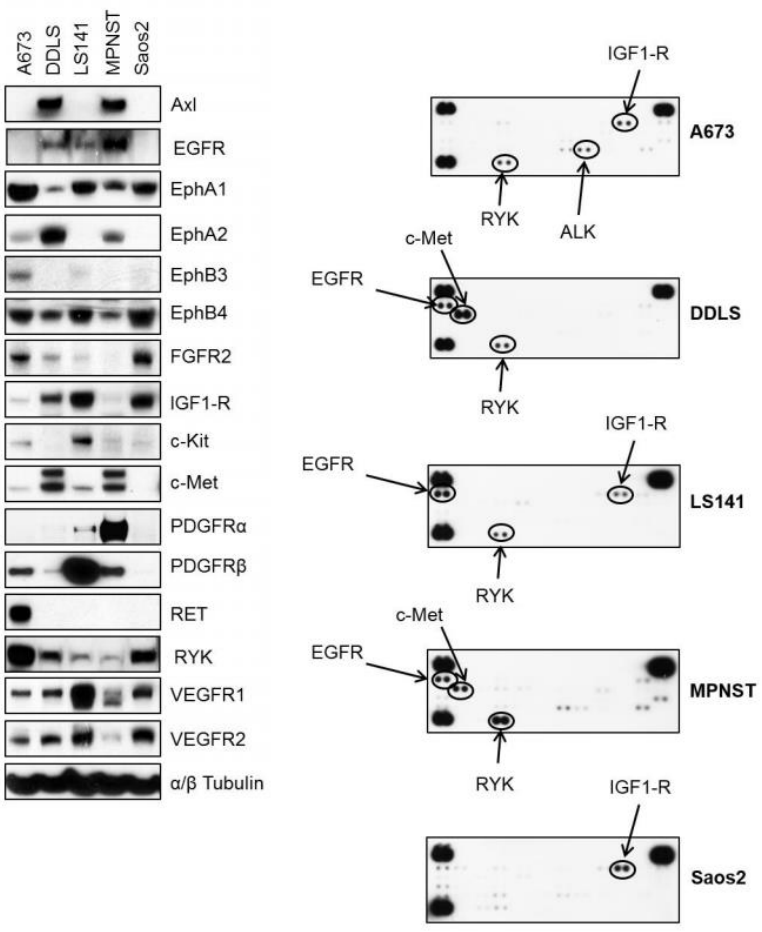


Figure 1 A (left) and B (right)

The antiproliferative activity of MGCD516 was then explored in the five chosen cell lines: A673, DDLS, LS141, MPNST and Saos2. All cell lines were found to be sensitive to the drug in a concentration-dependent manner (figure 2a). IC_{50} values for the three sensitive cell lines (DDLS, MPNST, and LS141) ranged from 250-750 nmol/L, and for the less sensitive cell lines (A673 and Saos2) ranged from 1.5-2.0 micromolar/L.

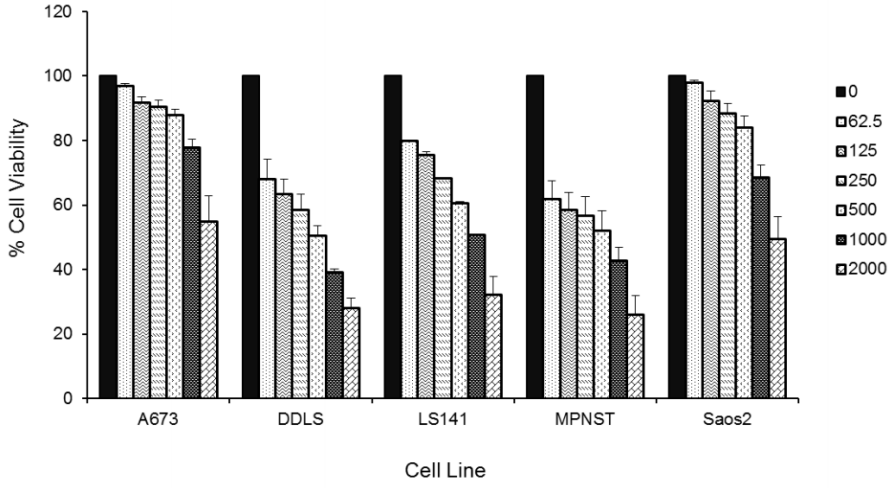


Figure 2A

In order to demonstrate the proposed mechanism, MGCD516 was shown to inhibit phosphorylation of target kinases within these cell lines at low nanomolar concentrations by Western blotting. Complete inhibition of phosphorylation of IGF1-R, PDGFRb and MET was demonstrated, as was downregulation of the downstream pathway member pAKT (figure 2B).

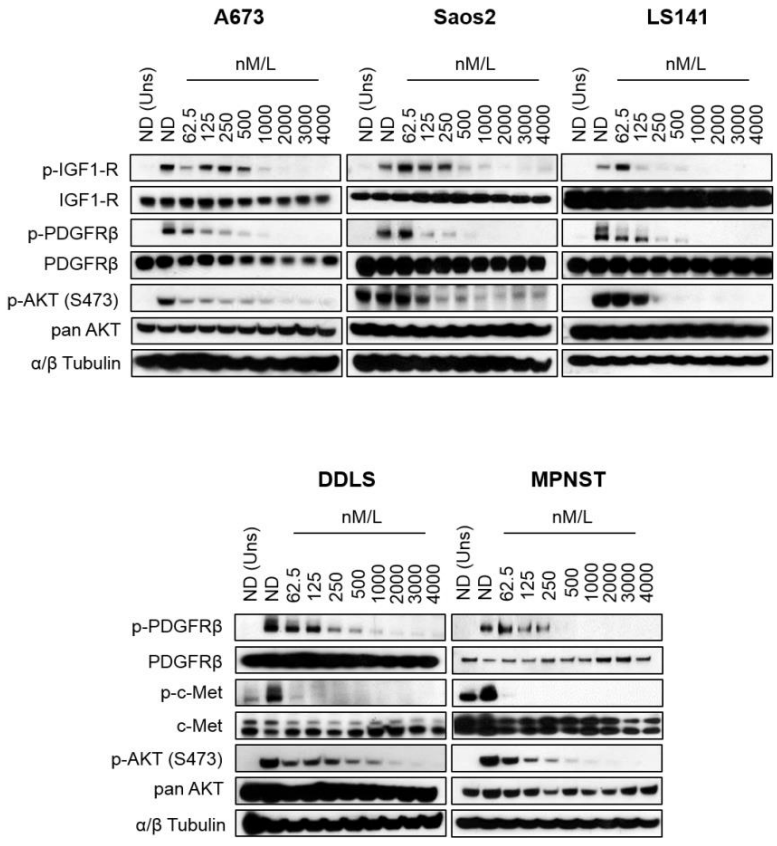


Figure 2B

This inhibition of phosphorylation of target kinases was also confirmed by phospho-RTK proteome profiler analysis (figure 3). Again, MGCD516 demonstrated significant inhibitory effects on multiple RTKs including PDGFRa, PDGFRb, IGF1-R and MET, as shown in figure 3, with effects also noted on Axl and ALK. Interestingly, IGF1-R and ALK were not potently inhibited by MGCD516 in initial RTK enzymatic assays, suggesting that the inhibitor effects for these kinases may be mediated by an alternative mechanism, such as heterodimerization with direct RTK targets of the drug.

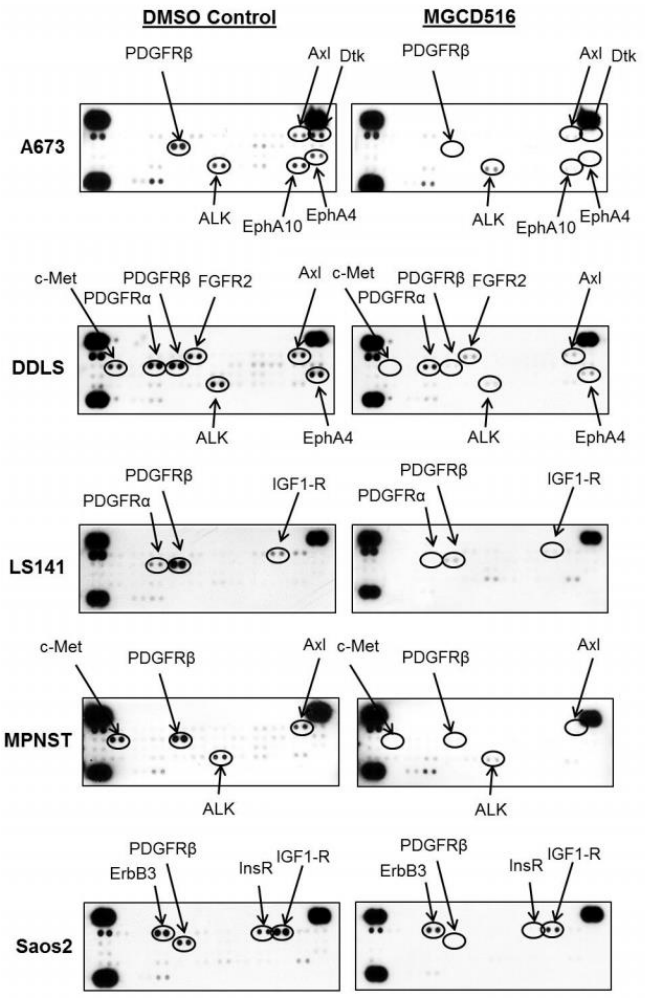


Figure 3

The efficacy of MGCD516 was then compared against imatinib and crizotinib, two other multi-kinase inhibitors with some target RTK overlap with MGCD516 (figure 4). MGCD516 was evaluated as compared these agents in the DDLS, LS141 and MPNST cell lines using 500 nanomolar of each agent. MGCD516 showed enhanced efficacy as compared either agent in all cell lines tested except for MPNST, where the effects of imatinib and MGCD516 appeared similar. Moreover, across all three cell lines, MGCD516 was at least as effective as combination treatment with imatinib and crizotinib. Furthermore, using Western blot, MGCD516 showed better inhibition of downstream targets such as pAKT as compared the other two drugs.

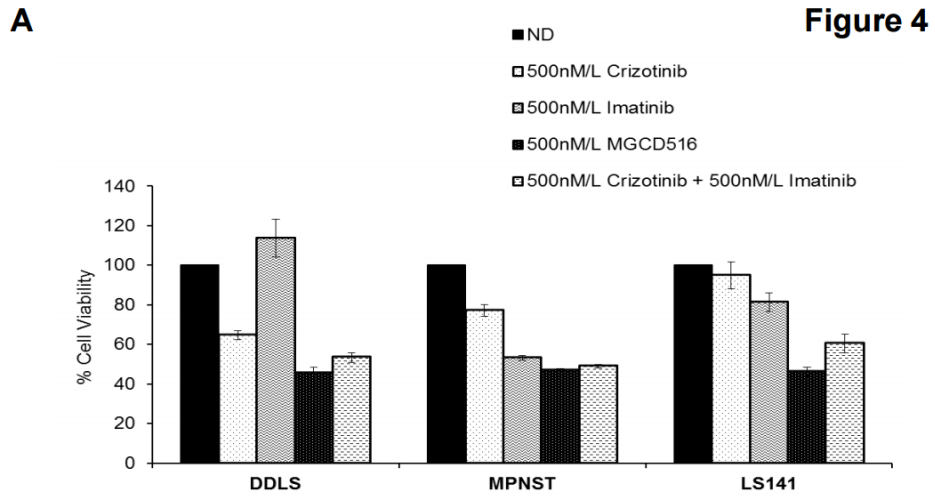


Figure 4

MGCD516 was further compared against pazopanib. Pazopanib is a multi-angiogenesis RTK inhibitor approved for use in non-adipocytic sarcomas on the basis of a multi-center randomized phase III trial which demonstrated improved progression free survival as compared placebo. The drug is also approved in advanced renal cell carcinoma. A cell viability assay was performed in MPNST, LS141 and DDLS cell lines treated with 500 or 1000 nanomolar of either agent. MGCD516 showed enhanced anti-tumor efficacy as compared pazopanib in all cell lines, with the most profound differences seen in the dedifferentiated liposarcoma cell line (figure 5).

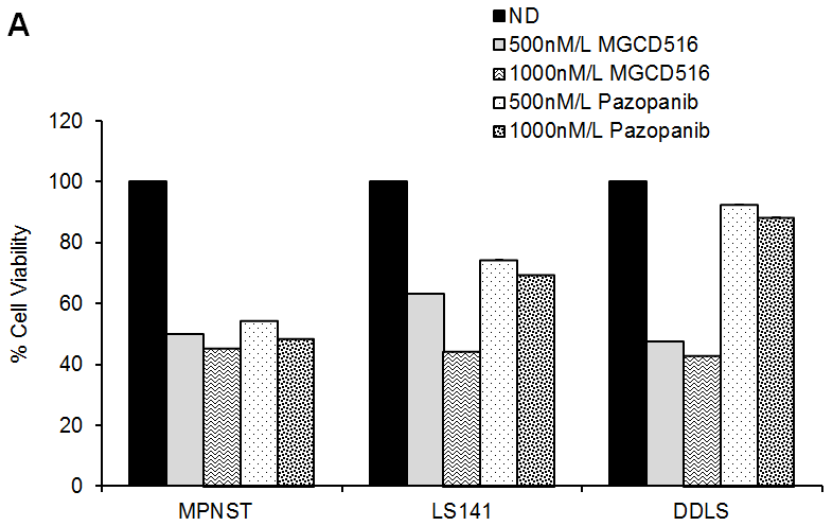


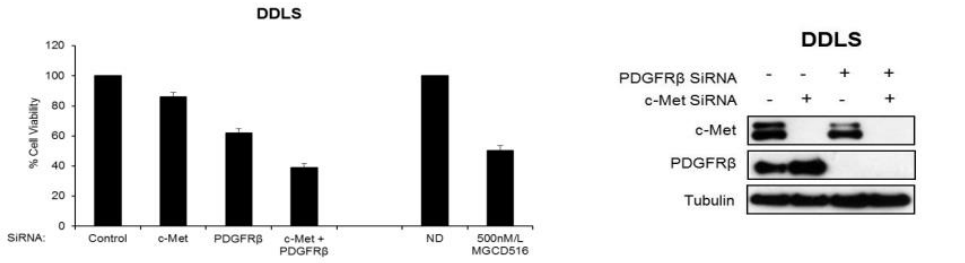
Figure 5

To demonstrate a driver role in tumorigenesis for the proposed kinases, siRNA mediated kinase knockdown was carried out in the various cell lines and compared with the effects of MGCD516 itself (figure 6).

DDLS and MPNST showed higher basal levels of MET and PDGFRb, whereas the LS41 cell line showed higher basal levels of IGFR-1 and PDGFRb. Therefore, siRNA mediated knockdown was performed for MET and PDGFRb in DDLS and MPNST, and for IGF1-R and PGDFRb in LS141, alone or in combination.

Cell viability assays showed that combined knockdown of the driver kinases by siRNA had a significant antiproliferative effect in all three cell lines. This suggests an important pathophysiologic role for these RTKs in tumor proliferation. MGCD516 demonstrated a similar antiproliferative effect as compared siRNA mediated knockdown of these kinases. Interestingly, in MPNST, combined knockdown of MET and PDGFRb resulted in a lesser anti-proliferative effect as compared knockdown of PDGFRb alone, possibly as a result of compensatory activation of alternative pathways.

