NCT01817751

Phase II Study of Sorafenib, Valproic Acid, and Sildenafil in the Treatment of Recurrent High Grade Glioma

04/22/2021

Virginia Commonwealth University Massey Cancer Center

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MCC Protocol #: MCC-14816 (CTC-11-011)

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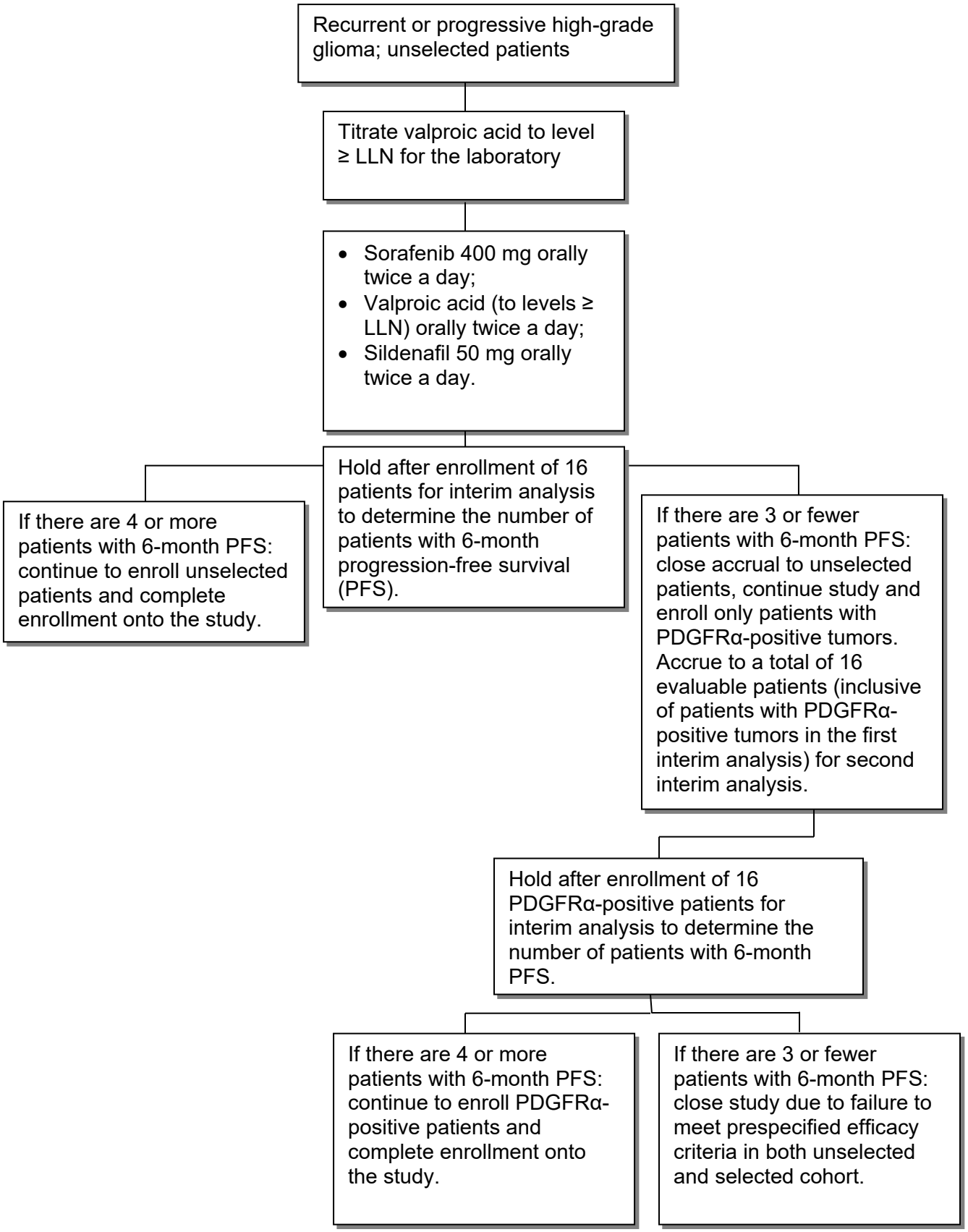
Version #: 12

Version Date: 04/22/2021

SCHEMA


Recurrent or progressive high-grade glioma; unselected patients
Titrate valproic acid to level ≥ LLN for the laboratory
• Sorafenib 400 mg orally twice a day;
• Valproic acid (to levels ≥ LLN) orally twice a day;
• Sildenafil 50 mg orally twice a day.
Hold after enrollment of 16 patients for interim analysis to determine the number of patients with 6-month progression-free survival (PFS).
If there are 4 or more patients with 6-month PFS: continue to enroll unselected patients and complete enrollment onto the study.
If there are 3 or fewer patients with 6-month PFS: close accrual to unselected patients, continue study and enroll only patients with PDGFRα-positive tumors. Accrue to a total of 16 evaluable patients (inclusive of patients with PDGFRα-positive tumors in the first interim analysis) for second interim analysis.
Hold after enrollment of 16 PDGFRα-positive patients for interim analysis to determine the number of patients with 6-month PFS.
If there are 4 or more patients with 6-month PFS: continue to enroll PDGFRα-positive patients and complete enrollment onto the study.
If there are 3 or fewer patients with 6-month PFS: close study due to failure to meet prespecified efficacy criteria in both unselected and selected cohort.

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LIST OF ABBREVIATIONS

ABC	ATP-binding cassette
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BBB	Blood brain barrier
BP	Blood pressure
CBC	Complete blood count
cGMP	Cyclic guanosine monophosphate
CrCL	Creatinine clearance
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTRL	Clinical and Translational Research Laboratory
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EIAED	Enzyme-inducing antiepileptic drug
GBM	Glioblastoma
HDAC	Histone deacetylase
Hgb	Hemoglobin
IHC	Immunohistochemistry
IRB	Institutional Review Board
LLN	Lower limit of normal
MCC	Massey Cancer Center
NO	Nitric oxide
PDE5	Phosphodiesterase type 5
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
PI3	Phosphoinositide 3
PRMC	Protocol Review and Monitoring Committee
RANO	Response Assessment in Neuro-Oncology
SAE	Serious adverse event
UP	Unanticipated problem
VCU	Virginia Commonwealth University
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell count
WNL	Within normal limits

1 BACKGROUND

1.1 Recurrent or Progressive High-Grade Glioma

High-grade gliomas are the most common malignant primary brain tumors in adults (2) and are associated with poor prognosis. Despite optimal therapy, nearly all high-grade gliomas eventually recur. The median survival following recurrence is only 25 to 30 weeks for World Health Organization (WHO) grade IV gliomas and 39 to 47 weeks for WHO grade III gliomas (3, 4). GBMs account for approximately 60% to 70% of high-grade gliomas. Anaplastic astrocytomas comprise 10% to 15%. Anaplastic oligodendrogliomas and anaplastic oligoastrocytomas combined represent 10% of high-grade gliomas. Less common tumors such as anaplastic ependymomas and anaplastic gangliogliomas make up the rest (5).

Many targeted agents against these aberrant pathways or affecting glioma stem cell growth are under investigation in recurrent high-grade glioma. Bevacizumab (Avastin; Genentech, South San Francisco, CA), a monoclonal antibody against VEGF, has been studied extensively in this patient population. In a randomized, multicenter, noncomparative phase 2 trial, the estimated 6-month progression-free survival (PFS) rates for patients with recurrent GBM were 42.6% for bevacizumab alone and 50.3% for bevacizumab plus irinotecan (6). Additional therapies are urgently needed.

1.2 Sorafenib

Sorafenib is a multi-targeted protein kinase inhibitor that was originally developed as an inhibitor of RAF-1, a component of the ERK1/2 pathway. Sorafenib was subsequently shown to inhibit multiple other kinases, including class III tyrosine kinase receptors such as platelet-derived growth factor receptors (PDGFRs), vascular endothelial growth factor receptors (VEGFRs), c-Kit, and FLT3. VCU investigator Dr Paul Dent and collaborators have shown *in vitro* that sorafenib, through its effects on the PDGFRs, can activate Src non-receptor tyrosine kinases, and that this effect plays a role in the activation of death receptors resulting in tumor cell death (7, 8). Lethality of sorafenib in cancer cells is enhanced by concomitant histone deacetylase (HDAC) inhibitor exposure (9, 10). Cell death is through the extrinsic pathway of apoptosis.