A **Figure 5**



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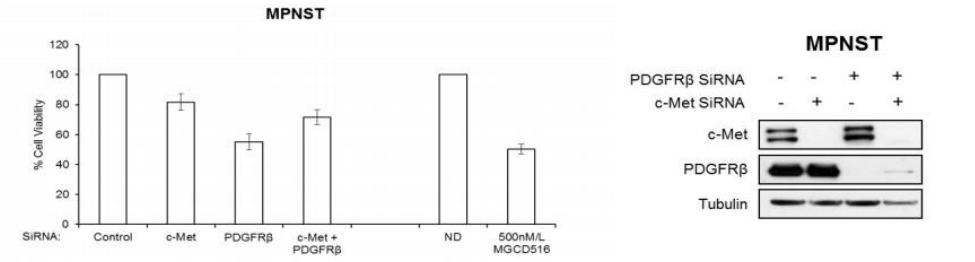

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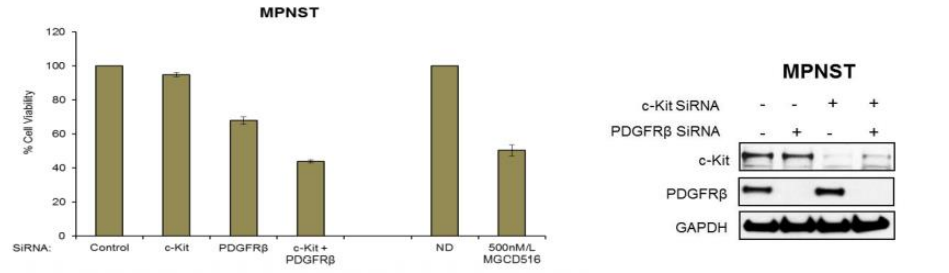

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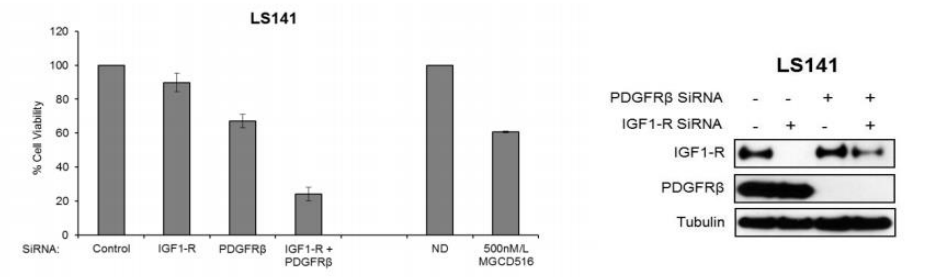


Figure 6

The effect of MGCD516 was studied in mouse xenograft models of MPNST and LS141 and treatment was compared against imatinib and crizotinib. The treatment resulted in no toxicity to the animals as measured by weight loss (figure 7b and 7c). In both xenograft models, treatment with MGCD516 resulted in profound suppression of tumor growth as compared vehicle and also resulted in enhanced anti-proliferative effects as compared imatinib and crizotinib (figure 8a and 8b). Tumor tissue was analyzed by Western immunoblotting after 3 weeks of treatment. This analysis demonstrated greater inhibition of driver kinases by MGCD516 as compared imatinib or crizotinib. Moreover, Ki-67 assessed in tumor biopsies at 3 weeks showed substantially lower Ki-67 in the MGCD516 treated animals as compared the vehicle controls.

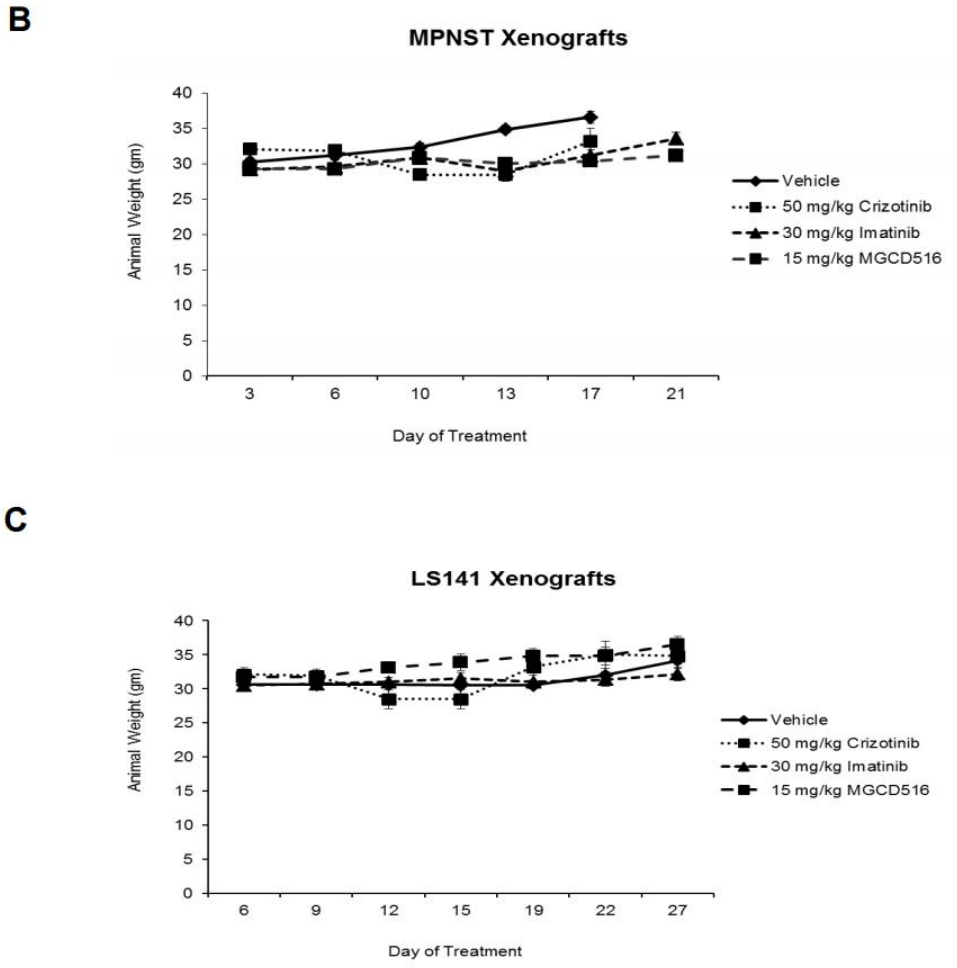


Figure 7

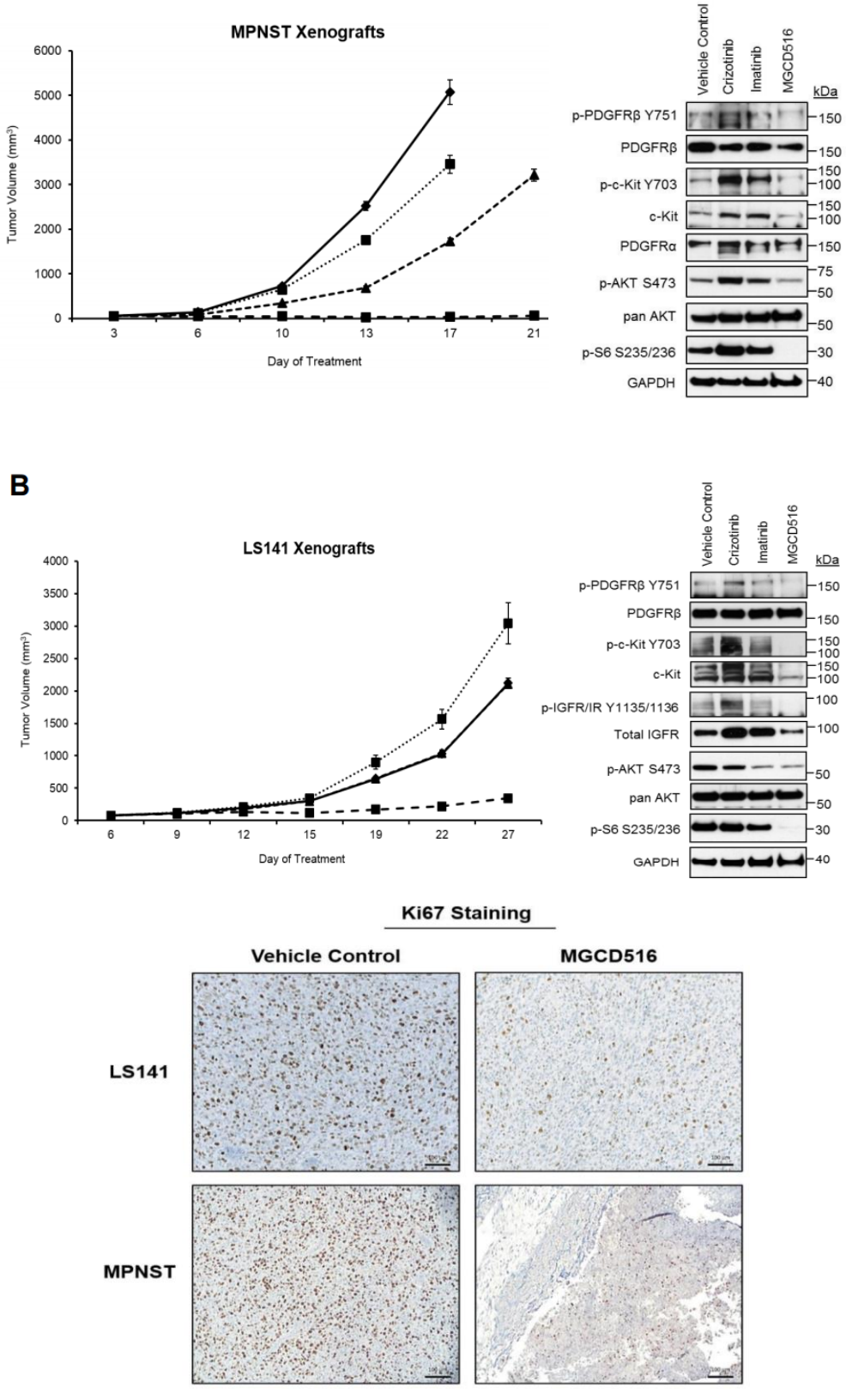

MPNST Xenografts
Tumor Volume (mm³)
Day of Treatment
Vehicle Control
Crizotinib
Imatinib
MGCD516
kDa
p-PDGFRβ Y751
PDGFRβ
p-c-Kit Y703
c-Kit
PDGFRα
p-AKT S473
pan AKT
p-S6 S235/236
GAPDH
B
LS141 Xenografts
Tumor Volume (mm³)
Day of Treatment
p-IGFR/IR Y1135/1136
Total IGFR
Ki67 Staining
Vehicle Control
MGCD516
LS141
MPNST

Figure 8

1.4 Rationale for Selection of Subtypes

Clinical trials in sarcoma must balance the biological heterogeneity of over fifty subtypes with the feasibility of conducting clinical trials in rare diseases and the availability of funding and industry support to conduct such trials. The preclinical data obtained at CUMC and by Mirati Therapeutics support liposarcoma as a sarcoma subtype especially responsive to MGCD516 on the basis of *in vitro* and *in vivo* data. Our preclinical studies established IGF-1R, MET and PDGFR are important for liposarcoma tumorigenesis, and MGCD516 is active against these targets. In addition to the encouraging preclinical data, we have also chosen to focus this study on liposarcoma because:

(1) Liposarcoma is the most common sarcoma subtype. This would facilitate accrual of the study and enhance the clinical utility of the agent if found to be active.

(2) Liposarcoma is in urgent need of active therapies. There are only 2 FDA-approved agents for this disease, the chemotherapeutic agents eribulin and trabectedin, both of which have limited clinical activity and considerable toxicity.

(3) There is currently no approved receptor tyrosine kinase inhibitor for liposarcoma. Pazopanib, a small molecule receptor tyrosine kinase inhibitor, was approved in *non-adipocytic sarcomas* and phase II studies found the drug ineffective in liposarcoma. Our correlative studies may help elucidate the basis for the variable sensitivity of liposarcoma to pazopanib. Our preclinical data, and work by others, suggests that liposarcoma depends upon MET, IGF1-R and PDGFR signaling; notably, pazopanib is inactive against the first two of these RTKs, whereas MGCD516 has considerable activity. The broader profile of MGCD516 targets may also abrogate activation of compensatory signaling pathways, a well characterized mechanism of resistance to RTK inhibitors.

Preclinical studies at CUMC and Mirati have suggested efficacy for MGCD516 in numerous other sarcoma subtypes aside from liposarcoma. In view of this and the limited resources available for clinical trials in sarcoma, we have proposed a Simon 2 stage design in which stage I will accrue liposarcoma patients and will continue to stage 2 and complete accrual in liposarcoma alone if the study meets the stage I endpoint. If, however, the study fails in stage I, we will enroll an additional 16 patients across 4 other sarcoma subtypes found promising on the basis of preclinical data as an exploratory cohort which will be hypothesis generating for future clinical studies, including phase II trials. This design allows for maximal use of resources and only enrolls patients whose disease subtype is suggested sensitive on the basis of the available preclinical data. In view of our preclinical data and the Mirati data, the exploratory subgroup would include MPNST, synovial sarcoma, alveolar rhabdomyosarcoma and alveolar soft part sarcoma.

In the CUMC preclinical studies MPNST was among the most sensitive to MGCD516 in cell line viability assays (figure 2A above) and treatment of an MPNST xenograft with MGCD516 showed complete suppression of tumor growth (figure 8A above) and compared favorably with imatinib and crizotinib, RTK inhibitors of KIT/PDGFR and MET, respectively. Synovial sarcoma cell lines were also responsive to MGCD516 (figure 2A above).

In preclinical studies performed by the Mirati Therapeutics, MGCD516 was evaluated in 3-day cell viability assays across a panel of over 550 cancer cell lines characterized for cancer type and genomic characteristics with the intention of identifying patterns of cell line sensitivity and resistance to treatment and linking these response patterns to tumor cell line phenotypic and genotypic characteristics. This cell line panel also contained 57 cell lines derived from sarcoma and was comprised of over 8 different sarcoma sub-types. Among the sarcoma cell lines the top 4 most sensitive subtypes (lowest IC50 values and greatest degree of lethality) were comprised of liposarcoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, and malignant peripheral nerve sheath tumor derived cell lines. In contrast, leiomyosarcoma, osteosarcoma, and Ewing's sarcoma were among the more resistant subtypes in the Mirati studies. Alveolar rhabdomyosarcoma and alveolar soft part sarcoma are thus included on the basis of the Mirati studies.

1.5 Clinical Experience with MGCD516

MGCD516 is currently being evaluated in the first in human study 516-001, a phase 1 dose escalation study in solid tumors. Data was recently updated at the European Cancer Conference in September 2015. Safety and pharmacokinetic data from this study were favorable and are discussed in section 3. With respect to efficacy, prolonged disease stabilization was observed, with 6 patients completing at least 5 cycles of therapy, including one patient with liposarcoma completing 8 cycles. Pharmacodynamic studies in human plasma confirmed modulation of circulating biomarkers, including VEGFR and sMET. The study will proceed to a phase 1b which will enroll patients with non-small cell lung cancer and other tumors with genetic alterations in RET, TRK, and other MGCD516 targets to further evaluate clinical activity at the recommended phase 2 dose.

2. STUDY OBJECTIVES

This is an open-label, multi-center, single-armphase II study of the oral small molecular multi-receptor tyrosine kinase inhibitor MGCD516 in adult patients with unresectable and metastatic well-differentiated and de-differentiated liposarcoma who have received one prior line of systemic therapy and who demonstrate evidence of disease progression prior to study entry. . The study will use a Simon optimal 2-stage design, but if liposarcoma fails in the first stage, the study will enroll additional patients with other sarcoma subtypes found promising on the basis of preclinical data in an exploratory cohort.

2.1 Primary Objective

To assess the efficacy of MGCD516 in patients with advanced liposarcoma by evaluating the progression free rate at 12 weeks as compared historical controls.

2.2 Secondary Objectives

2.2.1 To further evaluate the safety profile of MGCD516 by assessing adverse event rates (according to National Cancer Institute CTCAE version 4.0 criteria) in

patients treated with this agent.

2.2.2 To assess the efficacy of MGCD516 in patients with advanced liposarcoma by evaluating the overall response rate (according to RECIST 1.1 criteria), progression free survival and overall survival in patients treated with this agent.

2.2.3 If MGCD516 fails to show efficacy in the first stage of the study (liposarcoma patients), to evaluate a cohort of other sarcoma subtypes (malignant peripheral nerve sheath tumor, synovial sarcoma, alveolar rhabdomyosarcoma and alveolar soft part sarcoma), for preliminary signs of efficacy to inform future studies.

2.3 Correlative Science Objectives

2.3.1 To use reverse phase proteomic arrays (RPPA) to evaluate changes in total and phosphorylated MGCD516 target RTK expression in tumor specimens from a subset of liposarcoma patients at baseline and while on treatment with the study agent to confirm evidence of on-target effects and evaluate potential predictive biomarkers.

2.3.2 To use next generation sequencing techniques to evaluate pre-treatment tumor biopsies from liposarcoma patients for a defined set of genetic alterations involving MGCD516 targets, and to assess the relationship between the presence of such genetic alterations and clinical efficacy.

For details on the reporting of the endpoints, see section 15, Statistical Considerations.

3. INVESTIGATIONAL AGENT

MGCD516 is an orally available, potent small molecular inhibitor of several related receptor tyrosine kinases, including VEGFR, PDGFR, MET, KIT, Axl, FLT3, RET, DDR and certain Eph family members. These receptors have been implicated in numerous processes that support a malignant phenotype in human cancer.

3.1 Preclinical Data

MGCD516 has been extensively studied in the preclinical setting. The following information is referenced from the Investigator's Brochure for MGCD516, version 2.0, as provided by Mirati Therapeutics, unless otherwise referenced.

3.1.1 Pharmacokinetics, Absorption, Distribution, Metabolism and Excretion

The pharmacokinetics, distribution and metabolism of MGCD516 were examined in vitro and in mice, rats and dogs in non-good laboratory practice (GLP) pharmacokinetic studies. Plasma pharmacokinetics were determined after single intravenous and oral administration of the agent to mice, rats and dogs across a range of dose levels. After IV administration of MGCD516 at 2.5 mg/kg in mice, 5 mg/kg in rats and 1 mg/kg in dogs, the volume of distribution was 6.28, 0.980 and 11.1 L/kg, respectively. Total clearance values were 1.38, 0.279 and 1.49 L/h/kg. The half-life of elimination was 6.23, 3.50 and 7.11 hours in mice, rats and dogs, respectively. Mean C_{max} and AUC generally increased in a dose-dependent fashion. After oral administration of 2, 5 and 5 mg/kg to mice, rats and dogs, respectively, the drug was systemically absorbed with absolute bioavailability values of 72.2%, 19.6% and 56.4%, respectively.

Repeat dose pharmacokinetics were conducted by oral administration of the agent in rats for 7 days (12.5-75 mg/kg/day) or 4 weeks (2.5-25 mg/kg/day) and in dogs for 7 days (1-8 mg/kg/day) or 4 weeks (0.3-3 mg/kg/day).The T_{max} ranged from 4 to 12 hours in rats and 2 to 6 hours in dogs. Mean $t_{1/2}$ was 3 to 9 hours in rats and 3 to 6 hours in dogs. Increases in C_{max} and AUC_{0-24} were generally dose proportional. There was no evidence of accumulation in any of these studies.

3.1.2 Plasma protein binding

The binding of MGCD516 to human, mouse, rat and dog plasma proteins was assessed using an ultracentrifugation approach with frozen K_3EDTA plasma for all species. The percentage of MGCD516 bound to protein was 99% in mouse plasma, 99.5% in rat plasma, 99.3% in dog plasma and 98.6% in human plasma. Results from the positive control, warfarin, indicated acceptable performance for this assay. The effects of plasma from multiple species on inhibition of MET phosphorylation by MGCD516 in MKN45 (gastric cancer) cells was studied. The presence of 100% plasma increased the concentration of MGCD516 needed to achieve 50% MET inhibition as compared 10% plasma by a factor of 1.4 to 8.8 across species and by 1.45 in humans.

3.1.3 Metabolism

In-vitro metabolic profiling studies were performed in mouse, rat, dog, monkey and human hepatocytes and 8 putative metabolites were identified, with none unique to humans. After 120 minutes of incubation with human hepatocytes, 88% of the drug remained. Phenotyping of the drug in human liver microsomes and recombinant human P450 enzymes suggested that multiple enzymes contributed to the metabolism of MGCD516 including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1 and CYP3A4. In rat and dog studies, no phase II metabolites were detected.

3.1.4 Enzyme Interactions

Primary cultures of cryopreserved human hepatocytes were treated with MGCD516 and expression of cytochrome P450 enzymes was assessed. Treatment of human hepatocytes with up to 30 micromolar MGCD516 resulted in little or no induction of CYP1A2 activity or mRNA levels, or of CYP3A4 activity. MGCD516 at doses of 3 and 10 micromolar did cause concentration dependent increases in CYP2B6 activity, CYP2B6 mRNA levels and CYP3A4 mRNA levels.

There was no substantial evidence of direct inhibition of CYP1A2, CYP2A6 or CYP2E1, and no substantial evidence of time or metabolism dependent inhibition of any of the CYP systems evaluated. The drug did demonstrate evidence of direct inhibition of CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 with IC_{50} values of 2.9, 11, 10, 1.9 and 11 micromolar, respectively. About 50% direct inhibition of CYP2B6 was observed with 20 micromolar MGCD516.

Because the potency of MGCD516 against is receptor tyrosine kinase targets is generally less than 0.1 micromolar, it is unlikely that MGCD516 at therapeutic levels will result in clinically significant inhibition or induction of the cytochromes at dosing that will be clinically used.

3.1.5 Toxicology

Toxicology of MGCD516 was evaluated in 7-day dose range-finding studies and 4-week oral toxicity and toxicokinetic studies (followed by 2 week recovery period) in both rats and dogs.

Studies in rats

In a 7-day repeat dosing study, rats were administered MGCD516 at doses of 0, 12.5, 25, 50 and 75 mg/kg/day by oral gavage (3/sex/group for control, 9/sex/group for treated). One male administered a dose of 75 mg/kg was found dead on day 7 with autopsy evidence of adrenal cortical hemorrhage. Pathologic findings were evaluated at the 12.5 mg/kg and 75 mg/kg dose levels. At the 12.5 mg/kg dose level, findings were of minimal to slight severity and included: adrenal cortex (congestion/hemorrhage), duodenum (villi blunting/fusion), bone marrow (osteodystrophy, congestion/hemorrhage), and thymus (apoptosis/necrosis). These findings were also seen in animals administered 75 mg/kg/day but with increased frequency and severity and further included kidney (tubular necrosis) and pancreas (apoptosis, increased lymphocytes).

For the 4 week toxicity and toxicokinetic study, male and female rats were assigned to four groups (15/sex/group) and doses administered via oral gavage for 29 days followed by a 14 day recovery period. Doses of 2.5, 10 or 25 mg/kg/day in control article or a control article alone were evaluated. Effects were studied on the respiratory and nervous systems. In summary, the dose level of 25 mg/kg/day was not tolerated and resulted in mortality, adverse clinical observations and considerable changes in body weight. The *no observed adverse effect level* was found to be 2.5 mg/kg/day. Two animals given 10 mg/kg/day and 9 animals given 25 mg/kg/day were sacrificed in moribund condition during the dosing phase, with the cause of death assessed as adrenal hemorrhage in at least 8, and septicemia in 1. There were no changes in hematologic, coagulation or chemistry parameters of significance. Autopsy demonstrated findings generally consistent with other studies of anti-angiogenic compounds, and most such findings were reversible. Organs with changes that did not reverse at the recovery sacrifice included changes in the kidney, ovary, testes and epididymis. No effects were seen on the respiratory and nervous systems.

Studies in dogs

In a 7-day dose range-finding study in dogs, MGCD516 was administered at 0, 12.5, 25, 50 or 100 mg/kg/day, but was not tolerated at any dose level. Therefore, a second study was conducted in dogs at doses of 0, 1, 2, 4 and 8 mg/kg/day. The 8 mg/kg/day was not tolerated requiring sacrifice of 3 animals in moribund condition, with weight loss and liquid/mucoid feces observed in a fourth. No adverse microscopic changes were seen at a dose of 4 mg/kg/day, but a decrease in body weight and food consumption was observed at this dose level.

A toxicity and toxicokinetic study was carried out in dogs. Animals received a control article or MGCD516 at doses of 0.3, 1 or 3 mg/kg/day daily for 4 weeks by oral gavage followed by a 2-week recovery phase. All animals survived to scheduled sacrifice. One animal administered 3 mg/kg/day had dosing discontinued on day 8 due to anorexia, dehydration, liquid feces, vomit and marked body weight loss. Other clinical observations were limited to thin appearance and discolored or liquid feces in animals given 3 mg/kg/day. No adverse changes in hematology, chemistry, coagulation or urinalysis were seen. There were no effects on ophthalmic or electrocardiogram studies and there were no adverse macroscopic or microscopic findings. In summary, the 3 mg/kg/day dose was not tolerated and the *no adverse effect level* was felt to be 1 mg/kg/day.

3.1.6 Cardiovascular Effects

Telemetry-instrumented male beagle dogs were administered MGCD516 at doses of 0, 0.5, 1 and 4 mg/kg by oral gavage in a Latin square dosing design. No qualitative ECG abnormalities were observed at any dose level. Significantly higher systolic (up to 12 mmHg), diastolic (up to 14 mmHg) and mean arterial (up to 14 mmHg) pressures were seen with doses above 1 mg/kg which persisted fifteen hours post dose. At the 4 mg/kg dose level, heart rates were significantly lower, which persisted through 25 hours post dosing, likely due to a compensatory mechanism. Although mild prolongation of PR and QT intervals was seen, there was no change in the qTC interval. Although all of these effects were mild, they were attributed to MGCD516 owing to

dose dependency, and, with respect to cardiovascular toxicity, the *no observed-adverse effect level* was determined as 4 mg/kg.

3.1.7 Genotoxicity

MGCD516 was evaluated in a standard array of GLP genotoxicity studies. In a bacterial mutagenicity assay, MGCD516 was found to be non-mutagenic at doses up to 5000 micrograms per plate. The agent was also considered negative for inducing chromosomal aberrations in cultured human hepatocytes. An in vivo rat micronucleus assay was conducted at dose levels of 0, 375, 750 and 1500 mg/kg/day and the agent was negative for inducing micronuclei in the bone marrow of male Sprague-Dawley Rats.

3.1.8 Carcinogenicity

None performed.

3.1.9 Developmental and Reproductive Toxicity

None performed.

3.2 Clinical Data to Date

MGCD516 is being evaluated in a first-in-human study, 516-001, a multi-center, open-label phase 1/1b clinical trial evaluating the safety, metabolism, pharmacokinetics and pharmacodynamics of this agent in patients with advanced solid tumors. The phase 1 portion of this study is a dose escalation study in unselected patients using a modified toxicity probability interval design. Key inclusion criteria include advanced metastatic or unresectable solid tumor malignancies, an ECOG performance status of 0 or 1 and no history of symptomatic or uncontrolled brain metastases. The initial starting dose was MGCD516 at 10 mg once daily, based on one-tenth of the severely toxic dose observed in 10% of animals, derived from the 4 week toxicology study in rats described in section 3.1. Cohorts of 3-5 patients were enrolled per dose level.

As of 11/2015, a total of 32 unselected patients had been accrued to the phase 1 dose escalation phase, including 5 with soft tissue sarcoma. 6 dose cohorts were evaluated ranging from 10 mg to 200 mg orally daily. Dose escalation proceeded through three dose levels (10, 20 and 40 mg) without a dose limiting toxicity. At the 80 mg level, one dose limiting toxicity of grade 3 palmar plantar erythrodysesthesia was noted. Subsequently, 3 additional patients were added with no further DLTs observed. The dose was escalated to 200 mg with no dose limiting toxicities seen at 110 or 150 mg. However, at the 200 mg dose level, 3 DLTs were observed: grade 2 intolerable neuropathy, fatigue and stomatitis, each in 1 of 3 patients treated at this dose level. The patient who experienced neuropathy had been previously treated with the chemotherapy agent docetaxel. A maximum tolerated dose/recommended phase 2 dose of 150 mg orally daily was established.

Single dose pharmacokinetic parameters were evaluated in 24 patients, and steady state parameters in 20 patients. Plasma samples for pharmacokinetic analyses were collected over a 168-hour period following single dose administration and a 24-hour period following repeat dose administration. Drug concentrations were determined using a validated LC MS/MS method. After single administration, the drug reached peak concentration over a median time of 3 to 9 hours. Plasma exposure levels were found to increase in a dose proportional fashion. Mean elimination half-life varied between 40 and 53 hours. Steady state pharmacokinetics were reached in 11-15 days. Drug accumulation was observed following multiple dosing, averaging 4.2-fold for C_{max} and 4.7-fold for AUC_{0-24}. Mean value for peak to trough fluctuation was 53.8%. At the 100 mg dose level, mean steady state C_{avg} was 123 ng/mL, C_{max} was 151 ng/mL and AUC was 2590 ng*h/mL.

On 2/6/2018, Mirati Therapeutics provided updated guidance to investigators participating on the industry sponsored phase 1/1b study of Sitravatinib in solid tumors. In this study, Sitravatinib appeared to have improved long-term tolerability at a dose of 120 mg based on assessment of toxicities observed in patients starting at this dose, and in patients dose reduced from 150 to 120 mg. Furthermore, analysis of pharmacokinetic data suggest plasma concentrations for Sitravatinib are comparable at the 120 and 150 mg dose levels. Therefore, the recommended starting dose of Sitravatinib for the phase 1/1b study was modified to 120 mg, which has also been adopted in this study effective in 5/2018. Patients already enrolled on this study may continue at the 150 mg dose level, or reduce the 120 mg level, as determined by the treating investigator.

4. STUDY DESIGN

4.1 General Design

This is a phase II, single-arm, open-label, Simon optimal 2-stage study evaluating the efficacy of MGCD516 in patients with unresectable or metastatic well-differentiated or de-differentiated liposarcoma who have received treatment with at least one prior systemic therapy and demonstrate evidence of disease progression prior to study enrollment. If the study fails to reach its endpoint in the stage I liposarcoma cohort, it will enroll additional patients with other sarcoma subtypes which may be responsive on the basis of preclinical data as an exploratory cohort which may inform future clinical studies.