In the USA, sorafenib is approved for the treatment of differentiated thyroid carcinoma refractory to radioactive iodine treatment, and renal cell and hepatocellular carcinomas.

Ongoing studies in GBM have investigated sorafenib as a single agent and in combination with mTOR inhibitors, epidermal growth factor receptor (EGFR) inhibitors, and bevacizumab. To date, there are no studies combining sorafenib with HDAC inhibitors in high-grade glioma.

1.3 Valproic Acid

Valproic acid (sodium valproate, valproate) is an anti-seizure medication in common medical use, and is referred to as a non-enzyme-inducing antiepileptic drug (non-EIAED). It is frequently used in chemotherapy regimens due to the fact that it does not modulate the cytochrome p450 system; thus, valproic acid does not have many of the drug-drug interactions with standard chemotherapy agents that are common for other antiepileptic drugs. It has subsequently been shown that valproic acid also acts as a HDAC inhibitor

(11). Valproic acid has been demonstrated at clinically relevant concentrations to inhibit class I (HDAC 1, 2, and 3, along with HDAC 8) and class II, subclass I HDACs (HDAC 4,5, and 7) (11).

HDAC inhibitors are a class of drugs that inhibit the enzymes that deacetylate histones (12). By regulating histone acetylation, chromatin condensation is changed and the levels of transcription may be altered. Many other proteins, including those that are cytosolic, are also acetylated and it is probable that the actions of HDAC inhibitors involve both the regulation of gene expression (eg, FAS-ligand), as well as regulating acetylation of other cytosolic proteins (eg, HSP90) (13). In previously published work in GI tumor cells by Dent and colleagues, HDAC inhibitors were shown to increase the levels of FAS-ligand, as well as its receptor CD95, both of which played a role in HDAC inhibitor toxicity (7, 8). His group has more recently demonstrated that knockdown of CD95 protected CNS tumor cells from the combination of sorafenib and valproic acid (14).

Valproic acid in combination with temozolomide and radiotherapy is currently under investigation in the treatment of newly diagnosed GBM. There are over 10 studies, ongoing or recently completed, that have evaluated HDAC inhibitors in the treatment of CNS tumors, none of which are combined with sorafenib.

1.4 Sildenafil

Sildenafil is FDA approved for the treatment of both erectile dysfunction and pulmonary hypertension, and has been administered to men, women, and children on a chronic daily basis.

Intracellular cyclic guanosine monophosphate (cGMP) levels reflect the balance of synthesis by guanylate cyclases and degradation by phosphodiesterases. Nitric oxide (NO) activates guanylate cyclase in diverse tissues including vasculature, and cGMP is the second messenger that induces smooth muscle relaxation and vasodilation. Sildenafil increases intracellular cGMP and induces vasodilation. This activity is generally attributed to selective inhibition of cGMP-specific phosphodiesterase type 5 (PDE5). Sildenafil and PDE5 inhibitors may also have other functions that relate to anticancer therapy, specifically relating to blood brain barrier (BBB) interactions and drug efflux mechanisms. PDE5 inhibitors have been shown to increase chemotherapy delivery to brain tumors in animal models, through increased tumor cGMP levels (15). ATP-binding cassette (ABC) proteins transport various molecules across extra- and intracellular membranes. Sildenafil has also been shown to inhibit the ABCB1 and ABCG2 drug efflux pumps, and reverse ABCB1 and ABCG2 mediated chemotherapeutic drug resistance (16). The ABCG2 transporter has recently been shown to be the dominant transporter that limits transport of sorafenib into the brain (17). This is clinically relevant as GBM is considered to be a diffuse disease, with many areas of tumor residing in areas of the brain with an intact BBB. Inhibition of the ABCG2 transporter with sildenafil may increase sorafenib drug concentrations in the brain, improving sorafenib anti-tumor efficacy.

To date, there are no CNS tumor studies utilizing drug efflux pump modulators, like sildenafil, in conjunction with sorafenib.

1.5 Sorafenib + Valproic Acid Preclinical Data

Dent and colleagues have tested the combination of sorafenib and HDAC inhibitors in multiple GBM isolates. These studies have included: GBM cells expressing mutant active forms of the EGFR (GBM6, EGFR vIII; GBM12, mutant active full-length EGFR), GBM cells lacking PTEN function (GBM14), GBM cells expressing a mutant active phosphoinositide 3 (PI3)-kinase and PDGFRα (GBM5), or GBM cells with low levels of growth factor receptors (GBM15). There appear to be differences in drug combination sensitivity based on the molecular phenotype of the GBM cell line. Sorafenib toxicity was enhanced by valproate in the GBM6 EGFR mutant variant III cells in a dose-dependent fashion (Figure 1). This mutation in EGFR leads to a truncated EGFR that is constitutively active, but does not bind ligand. GBM15 and GBM14 were both sensitive to the drug combination, similar to GBM6 (data not shown).

In the following figures, valproic acid (VAL) was the HDAC inhibitor used in combination with sorafenib (SOR).

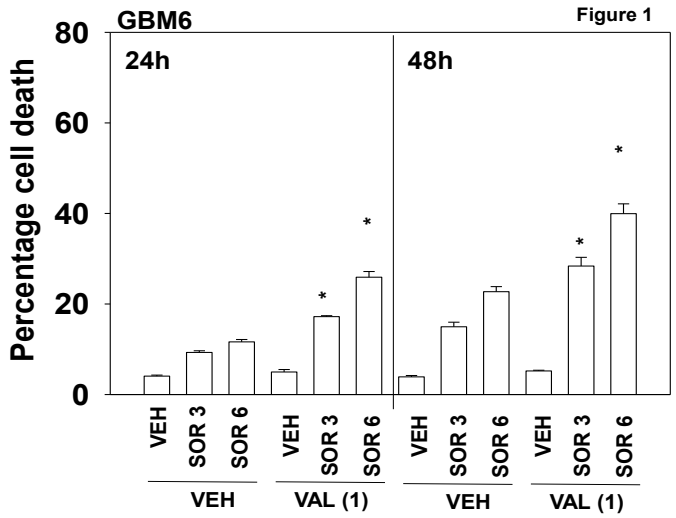

Figure 1. GBM6 cells were treated with vehicle or sodium valproate (1 mM). Thirty minutes later cells were treated with vehicle or sorafenib (3 μM; 6 μM). Cells were isolated 24 h and 48 h later. Viability was determined by trypan blue exclusion (n=3, +/- SEM) * $p<0.05$ greater than corresponding vehicle-control treated cells.

GBM12 full-length EGFR mutant cells appear to be more resistant to the drug combination than GBM6 truncated EGFR mutant cells (Figure 2).

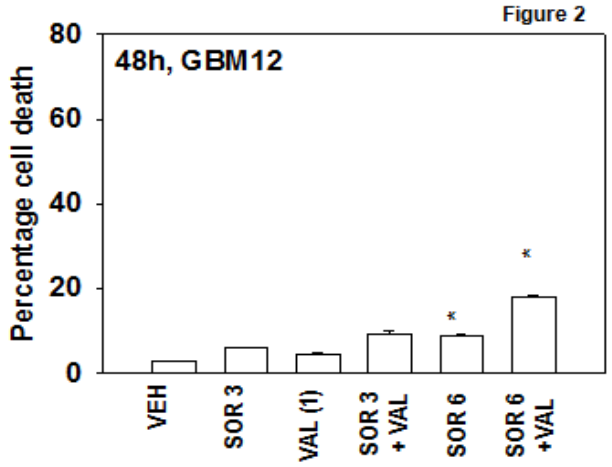

Figure 2. GBM12 cells were treated with vehicle or sodium valproate (1 mM). Thirty minutes later cells were treated with vehicle or sorafenib (3 μM; 6 μM). Cells were isolated 48 h later. Viability was determined by trypan blue exclusion (n=3, +/- SEM) * p<0.05 greater than corresponding vehicle control treated cells.

The cells that were clearly most sensitive to the sorafenib and valproic acid drug combination were GBM5 cells; cells that express one of the growth factor receptor targets of sorafenib, PDGFRα (Figure 3).