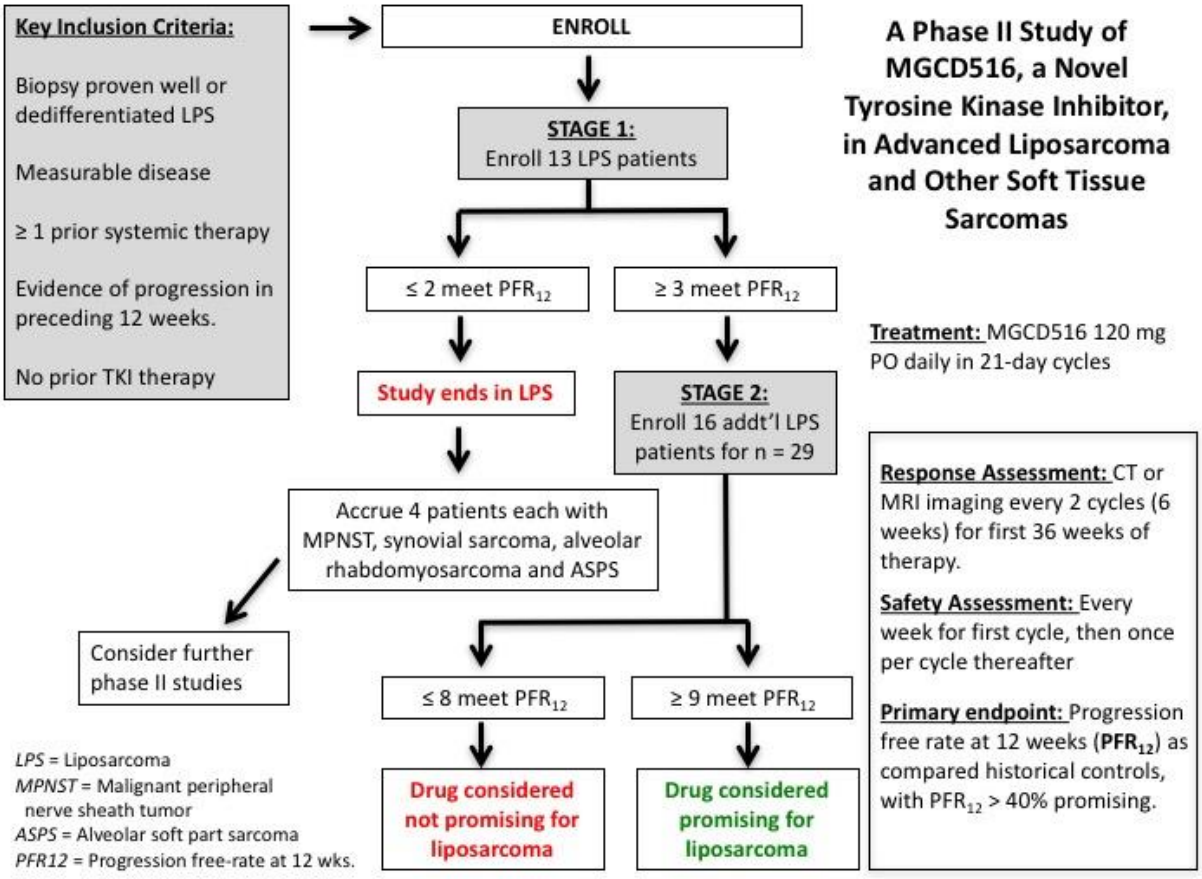
The study will be conducted at two institutions. All subjects will be treated with the same agent and dose, MGCD516, at 120 mg in continuous 21 day cycles. Patients will receive treatment at the discretion of the principal investigator until disease progression, unacceptable toxicity or adverse event(s) or withdrawal of consent.

The primary endpoint is the progression free rate (PFR) at 12 weeks, which will be evaluated against historical controls for active and inactive agents in sarcoma. Secondary endpoints include overall survival, progression free survival, overall response rate and safety profile. Correlative science endpoints will be exploratory and hypothesis generating. A subset of liposarcoma patients will undergo baseline and on-treatment tumor biopsies. Reverse phase protein arrays will be used to assess for changes in total and phospho-protein RTK targets of the drug between these biopsies. In another correlative study, all liposarcoma patient's existing tumor specimens

will be assessed by next generation sequencing to identify a panel of predefined genetic alterations in MGCD516 RTK targets.

We will use a Simon optimal 2-stage design. The study will enroll 13 liposarcoma patients in the first stage. If 3 or more liposarcoma patients meet the PFR endpoint described above in the first stage, the study will be expanded to a total of 29 liposarcoma patients. If a total of 9 or liposarcoma more patients demonstrate the PFR endpoint, the agent will be considered promising in liposarcoma. This design provides for a type 1 error of 0.10 and type 2 error of 0.14. The study has a power of 85% to detect a difference between PFS of 20% versus 40% at 12 weeks.

If the study does not meet its endpoint in liposarcoma patients during stage 1 of the Simon 2-stage design, an additional 16 patients will be enrolled, composed of 4 each of MPNST, synovial sarcoma, alveolar rhabdomyosarcoma and alveolar soft part sarcoma, to evaluate for potential signs of efficacy in those subtypes as part of an exploratory cohort which may inform the design of future phase 2 studies.



For further details regarding the study design, see the following sections:

Section 5:	Inclusion and exclusion criteria
Section 7:	Treatment plan

Section 11:	Study calendar
Section 13:	Correlative studies
Section 15:	Statistical considerations

4.2 Dose Limiting Toxicities

Not applicable.

4.3 Number of Patients

The study size is 29 patients.

5. SUBJECT SELECTION AND WITHDRAWAL

This clinical trial can fulfill its objectives only if appropriate patients are enrolled. All clinically relevant considerations should be made when deciding whether this protocol is appropriate for a particular patient. Waivers to eligibility requirements cannot be granted by any party. In order to be considered eligible, a patient must meet all of the inclusion criteria and be free of all of the exclusion criteria as stated below.

5.1 Inclusion Criteria

5.1.1	Stage 1: Histologically confirmed well-differentiated or dedifferentiated liposarcoma. If stage 1 of the Simon II stage design fails to meet its endpoint for liposarcoma patients, an additional 16 patients will be enrolled, composed of 4 each of MPNST, synovial sarcoma, alveolar rhabdomyosarcoma and alveolar soft part sarcoma (otherwise, an additional 16 patients with well-differentiated or de-differentiated liposarcoma would be enrolled). Pathology review occurs at the center enrolling the patient on this trial.
5.1.2	Disease must be locally advanced and unresectable or metastatic. Disease which may be resected but with an associated level of morbidity deemed unacceptable by the treating clinician is considered eligible.
5.1.3	Patients must have measurable disease by RECIST criteria version 1.1.
5.1.4	Patients must evidence of disease progression, either clinically or radiographically, within the 12 weeks prior to study enrollment, as determined by the investigator enrolling the patient on the study.
5.1.5	Patients must have been treated with at least one prior systemic regimen for sarcoma. Neoadjuvant or adjuvant systemic therapy qualify as prior therapy for the purposes of this study. There is no upper limit on previous lines of therapy received. A prior line of systemic therapy may include prior investigational agents received as part of other clinical studies.
5.1.6	Patients must be age 18 years or older. Because no dosing or adverse event data are currently available for MGCD516 in patients less than 18 years of age, children are excluded from the present study, but will be eligible for future pediatric trials.

5.1.7	Patients must demonstrate an ECOG performance status of 0 or 1.
5.1.8	Patients must demonstrate normal organ and marrow function as defined below: Absolute neutrophil count (ANC) ≥ 1,500/mm^3 Platelet count ≥ 100,000/mm^3 Creatinine ≤ 1.5 times upper limit of normal OR Calculated creatinine clearance > 45 mL/min* Total bilirubin ≤ 1.5 times upper limit of normal** AST/ALT ≤ 1.5 times upper limit of normal** *Notes:* Upper limit of normal is defined by the clinical laboratory performing the test. * Using the lean body mass formula only (Modified Cockcroft Gault) ** If transaminase elevation and/or bilirubin elevation is attributed to the presence of liver metastases, a total bilirubin ≤ 2.5 times the upper limit of normal and an AST and ALT ≤ 2.5 times the upper limit of normal are permissible. Patients with an elevated bilirubin level that is attributed to an inherited disorder, such as Gilbert's disease, may be enrolled at the discretion of the principal investigator.
5.1.9	Patients must demonstrate adequately controlled blood pressure at the time of study entry, as defined by a blood pressure ≤ 150/100 mmHg at study screening on at least one of two screenings conducted at least 24 hours apart. If blood pressure meets these guidelines on initial measurement, no subsequent measurement for screening is needed. Blood pressure may be assessed by automated or manual methods by an appropriately trained clinician or nurse.
5.1.10	Patients must have normal left ventricular systolic function, as demonstrated by a transthoracic echocardiogram or MUGA scan showing a normal left ventricular ejection fraction.
5.1.11	The effects of MGCD516 on the developing human fetus are unknown. For this reason, women of child-bearing potential and all men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of MGCD516 administration. If patients do not agree to the above, they are not considered eligible.
5.1.12	Ability to understand and willingness to sign a written informed consent document.

5.2 Exclusion Criteria

5.2.1	Patients must not have received treatment with any chemotherapy, immunotherapy, radiotherapy or an investigational agent for malignancy within the 28 days

	preceding study registration. Patients may not have received treatment with nitrosureas or mitomycin within the 42 days prior to study registration. Patients may not have received treatment with a small molecule targeted agent (including off-label or investigational use) within 14 days preceding study registration, provided this represents at least 7 half-lives for that agent. Toxic effects from any prior therapy (except alopecia) must have resolved to grade 1 or less according to NCI CTCAE v4.0 or to the patient's baseline by the time of registration.
5.2.2	Patients may not be receiving any other investigational agent for any purpose concurrently. Patients may not require ongoing treatment with (a) gastric pH modifying medications including proton pump inhibitors or H2 blockers (patients may switch to antacids), (b) medications which are known to be sensitive substrates or substrates with a narrow therapeutic index for the P-gp and BCRP transporters and/or (c) medications known to cause QTc prolongation with risk of Torasades. Please see Appendix 1 for a list of such prohibited concomitant medications at study entry.
5.2.3	Patients may not have a history of allergic reaction or hypersensitivity to microcrystalline cellulose (Avicel PH302) or polysorbate 80 (Tween 80), which are components of the drug product MGCD516.
5.2.4	Patients may not have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, uncontrolled diabetes mellitus or uncontrolled psychiatric illness that would limit compliance with study requirements in the opinion of the principal investigator. Additionally, patients must be free of any impairment in the ability to swallow and absorb the oral study drug.
5.2.5	Patients may not be pregnant or nursing. Pregnant women are excluded from this study because the teratogenic effects of MGCD516 have not been adequately studied. A negative pregnancy test must be documented 7 days or less prior to registration. Because there is an unknown but potential risk for adverse events to nursing infants secondary to treatment of the mother with MGCD516, breastfeeding must be discontinued prior to registration for this clinical trial.
5.2.6	Patients may not have known HIV infection. HIV-positive patients on combination antiretroviral therapy are ineligible because these patients are at increased risk of lethal infections when treated with potentially marrow suppressive therapy. Although marrow suppression was not an observed toxicity in the phase 1 trial of this agent, this side effect has been observed with other pan-receptor tyrosine kinase inhibitors.

5.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. In accordance with the NIH guidelines on the inclusion of women and minorities as subjects in clinical research, the Department of Health and Human Services (HHS) requires that all pilot, phase 1, phase 2, and phase 3 trials must include accrual targets for males, females, and minorities. The accrual targets

reflect the expected accrual over the life of the study.

5.4 Subject Recruitment

Patients will be recruited from investigator and co-investigator practices.

5.5 Early Withdrawal of Subjects

5.5.1 When and How to Withdraw Subjects

Patients will be removed from this study for failure to adhere to protocol requirements, withdrawal of consent, disease progression, unacceptable toxicity, global deterioration in health status, study termination or death. There is no evidence to suggest that abrupt withdrawal of this study agent would result in adverse clinical effects and therefore there is no taper of study drug in the event of withdrawal.

5.5.2 Data Collection and Follow-up for Withdrawn Subjects

Although subjects may be withdrawn prematurely from the study, follow-up will continue for all such subjects. Subjects withdrawn because of unacceptable adverse events will be followed-until resolution or stabilization of the adverse event. An attempt will be made to obtain survival information for all subjects for a period of at least 3 years following the time of registration or until death, whichever comes first. For more information, see section 11, study calendar. This will include attempts to contact subjects via telephone and by certified letter using information available to the investigators and the study team. When possible, at least two attempts will also be made to contact the subject's next of kin to obtain such information while observing relevant privacy laws, where applicable.

6. REGISTRATION PROCEDURES

6.1 CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirming subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures: Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@columbia.edu or fax to 212.305.5292, with the subject line "*Protocol Number:* Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist

- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by a Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:

  Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)

  Copy of pathology and surgical reports

  Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

  Protocol deviation/waiver approvals (if applicable)

Please note: subject line of email or fax should include the following: "AAAQ8661: Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subjects who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

7. TREATMENT PLAN

7.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for MGCD516 are described in Section 10. Appropriate dose modifications for MGCD516 are described in Section 9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
MGCD516	None	120 mg	Orally	Daily	21 days

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle of treatment.

The drug will be administered in the fasted state, at least 2 hours after the previous meal, and 1 hour before the next meal. The capsules will be taken in the morning hours (1 hour before breakfast or 1 hour before lunch). The study capsules will be taken with at least 200 mL (1 cup) of water. No predefined prophylactic or supportive care medications will be administered with the study agent for patients newly starting therapy. However, prophylactic or supportive care may be initiated in the event of toxicity as described in section 9.

7.2 General Concomitant Medication and Supportive Care Guidelines

MGCD516 has the potential to interact with certain other drugs which study patients may be taking, which could result in unforeseen toxicities. The case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Patients should be asked at each study-related clinical visit about new medications, including herbal medications or supplements, which they are taking.

7.2.1 Medications affecting the cytochrome system

In vitro experiments indicate that MGCD516 is a potential inducer of CYP2B6 and CYP3A4 as well as a potential inhibitor of CYP2C8, CYP2D6 and CYP3A4, although neither time dependent nor metabolism dependent inhibition have been observed. Nonetheless, medications that are substrates for CYP2B6, CYP2C8, CYP2D6 or CYP3A4 and are either sensitive substrates or have a narrow therapeutic index should be used with caution during treatment with MGCD516. An alternative agent should be employed if possible; otherwise, patients should be monitored at each study visit for signs or symptoms suggestive of subtherapeutic or supratherapeutic levels of these agents. A list of substrates for CYP2B6, CYP2C8, CYP2D6 and CYP3A4 which are either sensitive substrates or have a narrow therapeutic index is provided in Appendix 1 for reference.

Furthermore, in vitro experiments in microsomes and recombinant human P450 enzymes suggest that MGCD516 is itself metabolized by several cytochromes including CYP3A4, CYP2B6 and CYP2D6, although with a low risk of any single CYP having a disproportionate contribution to its metabolism. Caution should therefore be used when administering MGCD516 to patients taking medications that are strong inhibitors or inducers of these cytochromes. A list of such medications is provided in Appendix 1.

7.2.2 Medications affecting gastric pH

The solubility of MGCD516 is pH dependent, therefore medications that are associated with a sustained increase in gastric pH should be avoided. Upon registration to the study, patients on PPIs or H2 agonists should attempt to discontinue use of these agents. Patients should pursue lifestyle modifications and may switch to the use of as needed antacids (including gaviscon) and/or carafate. If patients continue to experience significant GERD symptoms, a PPI or H2 blocker may be reinstituted at the discretion of the principal investigator and should be given 12 hours apart from the Sitrvatinib whenever possible.

7.2.3 Medications acting on the BCRP and P-gp transporters

MGCD516 is an inhibitor of the breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) transporters based on in vitro studies. Therefore, medications that are known substrates for the BCRP or P-gp transporters with a sensitive and/or narrow therapeutic index are prohibited. A list of such medications is provided in Appendix 1.

7.2.4 Medications affecting the qTC interval

The risk for qTC prolongation in patients receiving treatment with MGCD516 has not been adequately characterized in humans. Therefore, use of medications known to prolong the QTc interval and pose a risk of Torsades are prohibited during treatment with MGCD516. The use of medications known to prolong the QTc and pose a conditional risk of Torsades should be used with caution. Please see Appendix 1 for a list of medications to be avoided and used with caution in this setting.

7.3 Duration of Therapy

Treatment with the study drug will continue until one of the following applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event
- Patient’s decision to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Patients whose disease status remains complete response, partial response or stable disease may

continue on therapy indefinitely until one of the above conditions applies.

7.4 Duration of Follow Up

Patients who do not progress while on study treatment will be followed every 3 months after completion of study treatment for the first 12 months of follow up and then every 6 months for both survival and disease status until death or for a period of at least 3 years, whichever comes first. For patients who are taken off therapy due to progression, information on survival will also be collected every 3 months after completion of study treatment for the first 12 months of follow up and then every 6 months until death or for a period of at least 3 years, whichever comes first. Patients removed from study for unacceptable adverse events will also be followed for information on resolution or stabilization of the adverse event.

7.5 Criteria for Removal from Study

Patients will be removed from the study when any of the criteria listed in Section 7.3 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

7.6 Approach to COVID-19 Related Treatment Interruptions

Patients whose protocol treatment is interrupted because of COVID-19 infection and/or COVID-19-related effects on the conduct of this study may resume resume treatment at the discretion of the treating investigator if the investigator believes the potential benefits outweigh risks. In this situation, the patient's clinical situation, previous benefit from study treatment, and other available treatment options should be considered.

This applies to subjects whose treatment is delayed beyond the protcol allowed timeframe of 28 days and also to subjects whose study-specified restaging imaging performed around the time of treatment interruption shows disease progression, and this progression can reasonably attributed to the period treatment was withheld.

In these situations, the treating investigator will document the specifics of the situation and consideration of risk/benefit in the electronic medical record.

8. DOSING DELAYS/DOSE MODIFICATIONS

This section provides guidance on the management of adverse events and on dose delays and modifications for MGCD516. In the event of adverse events attributed to MGCD516 and deemed intolerable to the investigator, treatment may be temporarily or permanently discontinued. For patients who temporarily discontinue treatment, treatment may resume following resolution of treatment-related adverse events to grade 1 or baseline at a reduced dose level. Recommended dose modification algorithms are included for commonly observed adverse events. Adverse events are classified and graded according to CTCAE version 4.0. The following guidelines should also be observed:

- If a patient experiences multiple adverse events and there are conflicting recommendations as to management, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level of the available options.

- Any patient who requires a delay in therapy exceeding 28 days should be removed from the study. Any patient who requires more than three dose reductions should also be removed from the study.

- Patients should receive all relevant supportive care during the study, including, but not limited to: blood product support, antibiotic treatment, and management of other newly diagnosed medical conditions. All blood products and concomitant medications (such as antiemetics, analgesics, antidiarrheals) received from the first day of study drug treatment until 30 days after the final dose of study drug treatment must be recorded.

- Patients who require radiation therapy while on study must be removed from the study.

- Patients who require surgery while on study may proceed with surgery provided resection or removal of sarcoma is not part of the surgery. However, if a dose delay of more than 28 days is required, the patient must be removed from the study.

- Blood products and growth factors should be used as clinically warranted and in accordance with institutional policy at the institution where the patient is being treated. Specifically, the use of erythropoietin is permitted at the discretion of the treating physician. The use of filgrastim and related medications to avoid dose reductions or delays is discouraged. The use of these agents in the setting of complications from therapy, such as severe infection, is permitted and must be documented.

8.1 Dose Levels

Dose Level	MGCD516 Dose
-3	Off protocol therapy
-2	80 mg orally daily
-1	100 mg orally daily
0	120 mg orally daily*

* Note: The starting dose of Sitravatinib was modified from 150 to 120 mg daily in 5/2018. Patients already enrolled on the study at the time of this modification may continue at the 150 mg dose level, or reduce to the 120 mg dose level, at the discretion of the treating investigator. For patients continuing at 150 mg, 120 mg represents dose level -1, and so on.

8.2 Management Advice for Non-Hematologic Adverse Events

Hypertension	Management/Next Dose for MGCD516
≤ Grade 1	No change in dose

Hypertension	Management/Next Dose for MGCD516
Grade 2	Continue therapy. Institute anti-hypertensive agent or alter dose of existing anti-hypertensive agent.
Grade 3	Hold therapy. Institute anti-hypertensive agent or alter dose of existing agent. Resume therapy when hypertension resolved to grade 2 or less. For subsequent occurrences at grade 3, hold therapy until blood pressure resolves to grade 2 or lower, and reinstitute at one dose level lower, at investigator's discretion.
Grade 4	Off protocol therapy.
When anti-hypertensive therapy is indicated, the agent employed should be based upon review of the patient's clinical history to determine the most appropriate agent, with cardiology consultation as needed. The use of dihydropyridine calcium channel blockers such as nifedipine, amlodipine and nicardipine can be considered as first line agents, in the absence of contraindications.	

Palmar Plantar Erythrodysesthesia	**Management/Next Dose for MGCD516**
≤ Grade 1	No change in dose. Counsel on measures to mitigate the effects of palmar plantar erythrodysesthesia and institute topical therapies as described below.
Grade 2	Hold until ≤ Grade 1, counsel on measures to mitigate the effects of palmar plantar erythrodysesthesia, and resume at one dose level lower.
Grade 3	Hold until ≤ Grade 1, counsel on measures to mitigate the effects of palmar plantar erythrodysesthesia, and resume at one dose level lower, at investigator's discretion.
Grade 4	*Not applicable.*
Signs and symptoms of palmar plantar erythrodysesthesia include redness, swelling, pain and blistering on the palms of the hands and soles of the feet. Patients should be counseled to avoid exposure of hands and feet to hot water and other sources of heat, to avoid activities causing force or friction, and to avoid contact with harsh chemicals. Treatment includes the use of moisturizing agents, topical anesthetics, topical anti-inflammatory medications, and topical corticosteroids.	

Proteinuria	**Management/Next Dose for MGCD516**
≤ Grade 1	Continue therapy with close monitoring by urinalysis at least every cycle.
Grade 2	Hold protocol therapy. Perform 24 hour urine collection to confirm degree of proteinuria. May reinstitute at one dose level lower if and when protein levels decrease to 2g in 24 hours, at the discretion of the principal investigator.
Grade 3	Off protocol therapy.
Grade 4	*Not applicable.*
Patients who develop more than 2g proteinuria should undergo 24 hour urine collection for definitive assessment of urine protein. Patients who develop nephrotic syndrome should be	

Proteinuria	Management/Next Dose for MGCD516
taken off protocol therapy and referred for further management by a nephrologist. ACE inhibitor therapy is permitted in study patients as clinically indicated.	

Diarrhea	Management/Next Dose for MGCD516
≤ Grade 1	No change in dose. Evaluate for infectious etiology if clinically indicated. Institute anti-diarrheal therapy.
Grade 2	No change in dose. Evaluate for infectious etiology if clinically indicated. Institute anti-diarrheal therapy. If diarrhea persists at grade 2 or higher for more than 5 days despite supportive care, hold protocol therapy and manage supportively. Reinstitute at same dose when symptoms improve to ≤ grade 1. On subsequent occurrences at grade 2, consider dose reduction when therapy reinstated.
Grade 3	Hold until ≤ Grade 1. Evaluate for infectious etiology if clinically indicated. Institute anti-diarrheal therapy. Reinstitute at one dose level lower when symptoms improve to ≤ grade 1.
Grade 4	Off protocol therapy.
If clinically indicated, evaluate patients for an infectious etiology of diarrhea using appropriate test for Clostridium difficile, stool cultures, and PCR for GI pathogens, where available. Treat infection as clinically indicated. First line supportive care should be instituted with the anti-diarrheal loperamide.	

Fatigue	Management/Next Dose for MGCD516
≤ Grade 1	No change in dose.
Grade 2	No change in dose.
Grade 3	Hold until ≤ Grade 2. Resume at same dose level. If recurs at grade 3, hold until ≤ Grade 2 and then resume at one dose level lower.
Grade 4	*Not applicable.*
Fatigue is commonly associated with receptor tyrosine kinase inhibitors. Evaluate and treat for other conditions which can manifest as fatigue, including but not limited to thyroid dysfunction, infection and anemia.	

Left ventricular systolic dysfunction	Management/Next Dose for MGCD516
≤ Grade 1	*Not applicable.*
Grade 2	*Not applicable.*
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy.

Liver Function Abnormality	**Management/Next Dose for MGCD516**
ALT or AST ≥ 3x ULN but ≤ 5x ULN **AND** TB ≤ 2x ULN	Continue study drug. Monitor liver function testing weekly until tests return to normal or baseline, or demonstrate stabilization (if tests demonstrate stability in the opinion of the investigator, monitoring may be changed to every 2-3 weeks.) If liver function testing worsens, follow applicable instructions below.
ALT or AST ≥ 5x ULN **AND** TB ≤ 2x ULN	Hold study drug. Monitor liver function testing weekly until tests return to normal or baseline. Reinstitute therapy at one dose level lower and monitor liver function testing at least weekly for a minimum of 4 weeks after restarting therapy. If ALT or AST again ≥ 5x ULN, discontinue further protocol therapy.
TB ≥ 2x ULN but ≤ 3x ULN regardless of AST/ALT	Hold study drug. Monitor liver function testing weekly until tests return to normal or baseline. Reinstitute therapy at one dose level lower and monitor liver function testing at least weekly for a minimum of 4 weeks after restarting therapy. *Note:* If patient enters the study with TB between ULN and 1.5x ULN (because attributed to presence of metastatic disease), no intervention is required unless increase in TB represents a change from baseline.
TB ≥ 3x ULN regardless of AST/ALT	Discontinue study drug.
Protocol modifications of 6/8/2017 reflect the lack of clinically significant hepatotoxicity observed in the phase 1/1b study of Sitravatinib in solid tumors (grade 3/4 AST/ALT observed in less than 3% of patients, no grade 3/4 TB abnormalities observed. (TB = total bilirubin).	

All Other Non-Hematologic Events	**Management/Next Dose for MGCD516**	
	Treatment delay	**Dose Modification**
≤ Grade 1	No delay	No change in dose
Grade 2	In general, hold until ≤ grade 1 or return to baseline	Not required
Grade 3 or 4 *manageable with supportive care.*	Hold until ≤ grade 1 or return to baseline	Not required
Grade 3 or 4 *not manageable with supportive care.*	Hold until ≤ grade 1 or return to baseline	Resume at one dose level lower than dose inducing toxicity.
Modifications apply to toxicities deemed related to study drug. Appropriate supportive care should be instituted.		

8.3 Management Options for Hematologic Adverse Events

Neutropenia	
Grade 1 (ANC < 1500 to < LLN)	Maintain dose level

Grade 2 (ANC 1000 to < 1500)	Maintain dose level
Grade 3 (ANC 500 to < 1000)	Hold therapy until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, reduce by 1 dose level
Grade 4 (ANC < 500 or febrile neutropenia)	Hold therapy until resolved to ≤ grade 2, then restart at one dose level lower.
Thrombocytopenia	
Grade 1 (PLT 750000 to < LLN)	Maintain dose level
Grade 2 (PLT 50000 to < 75000)	Hold therapy until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, reduce by 1 dose level
Grade 3 (PLT 25000 to < 50000)	Hold therapy until resolved to ≤ grade 1, then restart at one dose level lower.
Grade 4 (PLT < 25000)	

9. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

9.1 Adverse events

A summary list of reported treatment-related treatment-emergent adverse events for MGCD516 is provided below. For a detailed list of all treatment emergent adverse events reported in the phase 1 trial of MGCD516 in solid tumors, please see section 3.2. Based on the most recently available information the phase 1/1b study (as of 7/2016 and representing 61 patients treated with the drug), the following treatment-related treatment-emergent adverse events were reported:

Likely (>20%)	Less Likely (5-20%)	Rare but Serious (<3%)
• Diarrhea • Fatigue (feeling tired) • Hypertension (high blood pressure)	• Blood clots, in the veins or lungs • Change in voice • Constipation • Cough • Decreased appetite • Dry mouth • Low thyroid level (hypothyroidism) • Nausea • Mucosal inflammation and/or irritation, including mouth pain • Rash • Swelling and/or redness and/or pain of the hands and feet • Vomiting • Weakness • Weight loss	• Decrease in heart function or heart pumping • Fever with low white blood cells (infection fighting cells) • Increase in pancreas-related enzymes • Increase in heart rate (tachycardia) • Increase in liver function tests (possible liver damage) • Protein in the urine • Weakness, numbness and/or pain due to nerve injury (neuropathy)

MGCD516 is a small molecule multi-receptor tyrosine kinase inhibitor of a range of RTKs. As such, it may share some similar properties with other small molecule RTK inhibitors, although adverse events associated with the drugs are likely to vary based on the particular RTKs selectively inhibited.

9.2 Definitions

Adverse Event: An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality, results in study withdrawal**,** is associated with a serious adverse event, is

associated with clinical signs or symptoms**,** leads to additional treatment or to further diagnostic tests**,** is considered by the investigator to be of clinical significance

Serious Adverse Event: Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires inpatient hospitalization/prolongation of existing hospitalization, unless: (1) routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control); (2) elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug; (3) treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital administrations; (4) social reasons and respite care in the absence of any deterioration in the patient's general condition
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event. An important medical event is one that may not be immediately life threatening but is clearly of major clinical significance. It may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would all typically be considered serious.

Unanticipated Problem: An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Adverse Event Reporting Period: The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (after the first dose of study treatment) to the end of the study treatment (last dose of study treatment) and follow-up. For this study, the study treatment follow-up period is defined as 28 days following the last administration of study treatment.

Baseline/Preexisting Condition: A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

General Physical Examination Findings: At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event: All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values: A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

Hospitalization, Prolonged Hospitalization or Surgery: Any adverse event that results in hospitalization or prolongation of hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an

outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.3 Recording of Adverse Events

Signs or symptoms of the patient's cancer diagnosis and/or comorbidities at baseline will be recorded beginning on day 1. At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Assessment of adverse events will include type, incidence, severity (as graded by CTCAE version 4), timing, seriousness, and relatedness to study treatment. For each adverse event, the investigator will determine and document whether there exists a reasonable possibility that the study drug treatment caused or contributed to the adverse event. When the investigator does not know whether or not the study treatment is causally-related to the event, reporting for study purposes will be as "related" to study treatment.

Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

9.4 Reporting of Serious Adverse Events

9.4.1 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

9.4.2 FDA Notification by Sponsor-Investigator

Columbia University Medical Center will be responsible for all communication with the FDA. Columbia University Medical Center will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and for which there is evidence to suggest a causal relationship between the drug and the adverse event. These must be reported to the FDA and any affiliate sites as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. Columbia University Medical Center will also submit an IND annual report to the FDA in accordance with 21.CFR 312.33.

Columbia University Medical Center must report to the FDA and any affiliate site investigators as follows:

- Any unexpected fatal or life-threatening event must be reported as soon as possible, but no later than 7 calendar days after the sponsor investigator initial receipt of the information
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any findings from animal or in vitro testing whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any clinically important increase in the rate of a serious suspected adverse reactions over that listed in the protocol or Investigator Brochure
- Expected SAEs and AEs will be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor investigator must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

9.4.3 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

9.4.4 Reporting to Drug Manufacturer by Sponsor-Investigator

All Suspected Unexpected Serious Adverse Reactions (SUSARs) will be submitted to Mirati Therapeutics on a MedWatch Form 3500A within the timelines as follows:

- Reports of fatal or life threatening Serious Adverse Drug Reactions will be forwarded within five (5) calendar days of Receipt Data

Reports of Serious Adverse Drug Reactions (other than fatal or life threatening) will be forwarded within twelve (12) calendar days of Receipts Date.
Please FAX IND Safety Reports (SUSARS) to 1-888-488-9697. For FAX problems call 1-800-201-8725 to report the event via phone.