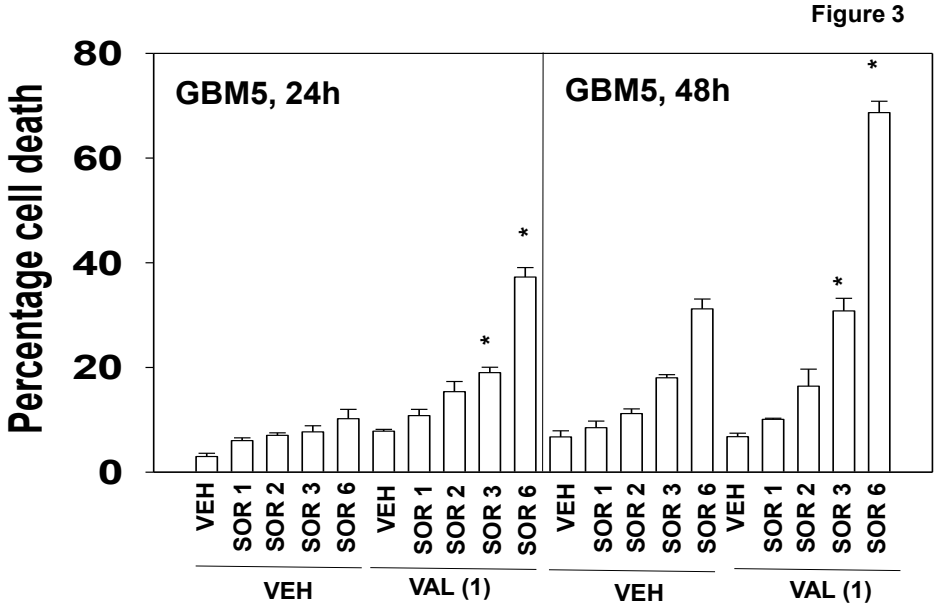

Figure 3. GBM5 cells were treated with vehicle or sodium valproate (1 mM). Thirty minutes later cells were treated with vehicle or sorafenib (1, 2, 3, or 6 μM). Cells were isolated 24 and 48 h later. Viability was determined by trypan blue exclusion (n = 3, +/- SEM) * p < 0.05 greater than corresponding vehicle-control treated cells.

Collectively, this data suggests that the combination of sorafenib and valproic acid is worth investigating in GBM. It appears from the preclinical data that different molecular phenotypes may have different sensitivities to the drug combination, and this will be investigated during the study.

1.6 Rationale

Promising single agent *in vitro* activities and potentially complementary mechanisms of action suggest that the combination of sorafenib, valproic acid, and sildenafil may have therapeutic potential for the treatment of high-grade glioma in the clinic. The combination of sorafenib and valproic acid is predicated on the basis that sorafenib activity is enhanced by HDAC inhibition. The addition of sildenafil is based on its ability to block ABCB1 and ABCG2 drug efflux pumps. As the ABCG2 transporter is the primary transporter involved in the efflux of sorafenib at the BBB, blocking its action is predicted to increase the concentration of sorafenib in the brain.

1.7 Clinical Considerations

One dose level of sorafenib will be tested in this phase 2 study. Sorafenib will be dosed at the FDA approved dose of 400 mg orally twice daily, which is well established as the maximum tolerated dose for continuous dosing. This dose of sorafenib has been tested in recurrent GBM in 5 separate phase 2 studies in combination with temozolomide (18, 19), temsirolimus (20), erlotinib (21), and bevacizumab (22).

In the study by Reardon et al (18), 12 patients were taking CYP3A EIAEDs, 10 patients were taking non-EIAEDs, and 10 patients were not taking any medication to prevent seizures (valproic acid is a non-EIAED). Overall, 4 patients (13%) required dose modification or discontinuation of sorafenib for grade 3 or 4 elevation of amylase/lipase, and 3 patients (9%) required dose modification or discontinuation of sorafenib for grade 3 PPE. Only 2 of the 4 patients with elevated amylase/lipase were symptomatic and in 1 of those 2 patients, underlying gallstones were the likely etiology. Of note, 5 out of 10 patients on the non-EIAED arm who underwent pharmacokinetic sampling required sorafenib dose interruption or modification during cycle 1 of therapy. For patients not on EIAEDs, day-28 sorafenib AUC 0-24 was significantly higher compared to day 1. This increase may also have been mildly augmented by the discontinuation of dexamethasone (a mild CYP3A inducer) in 3 patients.

In the study by Zustovich et al (19), all patients (n=43) received oxcarbazepine, a hepatic CYP3A inducer (EIAED). Grade 3-4 toxicity was observed in 4 patients (9%) with PPE, 1 patient (2%) with diarrhea and 1 patient (2%) with lipase elevation. It is possible that if these patients had been taking non-EIAEDs the toxicity ascribed to sorafenib would have been higher.

In the study by Lee et al (20), patients receiving EIAEDs were excluded. In the phase 1 component of the trial, 1/6 (17%) developed grade 3 diarrhea. In the phase 2 component of the trial, 1/19 patients (5%) developed grade 3 lipase elevation and 1/19 patients (5%) experienced grade 3 diarrhea. The frequency of these toxicities is well below the threshold of 35% that is proposed in the current study.

Similarly, in the study by Peereboom et al (21), patients receiving EIAEDs were excluded. Grade 3 or 4 events felt to be possibly, probably or definitely related to sorafenib or erlotinib ranged from 2% (elevated transaminases, PPE, diarrhea) to 7% (elevated lipase) to 9% (fatigue). The elevations of lipase were asymptomatic. The frequency of these toxicities is well below the threshold of 35% that is proposed in the current study. There were no unexpected toxicities.

In the study by Galanis et al (22), 3/19 patients (16%) experienced grade 4 non-hematologic toxicity and a 42% discontinuation rate. Fatigue (which could be ascribed to sorafenib and/or bevacizumab) and hypertension (due to bevacizumab) were the 2 most commonly observed toxicities. Decrease of the starting sorafenib dose from 200 mg twice daily to 200 mg daily resulted in improved treatment tolerance.

Unfortunately, in none of these 5 studies was notable efficacy seen. Partial response rates of 3-12%, 6-month PFS of 0-26% and overall survival of 5.6-9.6 months were reported. It is our hypothesis that the addition of valproic acid with its HDAC activity, coupled with sildenafil with its drug efflux pump inhibitory activity, could synergistically increase the likelihood of GBM tumor cell kill without concomitant unacceptable sorafenib (or valproic acid) toxicity.

Since the accepted and expected rate of grade 3+ toxicities of sorafenib alone is 35%, the safety component in this trial will focus on identifying a measurable increase in that rate of overall toxicities. The safety lead-in component of this study will serve to screen for an increase in early toxicities. The safety stopping rule will permit monitoring of both early and late toxicities, but practically speaking only becomes applicable if early toxicities are deemed not excessive. Note that grade 5 (fatal) toxicity was not seen in any of the 5 studies cited above.

If toxicity is observed that could be ascribed to sorafenib, then the sorafenib dose will be modified according to Section 7. Likewise, if toxicity is observed that could be ascribed to valproic acid, then the valproic acid dose will be modified according to Section 7, which simply follows Good Clinical Practice principles. Total and free serum valproate levels can be obtained on a same-day basis from the clinical laboratory to help guide the investigator to the appropriate dose modification. If toxicity is observed that could be ascribed to sildenafil, then the sildenafil dose will be modified according to Section 7. If sorafenib or valproic acid toxicity is observed, it is important to first modify the dose of sorafenib or valproic acid and maintain the sildenafil dose constant, since reducing the sildenafil dose may result in decreases of tumor tissue levels of both sorafenib and valproic acid, abrogating the therapeutic effect that this phase 2 trial is designed to achieve. If dose modification of sorafenib or valproic acid does not reverse drug toxicity attributable to those agents, then subsequent sildenafil dose reductions may also be needed to accomplish that goal. We believe this is a rational approach to optimize tumor cell kill while minimizing risk to study patients.

The FDA recommended initial dose of valproic acid is 10-15 mg/kg per day in divided doses; for the purposes of this study valproic acid will generally be dosed twice daily, to allow for ease of administration of all 3 agents at the same time. After initiation of therapy at 10-15 mg/kg/day, escalation of the dose over approximately 1 week to ≥ lower limit of normal (LLN) will be performed. Prior research with valproic acid suggests that therapeutic concentrations of valproic acid can inhibit histone deacetylation (11, 23, 24). For patients with a seizure disorder being treated with valproic acid, serum levels should be checked 1 week after the initial dose; therapeutic concentrations are usually in the 50-150 mcg/mL range. For patients who develop neurologic deterioration, valproic acid levels will be checked to make sure that supratherapeutic drug concentrations are not the source of the neurologic deterioration.