In addition, all reports prepared for FDA submission will be submitted to Mirati Therapeutics prior being submitted to the FDA. If no comment is received by Mirati Therapeutics within 48 hours, the report will be submitted to the FDA in its original form, so as to ensure timely submission of documentation.

9.5 Reporting Process

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse Event Reporting Form, or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 10. At the time of IRB renewal or at the request of the manufacturer, the Sponsor-Investigator will submit a summary of all serious adverse events that have occurred during the study to the manufacturer.

10. PHARMACEUTICAL INFORMATION

10.1 Description

MGCD516 is an orally available small molecular inhibitor of several closely related receptor tyrosine kinases. Detailed information on the drug's mechanism of action, as well as preclinical and clinical safety information, is provided in Section 4. The drug is currently supplied as 10 and 40 mg capsules. The composition of the drug product includes a blend of the free base substance MGCD516 with microcrystalline cellulose (Avicel PH302) and polysorbate 80 (Tween 80). The blend is filled into size 1 light blue opaque (10 mg) or size 1 Swedish orange opaque (40 mg) hard gelatin capsules. The 10 and 40 mg capsules are packaged into 60 cc bottles.

10.2 Treatment Regimen

The treatment regimen consists of MGCD516 at a dose of 120 mg orally daily in continuous 21 day cycles. This dose will be administered as three (3) 40 mg capsules. The drug will be administered in the fasted state, at least 2 hours after the previous meal, and 1 hour before the next meal. The capsules will be taken in the morning hours (1 hour before breakfast or 1 hour before lunch). The study capsules will be taken with at least 200 mL (1 cup) of water.

10.3 Method for Assigning Subjects to Treatment Groups

Not applicable. All study participants will be treated with the same treatment regimen.

10.4 Preparation and Administration of Study Drug

The study drug is an oral capsule which will be packaged, shipped and stored as described below. The drug will be received by the Research Pharmacy of Columbia University Medical Center, stored in a secure location and according to all institutional policies, and will be released to the research nursing staff who will distribute the agent to the patient. No other specific preparation of the drug is needed at the study site.

10.5 Subject Compliance Monitoring

Study subjects will complete a medication journal documenting compliance with the study drug. The medication journal will be reviewed after each cycle. Patients who are non-complaint with the treatment regimen may be removed from the study at the discretion of the principal investigator.

10.6 Prior and Concomitant Therapy

Information will be collected on all prior anti-cancer therapies. Patients may not receive any other agent which could be considered treatment for the primary neoplasm or which might affect the primary endpoint during their participation in the study. For other restrictions on concomitant medication use, see section 7.2.

10.7 Packaging

The MGCD516 drug product is packaged in 30 count, high-density polyethylene (HDPE) white opaque round bottles. The 10 and 40 mg unit dose capsules are packaged into 60 cc bottles. A tamper-proof heat induction seal and a child resistant closure are employed. Each bottle is labeled with contents, product lot number, required storage conditions and a regional specific cautionary statement.

10.8 Blinding of Study Drug

Not applicable. This is an open-label study.

10.9 Receiving, Storage, Dispensing and Return

10.9.1 Receipt of Drug Supplies

The study drug will be shipped by Mirati Therapeutics to the Research Pharmacy of Columbia University Medical Center. Upon receipt of the of the study treatment supplies, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented. The investigator must notify the agent manufacturer of any damaged or unusable study treatments that were supplied to the investigator's site.

10.9.2 Storage

Bottles of MGCD516 will be stored at room temperature, within a range of 15 to 30 degrees Celsius. The storage area should be secure with limited access. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling and safe disposal of small molecule chemotherapeutic agents such as MGCD516.

10.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form and signed and dated by the study team. Drug inventory forms will record the batch or lot numbers for disposition on a patient by patient basis and signed by the person dispensing the drug. Patients will receive study drug on the first day of each cycle while they remain on study. Sufficient supply will be provided for the cycle and up to 2 additional days in case of delayed clinic visits or lost capsules. Study site personnel will provide each patient with written dosing information. Patients will record their daily dosing on a provided form and report any missed doses or lost capsules.

10.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of the study drug.

11. STUDY CALENDAR

Procedure	***Screening (1)***	***Cycle 1(9)***			***Cycle 2 (9)***			***Cycle 3 + (9)***			***End of study (8)***
		1	8	15	1	8	15	1	8	15	
Informed consent	X										
Medical history	X										
Pathology confirmation	X										
Physical examination and vital signs	X	X	X	X	X			X			X
Height and weight	X	X	X	X	X			X			X
ECOG performance status	X	X	X	X	X			X			X
Adverse event assessment	X	X	X	X	X			X			X
ECG (1)	X										X
Echocardiogram (1)	X							X			
CBC w/differential (1,3)	X	X	X	X	X			X			X
Comprehensive metabolic panel (1,3,4)	X	X	X	X	X			X			X
Thyroid function tests (1, 3, 11)	X							X			X
Lipase (1, 3, 11)	X							X			X
Serum or urine pregnancy test (1)	X										
Urinalysis (1)	X							X (10)			X
CT or MRI of chest, abdomen, pelvis (2)	X							X			X
Tumor specimen submitted for next generation sequencing (5)	X										
Fresh tumor biopsy for RPPA studies (6)	X			X							
Follow-up telephone contact (7)											X

(1): History and physical, all laboratory studies, urinalysis and single EKG must be completed 14 days or less prior to registration, with the exception of the serum or urine pregnancy test, which must be performed 7 days or less prior to registration. The echocardiogram must be completed within 56 days of registration, unless there is clinical suspicion for a change in cardiac status since that time, in which case it should be repeated. An echocardiogram will be repeated at any point during week 1 of cycle 3. Protocol-specific screening procedures that are performed as part of standard of care and are within these specified timeframes may be used for screening purposes.

(2) Baseline imaging can include either (a) CT, spiral CT or MRI, or (b) FDG-PET with diagnostic CT performed with IV and oral contrast and CT acquired with 5 mm or less slice thickness. Imaging studies used for baseline tumor measurements must be obtained 28 days or less prior to registration. Imaging studies performed as part of standard care and within this

timeframe may be used for screening purposes. Imaging studies are performed every 2 cycles (6 weeks, 42 days) for the first 36 weeks of study treatment, and then every 3 cycles (9 weeks, 63 days) thereafter. Imaging studies may be performed +/- 5 days from the required date. In the event of dose delays/holds, imaging studies should still be obtained at the scheduled timepoints as determined from registration, without delays to account for the dose delays/holds. Confirmatory scans must be obtained at least 4 weeks after the documentation of an objective response as discussed in section 12. It is acceptable to perform confirmatory assessments at the next appointed evaluation per protocol. Response assessment should include assessment of all sites of disease and use the same imaging method as used at baseline whenever possible.

(3) All laboratory studies may be performed +/- 3 days from the required date.

(4) Comprehensive metabolic panel is to include albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT and sodium.

(5) *Applies to liposarcoma patients only:* All patients will have their most recent available biopsy material submitted for next generation sequencing to assess for genetic alterations of MGCD516 targets. See section 13 for more information on sample collection, processing and analysis. In cases were institutional policy or availability of prior specimens preclude this analysis, these studies will not be performed for that patient.

(6) *Applies to liposarcoma patients only:* A subset of 10 patients will undergo baseline and on-treatment tumor biopsies for RPPA studies. The first 10 patients with lesions amenable to biopsy who are enrolled to the study (beginning with the first patient enrolled in stage I) will undergo these biopsies. See section 13 for information on sample collection, processing and analysis. The baseline biopsy specimen will be obtained at any point between day -14 and the date of first treatment with the study drug (cycle 1, day 1) provided consent is obtained and the other eligibility criteria are met. The on-treatment biopsy specimen will be performed with a target timepoint of cycle 1 day 15 (with a window of cycle 1 days 15 through 20). Biopsies will be obtained from the site of disease. If the study fails in stage I and proceeds to the exploratory cohort, no further RPPA analyses will be performed.

(7) A post-study follow-up contact via telephone by research staff will be conducted every 3 months during the first year after the end of study participation, and then every 6 months thereafter. For patients who do not progress on study treatment, information is obtained on disease status, survival status, and new anti-cancer therapy received. For patients who do progress on treatment, information is obtained on survival status and new anti-cancer therapy received. Follow-up continues for at least 3 years as measured from the date of study registration or until death, whichever comes first.

(8) The end-of-study visit must be scheduled 28 days after the last dose of study drug (+/- 7 days) and before starting any new anti-neoplastic therapy. Imaging studies are only performed at this time if they would otherwise be indicated by that patient's study calendar.

(9) Clinical assessments will occur on days 1, 8 and 15 of cycle 1, and then on day 1 of all cycles

thereafter. Clinical assessments may occur +/- 3 days from the target date.

(10) The urinalysis is repeated on cycle 3 day 1. If there is no evidence of proteinuria, the urinalysis need not be repeated in subsequent cycles. If microscopic testing shows evidence of proteinuria, the study should be repeated on day 1 of subsequent studies.

(11) Thyroid function tests (TSH, reflexive free T4/free T3 if TSH is abnormal) and lipase should be performed at baseline, C3D1, every other cycle after C3D1 (i.e. C5D1, C7D1 etc.) and at end of treatment.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients will be re-evaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with MGCD516.

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

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by

clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

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

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

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

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

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

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All

baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers will not be used in this study.

Cytology/Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater

than twice that of the surrounding tissue on the attenuation corrected image.

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

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

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

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

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

12.4.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.4.3 Evaluation of Best Overall Response

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

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

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

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

12.5 Duration of Response

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

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

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

12.6 Progression-Free Survival

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

12.7 Response Review

Not applicable.

12.8 Unblinding Procedures

Not applicable.

12.9 Stopping Rules

Adverse event stopping rule: Accrual will be temporarily suspended to this study if (a) at any time, 2 patients have experienced a grade 5 event considered at least possibly related to the study treatment and not related to disease progression or (b) more than 40% of all patients, when accrual is equal to or greater than 10 patients, have experienced a grade 3 or higher adverse event. In addition, each grade 5 event will be reviewed at the time of occurrence to determine whether study accrual should be suspended to protect the safety of patients. This adverse event stopping rule may be altered in the event of the study reopening after a temporary suspension or should new information become available related to the safety of the study drug.

13. CORRELATIVE STUDIES

The correlative studies described below will be performed in liposarcoma patients only.

13.1 Proteomics studies

Introduction

Reverse phase protein array (RPPA) is a functional proteomics technology capable of profiling protein levels and post-translational modifications, including phosphorylation, across various biological specimens, including human tissue, using a miniaturized analyte-down dot-blot immunoassay.[26] The technique allows for monitoring of protein expression across a large number of samples in a quantitative, high-throughput and cost-effective manner not currently matched by other proteomics technologies.

In RPPA, analytes are immobilized on a solid phase, most often nitrocellulose, and probed with an affinity reagent, usually a high-affinity validated antibody. The technology is particularly well suited for profiling the state of cell signaling networks owing to small sample requirements, high sensitivity in the picomolar range and precision as demonstrated by coefficient of variance < 15%. RPPA has been used in a range of preclinical and clinic research applications for identification of novel therapeutic targets and predictive biomarkers, pharmacodynamic analysis and monitoring of therapeutic response.[27]

We aim to employ RPPA to analyze changes in total and phosphoprotein RTKs between baseline and on-treatment tumor biopsy specimens in order to demonstrate pharmacodynamic evidence of on-target activity by MGCD516, evaluate drug effects on activation/suppression of downstream signaling pathway components and assess for possible compensatory upregulation of alternative RTKs and signaling pathway components as a mechanism of acquired resistance. Specifically, we will study changes in total and phosphoprotein levels for the following proteins: 4E-BP1, Akt, AXL, EGFR, Eph family, ERK 1/2, FGFR2, IGF1-R, KIT, MEK 1/2, MET, p70 S6 kinase, RET, RYK, PDGFRa, PDGFRb and VEGFR1-2. Significant changes in total and phosphoRTKs will then be confirmed by Western Blot.

Prior Clinical Studies Employing RPPA

RPPA has been employed as a component of numerous clinical trials for a similar purpose, demonstrating the feasibility of this method in human tumor specimens obtained in a clinical trial setting. One of the earliest clinical trials to employ RPPA was a phase II trial of gefitinib in patients with refractory or recurrent epithelial ovarian cancer[28]. Core needle tumor biopsies were obtained before treatment and after 4 weeks on drug, and RPPA was used to characterize expression of total and phosphorylated EGFR, AKT and ERK in microdissected tumor specimens. The majority of patients demonstrated changes in EGFR and pEGFR although no clinical benefit was noted for the drug. There was a trend for increased toxicity with greater changes in phosphorylation of EGFR, ERK and AKT. The same group later carried out a phase II trial of vandetanib, a small molecule inhibitor of VEGFR2 and EGFR, in platinum-resistant ovarian cancer patients. Core needle biopsies were obtained at baseline and after 6 weeks on treatment. RPPA was then used to assess multiple RTK and signaling pathway component endpoints in the paired tissue biopsy specimens. The study used a Simon II stage design, and the drug failed to demonstrate sufficient clinical efficacy in the first stage. Interestingly, however, RPPA suggested potential reasons for the drug's lack of efficacy. A reduction in EGFR activation and downstream pAKT was demonstrated by RPPA but, despite measurable levels of total and activated VEGFR2 at baseline, no modulation of that target was seen across any of the paired biopsies. This was corroborated further by lack of significant changes in circulating VEGF levels in plasma.

In another study, RPPA was used in preclinical models (cell lines and xenografts) treated with the selective AKT inhibitor GDC-0068 to identify evidence of signaling pathway modulation with this drug[29]. Potential biomarkers were then analyzed in patient samples treated with the drug. Pharmacodynamic evidence of AKT inhibition was demonstrated in human tumor specimens at clinically achievable doses and the degree of biomarker inhibition correlated to tumor growth inhibition in preclinical models. Moreover, in both the preclinical and clinical samples, compensatory feedback activation of ERK and HER3 was observed using RPPA thereby identifying possible candidates for combination therapy to optimize use of the novel drug.

RPPA has also been employed in numerous clinical trials in breast cancer. Based on preclinical data showing that rapamycin synergistically enhances the cytotoxicity of paclitaxel in triple negative breast cancer, a randomized phase II trial was conducted in 50 patients evaluating

neoadjuvant chemotherapy with or without everolimus[30]. RPPA was used to measure molecular changes in the PI3K/Akt/mTOR pathway at baseline and at 48 hours and after surgery. These measurements were the primary endpoint of this clinical trial. Phosphorylation of ribosomal pS6 was significantly decreased in patients treated in the everolimus arm at 48 hours as shown by RPPA. A separate phase II breast cancer study randomized HER2 positive stage II or III breast cancer patients to trastuzumab, lapatinib or both agents with chemotherapy[31]. Core needle biopsies were obtained for RPPA analysis at baseline and after 2 weeks of anti-HER2 therapy. The study demonstrated a correlation between pathologic complete response at surgery and several protein biomarkers identified by RPPA. Mean expression levels of pEGFR Tyr1068 at baseline predicted response in the lapatinib treated patients. Across all treatment arms, the ratio of pTEN to pFOXO, and PI3K to pFOXO, correlated to likelihood of pathologic complete response.