It is generally accepted that patients with GBM and seizures should be treated with a non-EIAED to minimize CYP3A-mediated drug interactions and, more specifically, to avoid

inadvertent lowering of cytotoxic drug concentrations in GBM tumor cells. Which non-EIAED to choose is a matter of personal preference for the treating physician; there is no published practice parameter or “standard of care”. That said, there is a growing body of evidence that valproic acid is a logical first choice in this setting 1) because it is an effective AED and 2) because of its HDAC activity. Weller et al (25) showed that GBM patients receiving valproic acid appeared to derive more survival benefit from temozolomide/radiotherapy than patients receiving an EIAED or not receiving any AED. Guthrie et al (26) and Barker et al (27) came to a similar conclusion. Felix et al (28) corroborated this observation in 94 children with a variety of primary CNS tumors. Furthermore, Kerkhof et al (29) demonstrated that valproic acid monotherapy conferred equivalent freedom from seizures (78%) as did levetiracetam (70%) in patients with GBM. Therefore, we do not believe that patients in this trial will be placed at any seizure control disadvantage when treated with valproic acid and, indeed, may benefit from the associated HDAC activity directed against their tumor.

Of note, there is a single case report describing the use of sorafenib plus valproic acid in an infant with a spinal GBM (30). Marked clinical and radiographic improvement was shown, and no side effects of the combination were observed.

Sildenafil will be dosed at 50 mg orally twice daily, at the time of sorafenib dosing. The purpose of twice daily dosing is to have maximal sildenafil concentrations at the time of sorafenib dosing, to maximize inhibition of ABC transport system and to try to maximize increases in sorafenib transport across the BBB. This dosing schedule is less frequent than some dosing schedules used in pulmonary hypertension studies and heart failure studies. One study evaluating pulmonary hypertension in heart failure dosed sildenafil at 50 mg, 3 times a day, for a period of 12 months, and did not report significant toxicities (31).

There are no major overlapping toxicities relating to valproic acid, sorafenib, or sildenafil that suggest that the combination would be subject to higher rates of toxicity. There is a low incidence of diarrhea in patients treated with sorafenib that may be exacerbated with valproic acid; this will be monitored closely. There is an early stopping rule in place should there be unexpected significant toxicities from the combination. It is expected from clinical experience that a fraction of patients will not tolerate full dose sorafenib in the chronic setting, and these patients may continue therapy at reduced dose levels.

One previously published study has evaluated sorafenib in combination with sildenafil (32). This study was a non-cancer study, which treated patients with pulmonary hypertension with sorafenib and prostanoid therapy, half of whom were also on chronic sildenafil. No grade 3 or 4 drug-related toxicities were reported.

Children under the age of 18 will be excluded from study. There are no published reports regarding the safety of sorafenib at the fixed dose of 400 mg orally, twice a day, in the pediatric population, and evaluating the safety of full dose sorafenib in the pediatric population is beyond the scope of the study.

In patients with progressive high-grade glioma, survival time is generally short. Six-month PFS will be used as the primary endpoint in the study. This endpoint has been accepted by the FDA as a reasonable endpoint in recurrent or progressive GBM, and a positive 6-month PFS led to the approval of bevacizumab as second-line therapy in this disease.

1.8 Correlative Studies Background

Molecular profiling has identified various phenotypes of GBM. It has already been shown that the methylation status of the MGMT promoter is an important prognostic factor in predicting survival with alkylating therapy (33). More recently, The Cancer Genome Atlas (TCGA) Network catalogued recurrent genetic abnormalities in GBM, and established the existence of 4 subtypes (proneural, neural, classical, and mesenchymal) (34). Aberrations and gene expression of *EGFR*, *NF1*, and *PDGFRα/IDH1* each define classical, mesenchymal, and proneural, respectively. Gene signatures of normal brain cell types showed a strong relation between subtypes and different neural lineages. Additionally, response to aggressive therapy differs by subtype with greatest benefit in classical and no benefit in proneural (34). Given the differences in sensitivity to the combination of sorafenib and valproic acid in preclinical models, it will be important to characterize patient tumors, as this combination may be effective in one subtype of GBM but ineffective in another. PDGFRα is a target of sorafenib, and expression of this protein may predict drug efficacy. This study will evaluate PDGFRα levels in tumor specimens by immunohistochemistry (IHC), and correlate this sorafenib drug target to response. Consideration will be given to gene expression profiling at the conclusion of the study, based on responses to therapy. This may help to further characterize the patient population to be targeted in a phase 3 study.

1.9 Rationale for Adaptive Design

All patients with recurrent or progressive high-grade glioma will be eligible for the study. Sorafenib is a multikinase inhibitor, with a wide variety of cellular effects. Not enough is known about the *in vivo* mechanisms of action and resistance to the drug to justify initial exclusion of molecular subtypes of high-grade glioma. There will be an interim analysis, however; at which point the decision will be made whether or not to continue with all subtypes of high-grade glioma, based on pre-specified efficacy criteria. If efficacy criteria are not met for the combined group, the study will continue with only patients who have PDGFRα expressing tumors, since PDGFRα is a target of sorafenib and this is the most promising subgroup in preclinical models. A second interim analysis will be performed once enough patients with PDGFRα expressing tumors have been accrued, to determine if the drug combination is worth pursuing in this specific patient population.

2 OBJECTIVES

2.1 Primary Objective

2.1.1 Determine the efficacy of the combination of sorafenib, valproic acid, and sildenafil, in terms of 6-month PFS in high-grade glioma.

2.2 Secondary Objectives

2.2.1 Determine the efficacy of the combination of sorafenib, valproic acid, and sildenafil, in terms of 6-month PFS in high-grade glioma patients who are evaluable for response and who have tumors that express PDGFRα.

2.2.2 Evaluate the overall response rate, based on Response Assessment in Neuro-Oncology (RANO) criteria or Macdonald criteria, to the drug combination in patients

who are evaluable for response (those who express PDGFRα and those who do not).

2.2.3 Evaluate the overall response rate, based on RANO or Macdonald criteria, to the drug combination in PDGFRα expressing tumors in patients who are evaluable for response.

2.2.4 Determine the efficacy of the drug combination, in terms of 12-month survival and median overall survival in patients who are evaluable for response (those who express PDGFRα and those who do not).

2.2.5 Determine the efficacy of the drug combination, in terms of 12-month survival and median overall survival in high-grade glioma patients who are evaluable for response and who have tumors that express PDGFRα.

2.2.6 Evaluate the safety and toxicity of the drug combination.

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3 STUDY DESIGN

3.1 General Description

The study is a single-center, open-label phase 2 study, with an early stopping rule in place for safety. The trial will include patients with recurrent or progressive high-grade glioma. The trial will be conducted in an adaptive design, with a Simon's mini-max 2-stage design (35) incorporating an interim analysis for efficacy. If efficacy endpoints are not reached, the trial focus will be narrowed to include only the subgroup of patients whose tumors express PDGFRα. The trial will continue with this cohort in a second Simon's mini-max 2-stage design, with an additional interim efficacy analysis of this subgroup.

3.2 Primary Endpoint

Proportion of patients evaluable for response, regardless of tumor PDGFR status, with 6-month PFS defined as the time from the first day a patient receives study treatment until time of progression per RANO or Macdonald criteria or death, whichever occurs first.

3.3 Secondary Endpoints

3.3.1 Proportion of patients evaluable for response, with tumors that express PDGFRα, with 6-month PFS defined as the time from the first day a patient receives study treatment until time of progression per RANO or Macdonald criteria or death, whichever occurs first.

3.3.2 Overall response rate (CR+PR), using RANO or Macdonald criteria, in patients evaluable for response regardless of tumor PDGFR status

3.3.3 Overall response rate (CR+PR), using RANO or Macdonald criteria, in patients who are evaluable for response and who have tumors that express PDGFRα.

3.3.4 Proportion of patients evaluable for response, regardless of tumor PDGFR status, who are alive at 12 months after the first day a patient receives study treatment. OS defined as the time from the first day a patient receives study treatment until death by any cause.

3.3.5 Proportion of patients evaluable for response with tumors that express PDGFRα who are alive at 12 months after the first day a patient receives study treatment. OS defined as the time from the first day a patient receives study treatment until death by any cause.

3.3.6 AEs using NCI Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE v4.0).

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4 PATIENT SELECTION

4.1 Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible to participate in the study:

4.1.1 Pathologically confirmed high-grade glioma (WHO grade 3 or 4), with documented CT or MRI progression or recurrence. Biopsy is also an acceptable method of confirming progression. If initial tumor was grade 2 glioma, histological confirmation of high-grade recurrence is required.

- After first interim analysis, if the study proceeds to enrollment of selected patients (only those who have PDGFRα-positive tumors), patients will be pre-registered for PDGFRα analysis and registered to the combination treatment schema only if PDGFRα-positive and all other enrollment criteria are met.

4.1.2 Measurable or evaluable disease by RANO (MRI) or Macdonald (CT) criteria (see Section 10.2).

4.1.3 Fixed or decreasing dose of corticosteroids (or no corticosteroids) for at least 1 week prior to cycle 1 day 1.

4.1.4 Age ≥ 18 years.

4.1.5 At least 12 weeks since the completion of radiation therapy to a total of ≥ 50 Gy.

4.1.6 ECOG performance status of 0, 1, or 2 (Appendix 1).

4.1.7 Clinical laboratory parameters:

- WBC ≥ 3,000/mm^3
- ANC ≥ 1,500/mm^3
- Platelets ≥ 100,000/mm^3
- Hgb ≥ 8.5 g/dL
- AST, ALT ≤ 3 x upper limit of normal (ULN) for the laboratory
- Total bilirubin ≤ 1.5 x ULN for the laboratory(total bilirubin criteria may be waived if a patient has documented Gilbert's disease)
- Creatinine clearance (CrCL) ≥ 30 mL/min as calculated by the standard Cockcroft-Gault equation (Appendix 2)

4.1.8 Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of treatment.

4.1.9 Women of childbearing potential and men must agree to use a medically accepted form of birth control for the duration of study participation and for 2 months following completion of study treatment.

4.1.10 Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

A patient who meets any of the following exclusion criteria is ineligible to participate in the study:

4.2.1 Investigational agent within 4 weeks of first dose of study treatment.

4.2.2 Prior bevacizumab or tyrosine-kinase inhibitor.

4.2.3 History of allergic reactions or intolerance to any of the required agents on the study.

4.2.4 Any condition that would prohibit patient from initiating valproic acid. Current or prior valproic acid treatment is allowed (do not need to be ≥ LLN for laboratory for enrollment). See Section 6.2.7 for details on valproic acid titration prior to initiation of study therapy.

4.2.5 Seizure disorder necessitating the use of EIAEDs. Efforts may be made by the treating physician to change the antiepileptic drug from another agent to valproic acid or non-EIAED prior to excluding the patient from study.

4.2.6 Contraindication to antiangiogenic agents, including:

- Bronchopulmonary hemorrhage/bleeding event ≥ grade 2 (NCI Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) within 4 weeks or less prior to first dose of study drug.
- Any other hemorrhage/bleeding event ≥ grade 3 (CTCAE v4.0) within 4 weeks or less prior to first dose of study treatment.

- Radiological evidence of any intracranial hemorrhage within the 4 weeks or less prior to first dose of study treatment.
- History of significant intratumoral, intracerebral, or subarachnoid hemorrhage.
- Serious non-healing wound, ulcer, or bone fracture.
- Documented bowel perforation within 6 months of the start of study treatment.

4.2.7 Major surgery within 2 weeks of the start of study treatment, or ongoing complications from surgeries performed previously.

4.2.8 Clinically significant cardiac disease, including major cardiac dysfunction, such as uncontrolled angina, clinical congestive heart failure with New York Heart Association (NYHA) class III or higher (Appendix 3), ventricular arrhythmias requiring anti-arrhythmic therapy, recent (within 6 months) myocardial infarction or unstable coronary artery disease.

4.2.9 Systolic blood pressure (BP) > 160 mm Hg or diastolic pressure > 100 mm Hg despite optimal medical management.

4.2.10 History of priapism.

4.2.11 Known history of retinitis pigmentosa.

4.2.12 Known mitochondrial disorder caused by mutations in mitochondrial DNA polymerase γ.

4.2.13 Arterial thromboembolic or embolic events such as myocardial infarction, cerebrovascular accident, including transient ischemic attacks within 6 months prior to first study treatment.

4.2.14 Serious uncontrolled infection > grade 2 (CTCAE v4.0).

4.2.15 Known HIV positivity.

4.2.16 Unable to swallow medication or suspected malabsorption.

4.2.17 Patients on chronic nitrate therapy or alpha-blockers.

4.2.18 Exclude persons who require ongoing administration of STRONG CYP3A4 inhibitors and/or STRONG CYP3A4 inducers and/or STRONG CYP2C9 inhibitors. Examples of clinical inhibitors and clinical inducers for P450-mediated metabolisms and classification of strong, moderate, and weak interactions are available through the FDA website, Table 3-2 and 3-3: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

4.2.19 Women who are pregnant or nursing.

4.2.20 Persistent heart rate (HR) < 50 or > 120 beats per minute (bpm).

4.2.21 QTc > 480 ms (grade 2 or greater) on screening ECG*.

* If baseline QTc on screening ECG meets exclusion criteria on screening assessment:

  - Check potassium and magnesium levels
  - Correct any identified hypokalemia and/or hypomagnesemia and repeat ECG to confirm exclusion of patient due to QTc

- For patients with a HR 60-100 bpm, no manual read of QT is required.

- For patients with baseline HR < 60 or > 100 bpm, manual read of QT by cardiologist is required using Fridericia correction.

4.2.22 Other condition(s) that in the opinion of the investigator might compromise the objectives of the study.

5 STUDY ENTRY AND WITHDRAWAL PROCEDURES

5.1 Registration Procedures

To register a patient, the study team will provide the following to the registrar at VCU Massey Cancer Center [redacted]

- Registration cover sheet
- Completed eligibility checklist
- Signed & dated informed consent form

The registrar will complete the registration process by assigning a study ID number and forwarding the “Confirmation of Registration” form to the registering study team.

No patient may begin study treatment until the Confirmation of Registration assigning a study ID number has been received from the registrar. The registering study team will enter into the OnCore database the patient’s initial enrollment data (demographics, consent, eligibility, on study, treatment assignment) within 24 hours of registration and before treatment begins.

5.2 Study Discontinuation Procedures

5.2.1 A patient may decide to withdraw from study participation at any time.

5.2.2 Patients will be removed from study treatment and enter into the follow-up phase when any of the criteria listed in Section 7.6 “Duration of Therapy” applies.

5.2.3 A patient may be removed from the study follow-up phase and be taken off study for any of the following reasons:

- Investigator determination that discontinuation is in a patient’s best medical interest
- Withdrawal of support of study sponsor

5.2.4 The reason for study removal and the date the patient was removed must be documented in the source documents and the OnCore case report forms (CRFs).

6 TREATMENT PLAN

6.1 Baseline Tests and Procedures

Refer to Section 12, Study Calendar, for the screening tests and procedures that are required prior to treatment and/or registration, and for the timing of these events relative to the start of combination treatment.

6.2 Schedule

The treatment schedule is combined sorafenib, valproic acid, and sildenafil, administered orally, twice daily continuously. A cycle consists of 4 weeks. The first cycle begins once therapy begins with all 3 agents—after, if necessary, titration of valproic acid dosage, described in Section 6.2.7. Titration of valproic acid may occur as a matter of clinical preference, prior to study enrollment.

Study drug therapy is taken on an empty stomach, that is, at least 1 hour before or 2 hours after eating, due to absorption characteristics of sorafenib.

The first 6 patients evaluable for qualifying toxicity assessment will be treated as a safety lead-in; enrollment will be gated (the first 3 evaluable patients must complete 4 weeks of the combination therapy before the next 3 patients start combination treatment on protocol) and patients will undergo weekly evaluations for qualifying toxicities (Section 6.4.2) during the first 4 weeks of combination therapy.

6.2.1 Initiation of sorafenib and sildenafil will not take place until valproic acid levels are ≥ LLN for the laboratory, which generally takes 5-7 days after initiation.

6.2.2 Valproic acid will be administered orally, generally twice daily. The tablets or capsules should be swallowed without chewing to avoid local irritation of the mouth and throat. Patients who experience gastrointestinal irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

6.2.3 If a patient is already on valproic acid and blood levels are ≥ LLN for the laboratory, no further titration is necessary.