Tissue Procurement and Handling

A subset of liposarcoma patients will participate in this correlative study with a target sample size of 10 patients. The first 10 liposarcoma patients enrolled on the study (beginning with the first patient enrolled in stage I) with tissue suitable for biopsy will participate, regardless of the site at which the patient is accrued. If the study fails in stage I and proceeds to the exploratory cohort of various tumors, no further RPPA analyses will be performed. However, if the study proceeds to stage 2 in liposarcoma, and additional patients are needed to reach a total sample size of 10 for this correlative, further liposarcoma patients will participate to accrue a total of 10 liposarcoma patients with paired tissue biopsies.

Paired (pre-treatment and on-treatment) core biopsy specimens will be obtained. The baseline biopsy specimen will be obtained at any point between day -14 and the date of first treatment with the study drug (cycle 1, day 1) provided consent is obtained and the other eligibility criteria for the study are met. The on-treatment biopsy specimen will be performed with a target timepoint of cycle 1 day 15 (with a window of cycle 1 days 15 through 20).

The same tumor lesion should be biopsied at both time points whenever possible. Specimens are obtained using a 16-18 gauge core needle under imaging guidance by an interventional radiologist at the treating institution. At least 4 cores are obtained, and up to 6-8 cores if feasible (with safety of the procedure prioritized in all cases). The first 4 cores are placed in FFPE and the subsequent 2-4 cores are cryopreserved and flash frozen. From the FFPE material, an H&E section should be cut for confirmation/diagnostic purposes, to be reviewed at the institution collecting the sample as per standard of care. These following specifications apply:

(1) A 16 to 18 gauge needle is satisfactory;

(2) Time from core needle biopsy (CNB) removal to initiation of fixation should be $\leq$ 30 min;

(3) CNB material should be immersed in sufficient volume of 10% neutral buffered formalin to ensure adequate fixation ($\geq$15 to 20 times greater than estimated volume of CNB);

(4) Formalin fixation to last between 6-72 hours at room temperature; and after fixation, proceed

to paraffin embedding. Tissue blocks should be stored at ambient conditions.

(5) Material should be labeled, accessioned and stored consistent with standard of care policies and procedures at the participating institution.

Disposition of FFPE tissue:

Following the biopsy, material will be accessioned to the pathology department at the institution obtaining the material as per institutional standard of care guidelines. FFPE tissue blocks should be stored at ambient conditions. Once all samples have been obtained and only when directed by the investigators, sections from the pre-treatment and on-treatment biopsies for all study participants will be made as described below, appropriately labeled, and sent to Theralink Technologies where RPPA studies will be performed. Specifically, the following steps will be taken:

(1) Since tissue sections that are older than 6 weeks should not be used for RPPA analysis, **prepared tissue sections should be prepared and shipped within 2 weeks to allow for transportation and on-site sample preparation before the 6 week expiration date.** Thus this process should only be initiated when directed by the investigators.

(2) The initial, uppermost tissue section that had been exposed to air should either be discarded, or used for a non-RPPA purpose such as H&E staining.

(3) Six (6) sections should be prepared to a five (5) µm thickness and air-dried at room temperature. **Do not bake.** Alternatively, five (5) tissue sections and one (1) H&E-stained tissue section can also be supplied. Sections should be mounted onto either Fisherbrand™ Superfrost™ Excell™ Microscope Slides (cat# 22-037-247); or uncharged slides with no adhesives/treatment (e.g. poly-L-lysine). Each slide should be labeled with the study participant identification number and the timing of the biopsy (e.g. baseline/pre-treatment or on-treatment). This information will be provided by the clinical research team.

(4) FFPE samples should be shipped with cold packs to Theralink Technologies, Inc. at the address shown below. Please provide notification of all incoming shipments to include the name of the courier, tracking number for the shipment, and expected date of delivery to Brian Corgiat via e-mail to: brian.corgiat@theralink.com.

Theralink Technologies, Inc.
15000 West 6th Avenue
Suite 400
Golden, Colorado, 80016
ATTENTION: Brian Corgiat
Telephone number: 720.800.2160

Unused FFPE material will be returned to the sending institution.

Disposition of flash frozen tissue:

Cryogenic vials for flash frozen tissue should be labeled with the study number, study-assigned patient identification number, patient date of birth, and date and time at which the specimen was acquired. This tissue should be immediately placed into the labeled cryogenic vials. Tumor cores should be frozen individually in separate cryovials, as collected, in order to minimize the time between removal and freezing. Vials with tissue should be placed in liquid nitrogen for 2 minutes or longer until frozen solid. If obtained at CUMC, flash frozen tissue should be placed on dry ice and brought by a member of the clinical research team directly to the laboratory of Dr. Gary Schwartz where the material will be stored at -80°C until ready for further analyses. If obtained at a study site other than CUMC, the material should be stored at -80°C and, at the earliest convenience, packed on dry ice and sent by overnight shipping to the laboratory of Dr. Gary Schwartz by Federal Express or UPS with anticipated delivery on a Monday through Friday from 9 am to 4 pm, excluding holidays (procedures should be scheduled if necessary to accommodate shipping on this timeline). Samples can be sent to:

Dr. Parag Patwardahn
Attention: MGCD516 Study
Herbert Irving Comprehensive Cancer Center
Columbia University Medical Center
1130 Saint Nicholas Avenue, ICRC 207
New York, NY 10032

Regardless of the site at which the biopsy is obtained, an e-mail should be sent to ppp2115@cumc.columbia.edu at least 24 hours in advance to alert the laboratory to expect the arrival of a sample. All labeled flash frozen samples will be stored at -80°C in the laboratory of Dr. Gary Schwartz until such time as relevant correlative studies are performed.

Analytic Procedures

RPPA Tissue Study Procedures:

The following procedures and analysis will be performed by Theralink Technologies, Inc.. Sections are analyzed for adequacy by a pathologist and specimens with predominant necrosis or lymphocytic infiltration are not used. Tumor cells and/or stromal cells are microdissected using an Arcturus PixCell IIe (Invitrogen, Life Technologies, Grand Island, NY). Microdissected cells are stored at –80C prior to reverse phase protein microarray printing. Microdissected cells are subject to lysis with a 10% (v/v) solution of Tris(2-carboxyethyl) phosphine (Pierce, Rockford, IL) or a 2.5% solution of 2- mercaptioethanol (Sigma) in Tissue Protein Extraction Reagent (T-PER™, Pierce)/Tris-glycine 2X SDS buffer (Invitrogen). Cell lysates are stored at –80C prior to microarray construction.

Cellular lysates are printed on glass backed nitrocellulose array slides (FAST Slides, Whatman,

Florham Park, NJ) using an Aushon 2470 arrayer (Aushon BioSystems, Burlington, MA) equipped with 350-µm pins. Each array consists of microdissected tumor samples. The before/after pair for each patient are printed on the same array for most specimens. Samples are printed in duplicate in 4-point or 2-point dilution curves. Immunostaining is performed on a Dako Autostainer per manufacturer's instructions (CSA kit, Dako, Carpinteria, CA). Each slide is incubated with a single primary antibody at room temperature for 30 minutes. Reverse phase protein microarray analysis of phosphorylated/total protein endpoints is then conducted for the RTK targets described in section 13.1.1. Antibodies were validated by Western blotting. The negative control slide is incubated with antibody diluent as a substitute for the primary antibody. Secondary antibody is goat anti-rabbit IgG H+L (1:7,500) (Vector Labs, Burlingame, CA) or rabbit antimouse IgG (1:10) (Dako). Subsequent signal detection is amplified via horseradish peroxidase mediated biotinyl tyramide deposition with chromogenic detection per manufacturer's instructions (Dako). Array slides are scanned at 600dpi on a flatbed scanner (UMAX PowerLook) and saved in a tiff format (Adobe Photoshop). Spot intensity is analyzed using ImageQuant ver 5.2 (GE Healthcare). Total protein per microarray spot is determined with a Sypro Ruby protein stain (Invitrogen/Molecular Probes) per manufacturer's directions and imaged with a CCD camera (NovaRay, Alpha Innotech, San Leandro, CA).

Data compilation is performed with proprietary software for background correction and normalization. The mean local area background of each spot is used to assess spot intensity values greater than 2 S.D. above background. Replicate values are averaged. If the CV between replicates is >20%, the spot is flagged and a value of "CV too high" reported. Signal intensity from the secondary antibody alone (negative control) slide is subtracted from the signal intensity of the primary antibody slide. Each patient analyte sample is normalized to the corresponding Beta actin value. Total protein is analyzed as a quality control marker for each microarray spot. Total protein per spot is quantified as a means to assess overall sample and printing quality. Low total protein levels indicate inadequate sample quality or quantity. The results of the analysis will be reported to the study coordinators at CUMC along with the patient's identification number and date of birth and subsequently will be added to the case report form and appropriate files. Unused tissue will be returned by Theralink Technologies, Inc. to the institution which performed the procedure to obtain them.

Western Blot Procedures:

These studies will be performed in the laboratory of Dr. Gary Schwartz at CUMC. We will attempt to confirm RPPA findings by assessing changes in total and phosphorylated MET, IGF1-R and PDGFRb (RTKs identified as important for LPS proliferation in preclinical studies) by Western blot in the pre-treatment and post-treatment tumor biopsy specimens. Assessment of these targets in pre-treatment biopsies will also serve to evaluate whether phosphorylated expression of these targets demonstrated in cell lines is recapitulated in human tissue. We will also use Western blot to validate changes in other RTKs in which significant changes were identified by the RPPA analysis if available tissue permits. Briefly, protein extractions are prepared using a radio immunoprecipitation assay lysis buffer. Protein concentrations are measured using the BioRad protein assay and equal amounts loaded onto gradient gels. Membranes are probed with primary antibodies and bound antibodies are then detected with horseradish peroxidase and visualized by enhanced chemiluminescence reagents. Validated

antibodies for MET, IGF1-R and PDGFRb are obtained from Cell Signaling Technology. Unused tissue will be returned by CUMC to the institution which performed the procedure to obtain them. If the tissue was obtained at CUMC, the tissue will be sent for archival in the Department of Pathology using the patient's name and medical record number.

13.2 Genomic studies

Introduction

Genetic abnormalities are fundamental to cancer initiation and progression. Protein signaling networks, including RTKs, are dysregulated by multiple mechanisms, including changes at the genomic level, where receptor tyrosine kinase proteins and other components of downstream signaling networks are encoded. Point mutations (single nucleotide variations, insertions and deletions), gene amplification and chromosomal rearrangements all act to dysregulate the function of receptor tyrosine kinases.[32] The emerging concept of personalized medicine relies upon the use of targeted therapies directed against alterations in specific genetic targets demonstrated in a patient's tumor. This approach has already successfully entered the clinic, as exemplified by vemurafenib for BRAF mutant melanoma, cetuximab and panitumamb for RAS wild-type colorectal cancer, and crizotinib for ALK-translocated lung cancer, among others.

Sanger sequencing, the initial method of DNA sequencing, was initially developed in the 1970s, and was used in modified form for the Human Genome Project. Next generation sequencing techniques improved upon the low throughput of Sanger methods.[33] The scientific principles of both methodologies have been reviewed elsewhere.[34] Next generation sequencing is currently employed in the NCI's MATCH trial, in which tumor biopsies from 3000 patients will undergo next generation sequencing to identify genetic abnormalities relevant to currently available targeted agents. Patients will then enter a specific phase II trial with assignment based on genetic abnormality and not cancer subtype.

There are several different types of next generation sequencing, including whole genome sequencing, whole exome sequencing and targeted sequencing, as well as the use of next generation sequencing techniques to sequence RNA via cDNA and to study epigenetic changes within DNA. Most recently, so-called 'third generation sequencing' platforms, which remove the need for PCR amplification of genetic material, have been developed.

As discussed, genetic alterations in the RTK targets of MGCD516 have been well described in various cancers, including sarcoma. The use of this agent in patients with defined genetic alterations of these targets is central to the development of this agent as a targeted therapy in the era of personalized medicine. In the ongoing phase 1b study of MGCD516, enrollment criteria require patients to demonstrate genetic alterations in an MGCD516 target. In the present study, all patients are eligible for enrollment, however, we will use next generation sequencing to define relevant genetic alterations in baseline tumor specimens. We will then assess whether the presence of such an alteration predicts clinical efficacy.

Sample Procurement and Handling

This correlative study will be limited to liposarcoma patients and all such patients (including stage II if open to liposarcoma) will undergo the testing described herein. A custom targeted next-generation sequencing platform made available by ResearchDx Inc. will be employed in this clinical trial.

The clinical research team at the institution enrolling the patient onto this clinical trial will identify the date of the patient's most recent tumor biopsy and the institution at which that biopsy took place. If a patient underwent a new tumor biopsy for the purposes of this study (as described above for the proteomics section), FFPE tissue obtained from that procedure should be used for the genomic studies whenever possible, although RPPA studies will be prioritized. At the direction of the investigators, a request will be made by the clinical research team to the pathology department holding the relevant materials for a tumor block measuring at least $5mm^3$ (5 x 1 x 1 mm) or 20 unstained slides (each at least 20 mm^2 and 5 μm thickness; serial sections if possible). Samples should contain >20% tumor cellularity and 80% nucleated content. In addition, one H&E stained slide should also be obtained whenever possible. Slides will be labeled with the study number, study-assigned patient identification number, patient date of birth and date on which the specimen was initially acquired. Samples will then be packaged into the ResearchDx specific mailing kit which will be provided to all participating institutions and which contains further instructions for packing and labeling the samples. The kit will be mailed overnight by UPS or Federal Express at ambient temperature to:

ResearchDx
Attention: MGCD516 Study
5 Mason Street
Irvine, CA 92618

Analytic Procedures

The following procedures will be performed by ResearchDx. Genomic DNA is extracted from FFPE tissue, subjected to library preparation, followed by target enrichment via hybridization capture. Sequencing of uniquely indexed target enrichment libraries is performed using an Illumina MiSeq instrument, and bioinformatics analysis is performed using an assay specific pipeline. This assay was specifically developed and optimized to enrich specific portions of MET, AXL, EGFR, KRAS, ALK, BRAF, ROS, RET, NTRK1/2/3, DDR2, CBL, KIT, PDGFRa and KDR genes using Agilent biotinylated RNA oligomer libraries. The genes and alterations assayed are listed in the table below. Only variants with an allele frequency of greater than 5% are reported. The assay has a requirement for minimal 200x coverage to call variant at allele frequency less than 10%. For regions covered at a read depth of 100x-200x, variants must be present at greater than 10% allele frequency; although higher allele frequency variants in regions of reduced coverage (50-100x) may be reported as the discretion of the laboratory director. This assay only reports specific variants, and genomic alterations other than the below mentioned variants may be present. Unused material will be returned to the institution which initially obtained the tissue. Results will be reported to the clinical research coordinator using only the study assigned patient identification number as an identifier.