6.2.4 If a patient presents for evaluation for this study and are at risk for seizures, the patient may be started on valproic acid.

6.2.5 If a patient is already on non-valproic acid antiepileptic therapy, they may be transitioned to valproic acid, as a matter of clinical preference, prior to enrollment to obtain levels ≥ LLN for the laboratory prior to discontinuing the original antiepileptic therapy.

6.2.6 Patients with disease recurrence require routine maintenance on antiepileptic therapy. If a patient presents for study evaluation before initiation of antiepileptic

medication, patient may start valproic acid titration to ≥ LLN for the laboratory as a matter of clinical care.

6.2.7 Valproic acid titration: Titration to levels ≥ LLN for the laboratory generally takes 5-7 days. The FDA recommends that valproic acid doses start at 10-15 mg/kg/day. If a patient is already on a stable dose of valproic acid, the drug does not need to be titrated unless the dose is less than the LLN.

6.2.8 Sorafenib is dosed at 400 mg orally, twice daily, continuously. Subsequent dose modifications are allowed based on toxicity assessment.

6.2.9 Sildenafil is dosed at 50 mg orally, twice daily, continuously. Subsequent dose modifications are allowed based on toxicity assessment.

6.3 Radiographic Evaluations

6.3.1 MRI of the brain obtained within 3 weeks prior to entry into the protocol can be used as baseline staging evaluation. In the event that MRI scans cannot be performed, contrast-enhanced CT scans can be used. If scans were obtained from another institution, copies should be obtained and maintained in the research files.

6.3.2 A reasonable dose of corticosteroids will be determined on clinical grounds for each patient. An effort will be made to keep the patient on this steroid dose for at least 5 days prior to the next MRI or contrast-enhanced CT scan. If it is not possible to keep the steroid dose constant for 5 days then the MRI scan will be delayed until the dose has been stable for 5 days.

6.4 Toxicity Assessments

6.4.1 Toxicity Grading

Adverse events (AEs) will be characterized and graded according to NCI CTCAE version 4.0. See Section 8.

6.4.2 Qualifying Toxicities for the Safety Lead-In and Safety Stopping Rule

Qualifying toxicities for the safety lead-in are evaluated weekly during the first 4 weeks of combination treatment for each of the first 6 patients deemed evaluable for qualifying toxicity for the safety lead-in (see Section 10.1).

Qualifying toxicities for the safety stopping rule are evaluated regularly during the first 4-week cycle of combination treatment for patients deemed evaluable for the early stopping rule (see Section 10.1).

Qualifying toxicities are defined as any of the following that are possibly, probably, or definitely related to drug therapy:

Any grade ≥ 3 toxicity, except the following:

- nausea, vomiting, or diarrhea in the absence of adequate prophylaxis and/or responsive to medical management
- grade 3 thromboembolic event

- grade 3 hyperglycemia
- grade 3 PPE (hand-foot syndrome)
- fatigue responsive to medical management
- grade 3 hypertension
- electrolyte abnormalities that, once corrected, can be maintained with oral repletion
- grade 3 anemia, platelets, neutrophils, WBC, lymphocytes, febrile neutropenia

6.4.3 See Section 8.5 for AE and qualifying toxicity reporting procedures.

7 DOSE MODIFICATIONS

If the toxicity is not covered in Table 1, Table 2, Table 3, or Table 4, use the following general guidelines:

- Option to modify for grade ≥ 1 toxicity
- Recommendation to consider modification for grade ≥ 2 non-hematologic toxicity, other than PPE (see sorafenib dose-modification guidelines below)
- Requirement to modify for grade ≥ 3 non-hematologic toxicity
- Requirement to modify for grade 4 toxicity

Study treatment modification consists of dose omission and/or schedule adjustment of 1 or more agents as clinically appropriate and as described below. In general, agent(s) should be omitted pending resolution of toxicity to ≤ grade 1 and then resumed at the same or a lower dose or frequency.

Should the occasion arise that one or more of the study agents need to be discontinued due to dose modification requirements, patients may continue on study at investigator discretion, taking single- or dual-agent study drug treatment, with the following exception: if both valproic acid and sorafenib must be permanently stopped, study treatment will be discontinued.

Patients are not required to be removed from study treatment for a qualifying toxicity (Section 6.4.2). Removal from the study treatment for safety reasons may be considered at the treating physician's discretion, based on the severity/type of toxicity.

7.1 Sorafenib

Sorafenib dose reductions (to be followed decrementally in this order):

- 400 mg twice daily
- 400 mg daily
- 200 mg daily
- 200 mg twice daily dosed every other day
- If cannot tolerate lowest sorafenib dose, discontinue sorafenib

If toxicities leading to modification resolve to ≤ grade 1, the sorafenib dose may be escalated in increments of 200 mg per day after cycle 1 but not beyond a patient's enrollment dose.

7.1.1 Sorafenib Dose Modifications

Table 1. Sorafenib Dose Modifications

Toxicity		**Sorafenib Modification**
Cardiac		
Grade ≥2 acute coronary syndrome (myocardial ischemia) or Grade ≥2 myocardial infarction		Discontinue sorafenib permanently.
Heart failure	Grade 3	• Interrupt until ≤ grade 1; upon resumption, decrease by 1 dose level. • If no recovery after 30 day interruption, discontinue sorafenib permanently unless patient is deriving clinical benefit; confer with PI.
	Grade 4	Discontinue sorafenib permanently.
Skin and Subcutaneous Disorders		
Palmar-plantar erythrodysesthesia syndrome (PPE) (hand-foot syndrome)		See Table 2 'Sorafenib Dose Reduction Guidelines for PPE (Hand-Foot Syndrome).'
Grade 2 rash acneiform		At investigator's discretion, consider holding and/or reducing sorafenib to the next lower dose.
Grade 3 or grade 4 rash acneiform		Hold sorafenib. • Re-evaluate at least weekly until resolution to ≤ grade 1 or tolerable grade 2. • Re-start sorafenib at one dose reduction. • If toxicity persists > 14 days, discontinue sorafenib. • Patients with grade 4 acneiform rash related to sorafenib may be taken off sorafenib at investigator's discretion.
Stevens-Johnson syndrome or toxic epidermal necrolysis		Discontinue sorafenib if Stevens-Johnson Syndrome or toxic epidermal necrolysis are suspected.
Gastrointestinal Disorders		
Perforation (esophageal, gastric, colonic, duodenal, ileal, jejunal, rectal, or small intestine)		Discontinue sorafenib permanently.

Investigations	
Grade ≥ 3 ALT increase in the absence of another cause or AST or ALT >3x ULN with bilirubin >2xULN in the absence of another cause; or Grade ≥ 1 Alkaline phosphatase in the absence of known bone pathology with grade ≥ grade 2 bilirubin increase; or any 1 of the following INR ≥ 1.5, ascites and/or encephalopathy in the absence of underlying cirrhosis or other organ failure related to drug-induced liver injury	Discontinue sorafenib permanently.
Lab abnormalities - not clinically significant Note: For clinically significant lab abnormalities follow the dose modification guidelines for “All Other Non-Hematologic Toxicities.”	Continue sorafenib and institute supportive measures. At investigator’s discretion, consider holding and/or reducing sorafenib to the next lower dose.

Grade 3 electrocardiogram QT corrected interval prolonged	See also Section 7.4.8
	Hold sorafenib
	• Check and immediately administer potassium to achieve levels of ≥ 4 and magnesium to levels of ≥ 2.
	• Consider chronic oral supplementation of potassium and/or magnesium.
	• Review with principal investigator prior to patient's next scheduled treatment, considering the following options:
	  ○ STOP sorafenib until QTc recovers to pre-study treatment baseline (grade 1 or less, or ≤ 480ms).
	  ○ When QTc returns to baseline, reinitiate sorafenib cautiously, with additional QTc monitoring at earliest possible follow-up opportunity, but no more than 8 days from reintroduction of sorafenib.
	  ○ If QTc prolongation event felt attributable to sorafenib, reduce sorafenib to the next lower dose.
	• For recurrent QTc grade 3 felt attributable to sorafenib despite dose reduction, consider permanent discontinuation of sorafenib.

Grade 4 electrocardiogram QT corrected interval prolonged	Discontinue sorafenib. Do not restart.
Nervous System Disorders *(potentially reflective of cardio-toxicity)*	
Grade 2 pre-syncope or grade 3 syncope	See also Section 7.4.8 • Obtain ECG for cardiology review/consultation. • Check and immediately administer potassium to achieve level of ≥ 4 and magnesium to level ≥ 2. • If ECG shows new dysrhythmia or QTc ≥ grade 2 (> 480ms), hospitalize for monitoring with Cardiology consultation. • STOP sorafenib until any potassium and magnesium abnormalities are corrected, symptoms resolved and QTc returns to grade 1 or less (≤ 480ms). • Reintroduce sorafenib cautiously, with input from Cardiology and with additional QTc evaluation, either concurrent with reintroduction or at earliest possible follow-up opportunity and no more than 8 days from reintroduction. • If event felt attributable to sorafenib, reduce sorafenib to the next lower dose. • Consider chronic oral supplementation of potassium and/or magnesium. • For recurrent syncope or near-syncope felt attributable to sorafenib, consider permanent discontinuation of sorafenib.
Vascular Disorders	
Hypertension	See Table 3 'Management of Hypertension.'
All Other Non-Hematologic Toxicities	
Grade ≥2 hemorrhage (requiring medical intervention)	Discontinue sorafenib permanently.

Any grade 2 non-hematologic toxicity that is persistent, intolerable, or unresponsive to optimal management	At the treating investigator's discretion, consider holding or continuing treatment at 1 dose reduction.
Grade 3	1st occurrence: • Hold sorafenib until resolution to ≤ grade 2 or baseline. • When resuming sorafenib, decrease the sorafenib dose by one dose reduction. • If toxicity persists >14 days of treatment delay, discontinue sorafenib. No improvement within 7 days; or 2nd or 3rd occurrence: • Hold sorafenib until resolution to ≤ grade 2 or baseline. • When resuming sorafenib, decrease the sorafenib dose by 2 dose reductions. • If toxicity persists >14 days of treatment delay, discontinue sorafenib 4th occurrence: • Hold sorafenib until resolution to ≤ grade 2 or baseline. • When resuming sorafenib, decrease the sorafenib dose by 3 dose reductions. • If toxicity persists >14 days of treatment delay, discontinue sorafenib
Grade 4	Discontinue sorafenib permanently.

7.1.2 Sorafenib Dose Modification Guidelines and Management for PPE (Hand-Foot Syndrome)

Table 2. Sorafenib Dose Reduction Guidelines for PPE

Grade	Occurrence	Action
Grade 1	1st occurrence or recurrence	Continue sorafenib and institute supportive measures for symptomatic relief.*
Grade 2: Moderate and painful skin changes of hands and/or feet such as peeling, blisters, bleeding, hyperkeratosis, erythema, swelling; and/or any such changes that are limiting instrumental activities of daily living (preparing meals, shopping for groceries, using the telephone, managing money, etc).	1st occurrence	Decrease sorafenib dose by one dose level and institute or continue supportive measures for symptomatic relief.* If no improvement within 7 days, see below.
	No improvement within 7 days	Stop sorafenib treatment until toxicity resolves to grade 0-1. When resuming treatment, continue at ongoing dose reduction. Institute or continue supportive measures for symptomatic relief.*
	Recurrence beyond 1st occurrence	Stop sorafenib treatment until toxicity resolves to grade 0-1. When resuming treatment, decrease sorafenib by 1 dose level. Institute or continue supportive measures for symptomatic relief.*
Grade 3: Severe and painful skin changes of the hands and/or feet, such as moist desquamation, ulceration, blistering, bleeding, hyperkeratosis, erythema, swelling; and/or any such severe changes or pain that are limiting self-care activities of daily living (bathing, dressing, feeding self, using toilet, taking medications or becoming bedridden).	1st or 2nd occurrence	Stop sorafenib treatment until toxicity resolves to grade 0-1. When resuming treatment, decrease sorafenib by one dose level. Institute or continue supportive measures for symptomatic relief.*
	3rd occurrence	Discontinue sorafenib treatment.

*See also Section 7.4.7.

7.1.3 Sorafenib Dose Modification Guidelines and Management for Hypertension

The management of hypertension related to sorafenib, including the choice of antihypertensive medication, will be performed according to the treating physician's usual practice.

Every effort should be made to control BP by medical means other than sorafenib dose modification. If necessary, follow the sorafenib dose reduction instructions in Table 3.

Table 3. Management of Hypertension Related to Sorafenib

Grade	Antihypertensive Therapy	Sorafenib Dosing
Grade 1 Prehypertension Systolic BP 120-139 mmHg **or** Diastolic BP 80-89 mmHg	None	• Continue sorafenib • Consider increasing BP monitoring
Grade 2 Asymptomatic and diastolic BP 90-99 mmHg	Treat with the aim to achieve diastolic BP < 90 mmHg • If BP previously WNL, start antihypertensive • If patient is already on antihypertensive medication, increase the dose	Continue sorafenib and increase BP monitoring
Grade 2 Symptomatic or persistent **or** **Grade 2** Symptomatic increase in diastolic BP by > 20 mmHg (diastolic) or > 140/90 mmHg if previously within normal limits **or** **Grade 3** Systolic BP ≥ 160 mmHg **or** Diastolic BP ≥ 100 mmHg **or** More than one antihypertensive medication or indication for more intensive therapy than previously used	Treat with the aim to achieve diastolic BP < 90 mmHg Start antihypertensive medication **and/or** Increase current antihypertensive medication **and/or** Add additional hypertensive medications	• Omit sorafenib until diastolic BP ≤ 90 mmHg, and if symptomatic, until symptoms resolve • When sorafenib is restarted, resume at 1 dose reduction step
Grade 4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per treating physician	Discontinue sorafenib permanently.

* If BP remains controlled for at least one cycle, dose escalation, **up to the enrolled dose level**, is permitted at the investigator's discretion.

7.2 Sildenafil

Sildenafil dose reductions (to be followed decrementally in this order):

- 50 mg twice daily
- 25 mg twice daily
- 25 mg once daily
- If cannot tolerate lowest sildenafil dose, discontinue sildenafil

Sildenafil may be omitted for short periods at the treating physician's discretion, if it is believed that sildenafil is contributing to excess toxicity. If toxicities resolve to ≤ grade 1, the sildenafil dose may be escalated at the treating physician's discretion but not beyond a patient's enrollment dose.

The following toxicities require immediate discontinuation of sildenafil therapy:

- Prolonged erection for more than 4 hours
- Sudden loss of vision in one or both eyes
- Sudden decrease or loss of hearing

7.3 Valproic Acid

If toxicity is observed that is thought to be due to valproic acid then serum valproate levels should be obtained. If supratherapeutic valproate levels are observed (as described in Section 1.7) temporary interruption of valproate may be indicated until toxicity resolves to grade 1 or less. Upon resolution of toxicity, a repeat serum valproate level should be obtained. Resumption of valproic acid at a reduced dose to achieve a lower serum valproate level should be considered. In the setting of hypoalbuminemia, the serum valproate level may be falsely elevated and a free valproate level may be required.

Table 4. Vaproic Acid Dose Modifications

Toxicity	Valproic Acid Modification
General Disorders: Hypothermia	
Lethargy, confusion, coma, significant alterations in major organ systems (cardiovascular and respiratory) may signal hypothermia	Consider holding valproic acid while evaluating serum valproic acid levels. Blood ammonia level may be evaluated at investigator discretion.
Grade 2 or greater hypothermia	Consider discontinuing valproic acid. Discuss with principal investigator.
Investigations: Other – Hyperammonemia	
Symptomatic elevated ammonia level. Ammonia measured only as clinically indicated for clinical findings of unexplained lethargy, vomiting or changes in mental status.	Consider holding valproic acid while measuring serum valproic acid and ammonia levels. Consider evaluation for underlying urea cycle disorder and discontinuing valproic acid for elevated ammonia level. Discuss with principal investigator. If liver toxicity is suspected: • Discontinue valproic acid • Consider supplementation with L-carnitine
Investigations: Hepatotoxicity	
Grade 3 or grade 4 AST or ALT increase	Consider holding valproic acid while under evaluation to rule out hepatic dysfunction. Consider liver ultrasound, hepatology consult, tests of hepatic function (such as bilirubin, INR, GGT, ammonia). Consider supplementation with L-carnitine. If no alternative explanation for transaminitis can be determined (such as viral hepatitis, progressive underlying malignancy), discontinue valproic acid.
Gastrointestinal Disorders	
Abdominal pain, nausea, vomiting and/or anorexia that are not attributable to other causes can signal pancreatitis and require prompt medical evaluation	Consider holding valproic acid while under evaluation and ruling out pancreatitis.
Pancreatitis	Discontinue valproic acid. Note: Elevations in lipase are very common in patients taking sorafenib. A diagnosis of pancreatitis should not be made solely based on abnormal laboratory values.