Appendix: Genes and Alterations Assayed	
Gene	**Alteration**
*MET**	Point mutations and Ins/Del: V1088E, V1088R, V1110L, H1112L, H1112Y, H1112R, H1124D, M1149T, T1191I, V1206L, L1213V, D1246H, V1238I, Y1248C, Y1248H, Y1248D, Y1253D, Y1253H, M1268T, A1269T, R988C, P1009S, Y1003F, Y1003N, Y1003 frameshift_del. K1193_frame_shift_del, Q1029_G1105del, G1087splice, W911splice p.982_1028del47, intronic or splice site alteration surrounding exon 14 of MET including but not limited to point mutations, insertions, or deletions involving codon 2888 and 3028 splice sites
	Gene amplification: (Greater or equal than 7 copies)
	Chromosomal rearrangements including but not limited to KIF5B-MET, TPR-MET, or MET-CAPZA2 (or alternative)
AXL	Chromosomal rearrangements including but not limited to MBIP-AXL (or alternative) Gene amplification: (Greater or equal than 8 copies)
KRAS	Point mutations involving codon 12, 13, 61
EGFR	Point mutations and Ins/Del: L858R, T790M, G719A/D/S, S768I, L861Q/R, Exon 20ins, Exon 19del
ALK	Rearrangements including but not limited to EML4-ALK
BRAF	Point mutations: V600E, V600D, V600K, V600R, G464V, G466E, G466E, G466A, G469V, G469L, G469R, G469A, N581S, N581T, D594N, D594H, D594G
ROS	Chromosomal rearrangements including but not limited to CD74-ROS, EZR-ROS, SDC4-ROS, SLC34A2-ROS, TPM3-ROS
RET	Chromosomal rearrangements including but not limited to KIF5B-RET or CCDC6
NTRK1	Chromosomal rearrangements including but not limited to MPRIP-NTRK1, CD74-NTRK1, TPM3-NTRK1, TFG-NTRK1
NTRK2	Point mutations: R715G, M713I, A734C
NTRK3	Chromosomal rearrangements including but not limited to ETV6-NTRK3.
	Point mutations: L662M, A664S, H677Y, A731P, Y752P
DDR2	Point mutations: L63V, L239R, E625K, I638F, G774E/V
CBL	Mutations including nonsense and frameshift mutations or annotated missense mutations predicted to result in loss of protein function.
KIT	Gene amplification: (Greater or equal to 6 copies)
PDGFRA	Gene amplification: (Greater or equal to 6 copies)

14. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 12.2.

14.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based

and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

14.2 Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

14.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

14.4 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted

periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

14.5 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those

regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

14.6 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14.7 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

14.8 Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study. If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies); Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for

at least seven years, per CUMC and NYP policy which is based on state law.

15. STATISTICAL CONSIDERATIONS

15.1 Study Design/Endpoints

This is a phase II, single arm, open label, Simon optimal 2 stage study. The primary endpoint is the progression free rate (PFR), at 12 weeks. This corresponds to the number of patients who are alive and without evidence of disease progression at 12 weeks out of all evaluable patients. Evidence of disease progression is defined according to RECIST criteria as established in section 12.

This endpoint has been employed in numerous phase II clinical trials in sarcoma. The European Organization for Research and Treatment of Cancer (EORTC) - Soft Tissue and Bone Sarcoma Group conducted a comprehensive retrospective analysis of clinical trial data to determine outcomes in patients with advanced sarcoma to establish PFR as an endpoint in phase II studies[35]. This study established historical controls for active and inactive agents in the second line setting. On the basis of this EORTC study, PFR greater than 40% at 12 weeks was associated with an active agent and was considered promising for second line therapy, whereas PFR less than 20% at 12 weeks was associated with an inactive agent and was considered not promising.

These benchmarks have been used in numerous ongoing and completed phase II studies for targeted agents in sarcoma, including the phase II study of pazopanib, the only targeted therapy approved for a broad range of sarcoma subtypes. In that phase II study, 140 patients with advanced intermediate or high grade sarcoma were enrolled into four strata (leiomyosarcoma, adipocytic sarcoma, synovial sarcoma and other sarcomas) and a Simon two-stage design was used[36]. A favorable PFR was found in each subtype except for adipogenic sarcomas. In the adipogenic arm, PFR at 12 weeks was 26% and enrollment was closed in the first stage. However, PFR in the leiomyosarcoma, synovial and other cohorts was 44%, 49% and 39%, respectively. On the basis of this phase II study, a randomized double-blind phase III study was conducted with this agent in patients with non-adipogenic sarcomas previously treated with chemotherapy as compared placebo[37]. An improvement in progression free survival was demonstrated, and the drug subsequently received regulatory approval. Numerous other phase II studies using these endpoints have been conducted, including a phase II study of the CDK4 inhibitor palbociclib[38].This study will use PFR at 12 weeks as the primary endpoint.

We will use a Simon optimal 2-stage design. The study will enroll 13 liposarcoma patients in the first stage. If 3 or more patients meet the PFR endpoint in the first stage, the study will enroll an additional 16 patients to achieve a total of 29 liposarcoma patients. If a total of 9 or more such patients demonstrate the PFR endpoint, the agent will be considered promising in liposarcoma. This design provides for a type 1 error of 0.10 and type 2 error of 0.14. The study design has a power of 85% to detect a difference between PFS of 20% versus 40% at 12 weeks.

If the study does not meet its endpoint in liposarcoma patients during stage I of the Simon 2-

stage design, an additional 16 patients will be enrolled composed of 4 each of MPNST, synovial sarcoma, alveolar rhabdomyosarcoma and alveolar soft part sarcoma, to evaluate for potential signs of efficacy in those subtypes as part of an exploratory cohort which may inform the design of future studies.

15.2 Size/Accrual Rate

The sample size is 29 patients. We may enroll up to an additional 2 patients to account for patients declared non-evaluable and patients failing to initiate the first cycle of treatment. The planned accrual rate across both sites is 2-3 patients per month. Therefore, accrual is expected to be complete in approximately 10 to 15 months. Assuming patients are permitted to continue treatment for up to 1 year (12 months) and allowing 6 months for quality assurance, the anticipated duration of the study is approximately 28 to 33 months.

15.3 Stratification Factors

There are no prespecified stratification factors for the primary endpoint.

15.4 Analysis of Secondary Endpoints

Adverse event rates: Adverse events will be recorded at each clinical visit and will be categorized according to NCI CTCAE version 4.0. Adverse event rates will be reported as counts and percentages per adverse event basis by grade.

Overall survival and progression free survival: Overall survival is defined as the time from the date of first treatment with study drug to the time of death from any cause or last follow-up if alive. Progression free survival is defined as the time from first treatment with the study drug to the earliest of either disease progression or death from any cause. Patients who are alive and progression free will be censored at the time of their last follow-up. The Kaplan-Meir method will be used to evaluate all time to event endpoints[39]. Median overall survival and median progression free survival will be reported with 95% confidence intervals.

Response rate: Patient responses will be evaluated according to RECIST version 1.1 as described in section 12. The response rate is defined as the number of patients having a best objective tumor status of complete response or partial response lasting at least four weeks divided by the number of evaluable patients. The response rate will be reported with 95% confidence intervals.

15.5 Analysis of Correlative Science Endpoints

The relevant background, objectives and methodologies for the correlative studies are described in section 13, and statistical considerations relevant to these endpoints are considered here.

15.5.1 Proteomic studies

We will compare changes in the levels of specific total and phosphorylated proteins from

baseline tumor samples to samples obtained during cycle 1 week 2 of treatment with the study agent in a subset of 10 liposarcoma patients. This endpoint is analyzed with exploratory intent given the limited sample size, as we expect to obtain tumor tissue from only approximately 10 patients enrolled in the study. Spot intensity data from the RPPA platform are normalized prior to reporting. The RPPA technology is described in detail in section 13. If the data are normally distributed, a paired t-test will be employed to evaluate whether differences between the baseline and on-treatment spot intensity differ from zero for each protein studied. If the data are not normally distributed, the Wilcoxon-signed rank test will be used.

15.5.2 Genomic studies

We will conduct next generation sequencing in all baseline tumor tissue from all liposarcoma patients (when sufficient material exists) to assess for a set of predefined genetic alterations in known targets of MGCD516. The genetic status of the tumor will then be considered on a binary basis; that is, a patient tumor specimen either has or does not have one of the predefined genetic alterations. We will then assess for a relationship between the presence of a genetic alteration with clinical outcomes. For tumor response, the two groups will be compared using Fisher's exact test given the small sample sizes. Progression free and overall survival will be compared between the two groups by a log-rank test.

15.6 Reporting and Exclusions

15.6.1 Evaluation of toxicity

The safety population will consist of all patients who received at least one dose of study drug.

15.6.2 Evaluation of response

All patients included in the study who receive at least one treatment with the study drug will be assessed for response to treatment, even if there are major protocol deviations or if they are ultimately deemed ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death from other cause, or 9) unknown (not assessable or insufficient data).

All of the patients who met the eligibility criteria, with the exception of those who received no study medication, will be included in the main analysis of the response rate. Patients in response categories 4-9 are considered to have a treatment failure. An incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

15.6.3 Reporting of endpoints if study proceeds to exploratory cohort

If the study fails to meet the stage I endpoint in liposarcoma and proceeds to enroll the exploratory cohort, the primary endpoint (progression free rate at 12 weeks) and secondary efficacy endpoints (overall survival, progression free survival, response rate) will be reported separately for the liposarcoma population and the exploratory cohort population. The individual

best response of the patients in the exploratory cohort will be reported individually. The adverse event data will be reported in aggregate for the entire study population.

16. PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

17. STUDY FINANCES

17.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy.

17.2 Subject Stipends or Payments

No stipends or payments will be given to subjects.

18. PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

19. GUIDELINES FOR AFFILIATE INSTITUTIONS IN MULTICENTER STUDIES

19.1 Multi-site Communication

The CPDM Office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Office will coordinate regularly scheduled conference calls with affiliate sites.

The following issues will be discussed, as appropriate:

- Enrollment information
- Cohort updates (e.g., DLTs)
- Adverse events (e.g., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

19.2 New Protocol Distribution, IRB Submission, Modifications, Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

19.3 Regulatory Documents

Prior to Site Initiation, the Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- CV of PI, Co-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Co-I's (current copy)
- Human subjects training certificates for PI and Co-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)
- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to AAAQ8661@columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

19.4 Site activation

Columbia University will schedule a site initiation visit once IRB approval has been submitted from the affiliate site.

19.5 Central Registration Procedures - Participant Registration Process

All Affiliate Institutions **must** register subjects with the coordinating center (CUMC) **prior** to any administration of study drug/intervention/local institution registration. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's Multicenter Trials Core and the study email AAAQ8661@columbia.edu. The Multicenter Trials Core will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email, with a request to register the patient "pending eligibility." The title of the email should read, "AAAQ8661Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request, as applicable:
    a. Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
    b. Redacted Signed HIPAA (or institutional equivalent)
    c. MCT CPDM Velos Note to File form

2. The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (CUMC's Multicenter Trials Core) via telephone or email to communicate the following:

a. Notify of pending registration request
b. Confirm method of registration request submission (email or fax)
c. Communicate expected time-line of registration request submission (e.g., same day, next day, within the hour, etc.)

3. To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC Multicenter Trials Core via email at AAAQ8661@columbia.edu:
    a. A signed Affiliate Site Eligibility Checklist (signed by the investigator)
    b. Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
        i. Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
        ii. Copy of pathology and surgical reports
        iii. Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

    c. **Please note**: subject line of email or fax should include the following: "AAAQ8661Complete Subject Registration Request (PHI)".

4. Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC study specific designee will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.

5. Upon receipt of the subject registration notification email, the CUMC study specific designee will forward the notification email (which will include the study specific patient ID) to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.

6. All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration Office

in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

19.6 Protocol Deviation/Subject Waiver Request for Affiliate Sites

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB eligibility deviation approval letter(s)/correspondence should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described. Please note that the HICCC DSMC will no longer be approving deviations to eligibility criteria.

19.7 Guidelines for Affiliate Site Monitoring

On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
    a. The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

Remote MCT Monitoring:

- When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site by site basis.
- Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.
- Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case by case basis.
- The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.
- The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.
- The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:
    a. Informed consent procedures
    b. Eligibility criteria
    c. Protocol specific treatment compliance
    d. Protocol specific toxicity/outcome documentation/compliance
    e. Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
    f. Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc.).
    g. Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
    h. Pharmacy accountability records
    i. Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)
- Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

19.8 Dose Level Determinations

Not applicable.

19.9 Adverse event reporting

Sponsor reporting: It is the responsibility of the study sponsor to notify all affiliate sites, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Serious Adverse Event Reporting: Each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event **immediately** (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Matthew A. Ingham, MD
177 Fort Washington Avenue
Milstein Hospital Building Suite 6GN-435
New York, NY 10032
Telephone: 212-305-7115
Email: AAAQ8661@columbia.edu

Within the following 5 business days, the participating investigator must provide follow-up information on the serious adverse event. 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.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject **continued** or withdrew from study participation or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the sponsor-investigator may urgently require further information from the investigator for reporting to Health Authorities.

Non-Serious Adverse Event Reporting: Non-serious adverse events will be reported to the Columbia University Medical Center Overall Principal Investigator on the toxicity Case Report Forms.

Reporting to the Institutional Review Board (IRB) and the Data and Safety Monitoring Committee: All Unanticipated Problems (UPs) will be reported to the CUMC IRB. SAEs not constituting UPs will reported to the HICCC DSMC. Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP. Copies of each report and documentation of IRB notification and receipt must be included in the regulatory binder. Expected or unexpected AEs must be reported at the time of continuing review of a protocol.

Guidelines for Processing IND Safety Reports: The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Principal Investigator will review all applicable IND Safety Reports and has the responsibly for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

Reporting to Hospital Risk Management: Affiliate Site investigators will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

19.10 Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.

If the results of this research project are published or presented at a scientific or medical meeting,

the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

19.11 Data Reporting Plan

Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

19.12 Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

19.13 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).
Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.
In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

20. APPENDICES

20.1 Appendix 1: Supplementary List of Potential Drug Interactions

The following information was obtained by from the US Food and Drug Administration *Drug Development and Drug Interactions* website[40].

20.1.1 Sensitive substrates or narrow therapeutic index for CYP 2C8, 2D6 and 3A4

These agents should be used with caution.

Relevant CYP	Sensitive substrates	Substrates with narrow therapeutic range
CYP2B6	Bupropion, efavirenz	None known.
CYP2C8	Repaglinide	Paclitaxel
CYP3A	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine

20.1.2 Strong inducers or inhibitors for CYP 2B6, 2D6 and 3A4

These agents should be used with caution.

Relevant CYP	**Strong Inducers** *≥ 80% decrease in AUC*	**Strong Inhibitors** *≥ 5-fold increase in AUC* *or > 80% decrease in CL*
CYP2B6	None known.	None known.
CYP3A	Avasimibecarbamazepine, phenytoin, rifampin, St. John's wort	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir,telithromycin, voriconazole
CYP2D6	None known	Bupropion, fluoxetine, paroxetine, quinidine

20.1.3 Substrates of BCRP

These agents should not be used by study participants.

Imatinib	Mitoxantrone
Irinotecan	Rosuvastatin
Lapatinib	Sulfusalazine
Methotrexate	Topotecan

20.1.4 Substrates of P-glycoprotein

These agents should not be used by study participants.

Aliskiren	Nilotinib
Ambrisentan	Posaconazole
Colchicine	Ranolazine
Dabigatran	Saxagliptin
Digoxin	Sirolimus
Everolimus	Sitagliptin
Fexofenedine	Talinolol
Imatinib	Tolvaptan
Lapatanib	Topotecan
Maraviroc	

20.1.5 Common medications which prolong the QTc interval with risk of Torsades

These agents should not be used by study participants.

Amiodarone	Dronaderone	Pentamidine
Anagrelide	Droperidol	Pimozide
Arsenic trioxide	Erythromycin	Procainamide
Azithromycin	Escitalopram	Quinidine
Chloroquine	Flecainide	Sevoflurane
Chlorpromazine	Halofantrine	Sotalol
Citalopram	Haloperidol	Thioridazine
Clarithromycin	Ibutilide	Vandatenib
Cocaine	Methadone	
Disopyramide	Moxifloxacin	
Dofetilide	Ondansetron (high doses, e.g. single dose of 32 mg IV or above)	

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