Valproic acid should be immediately discontinued in the presence of significant hepatic dysfunction, suspected or apparent.

Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or unusual changes in mood or behavior.

Significant bleeding or coagulopathy is an indication for reduction of the dosage or discontinuation of valproic acid.

7.4 General Concomitant Medication and Supportive Care Guidelines

(see also Section 9)

7.4.1 Fluids should be administered as indicated to prevent/treat dehydration. Maintain appropriate electrolyte balance including correction of hypokalemia and hypomagnesemia, and hypophosphatemia, if possible, prior to and during study treatment. In those patients who demonstrate electrolyte abnormalities, oral supplementation should be considered as a standard supportive measure to keep magnesium levels at ≥ LLN for the laboratory, potassium levels at ≥ LLN for the laboratory, and phosphorus levels at or above 2.4 mg/dL.

7.4.2 Clinically significant diarrhea should be managed aggressively to prevent electrolyte abnormalities and dehydration.

7.4.3 Concurrent administration of other anti-neoplastic agents with the study combination regimen is prohibited.

7.4.4 Concurrent administration of organic nitrates or alpha-blockers with the study combination regimen is prohibited.

7.4.5 Cautionary statements about other concurrent medications:

Addition of any STRONG CYP inhibitors and/or inducers per examples on the FDA website (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm) during study participation should prompt treating investigator awareness of possible interactions. Specifically:

- Caution should be observed if sorafenib is to be coadministered with CYP3A4 inducers such as rifampin, rifampicin, St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone (for reference see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm) may increase metabolism of sorafenib, decreasing sorafenib plasma concentrations

- Caution should be observed if sildenafil is to be coadministered with CYP3A4 or CYP2C9 inhibitors (for reference see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)

7.4.6 Caution should be observed if valproic acid is to be coadministered with any of the following: aspirin, carbapenem antibiotics (ertapenem, imipenem, meropenem), rifampin.

7.4.7 PPE (hand-foot syndrome)

Biopsy specimens of patients with PPE secondary to tyrosine kinase inhibition show hyperkeratosis, keratinocyte necrosis, and dermal inflammation. Recommended management strategies for skin toxicities consistent with PPE are summarized in the following sections:

7.4.7.1 PPE Prevention

- Before initiating treatment with sorafenib, check the condition of the patient's hands and feet. Suggest a manicure/pedicure, when indicated. Recommend use of a pumice stone for callus or rough spot removal. During sorafenib treatment, instruct patients to avoid pressure points and items that rub, pinch, or create friction.

- Instruct the patient to apply moisturizing lotions to their hands and feet twice a day throughout treatment.

7.4.7.2 PPE Treatment

- Treatment may begin at the first clinical signs of PPE. At first occurrence, independent of grade, supportive measures should be promptly initiated.

- Tender areas should be protected as follows:

  - Use socks/gloves to cover moisturizing creams
  - Wear well-padded footwear; use insole cushions or inserts.
  - Foot soaks with tepid water and Epson salts.

- Creams may be used as follows:

  - Non-urea based creams may be applied liberally.
  - Keratolytic creams (eg, urea-based creams 10%, salicylic acid 6%) may be used on affected (hyperkeratotic) areas 3 times per day.
  - Alpha hydroxyl acids (AHA)-based creams may be applied liberally 2 times a day. Approximately 5% to 8% provides gentle chemical exfoliation.
  - Topical analgesics (eg, lidocaine 2%) may be used for pain control.
  - Topical corticosteroids like clobetasol 0.05% should be considered for patients with grade 2 or 3 PPE. Systemic steroids should be avoided.

  Use of Celecoxib

  A meta-analysis of PPE prevention strategies concluded that celecoxib, with statistically significant results, was the most promising agent (1). Therefore, celecoxib is recommended to reduce the severity of sorafenib-related PPE as follows:

  - Celecoxib 200 mg once daily should begin at the first clinical signs or symptoms of grade 2 PPE.

  Guidelines for sorafenib dosing modifications are listed in Section 7.

7.4.8 QT Prolongation Considerations

7.4.8.1 ECGs will be evaluated for QTc prolongation prior to next scheduled treatment

7.4.8.2 Any time QTc is evaluated during the course of the study:

- When HR is between 60-100 bpm, no manual read of QT required
- When HR < 60 or > 100 bpm, manual read of QT by cardiologist is required, using Fridericia correction

Any questions or concerns about ECG readings will be reviewed with a cardiologist.

7.4.8.3 To the extent possible, concurrent use of drugs known to cause clinically significant QT prolongation should be avoided. Such drugs may be identified at the Credible Meds website (http://crediblemeds.org/login). The Credible Meds website requires free user registration to view the list of clinically relevant QT prolonging drugs, eg, those known to carry a risk of causing Torsades de Pointes (TdP). QT prolonging drugs to be avoided during this trial are shown in the Credible Meds list of "drugs with known TdP risk."

7.4.8.4 When concurrent use of sorafenib and any drug on the Credible Meds list of "drugs with known TdP risk" cannot be avoided, review QTc prior to concurrent use. If pre-concuurent use QTc is:

- grade 0 (< 450 ms), follow-up QTc evaluation should be done at the next scheduled follow-up visit.
- grade 1 (450-480 ms), follow-up QTc evaluation should be done within 8 days after concurrent use starts.
- grade 2 (481-500 ms), withhold sorafenib until follow-up ECG at next possible opportunity shows QTc grade 1 or less (≤ 480 ms); evaluate QTc within 8 days after reintroduction of sorafenib.

7.4.8.5 Any new onset of dysrhythmia on ECG during study treatment phase will be reviewed and managed with input from cardiology.

7.4.8.6 For any episode of syncope (grade 3) or near syncope (pre-syncope grade 2) or QTc grade 3 or greater (> 500 ms on 2 ECGs), see Section 7.1.1.

7.5 Laboratory Monitoring and Clinical Exam

Patients in the safety lead-in cohort (for qualifying toxicity assessment) will be seen weekly for the first 4 weeks of combination study therapy, then every 2 weeks for the next 4 weeks, and then monthly. Visits for subsequently enrolled patients are required every 2 weeks for the first 8 weeks, then monthly. Assessments to be done at each visit are as shown in the Study Calendar. Serum valproic acid levels will be monitored every 2 weeks, or more frequently as clinically indicated through the end of cycle 2. After cycle 2 they will be checked as clinically indicated. Determination of steroid dose will be made at least

every 2 weeks (weekly in the safety lead-in cohort) and steroid dose may be tapered at the treating physician's discretion if the patient demonstrates a stable to improved neurologic exam.

In the event that a patient complains of abdominal pain, serum amylase and lipase will also be checked. Severe abdominal pain warrants a CT scan of the abdomen to rule out visceral perforation and pancreatitis.

7.6 Duration of Therapy

A cycle is defined as 4 weeks. Treatment will continue for the duration of response or stable disease.

Study treatment continues until one of the following:

- Investigator determination that discontinuation is in a patient's best medical interest
- Progression
- Withdrawal of support of study sponsor

The reason for study treatment discontinuation and the date treatment was discontinued must be documented in the OnCore CRF.

7.7 Monitoring Patient Compliance

A drug diary will be provided to each patient to use to track study drug administration. The diary will be reviewed by the study team periodically (see Study Calendar). Patient reports of self-administration, review of medication diary and pill counts will be used to assess study medication compliance. Concurrent medication assessments will be used to capture corticosteroid use and supportive care medications.

7.8 Duration of Follow Up

Patients who discontinue treatment **for any reason other than death or their choice to withdraw from all study follow-up** remain on study in follow-up status for an initial 30-day AE evaluation period following the last dose of study agent(s). This 30-day post-treatment follow-up period is meant to capture resolution or stabilization of ongoing treatment-related AEs or evolution of new treatment-related AEs.

The initial AE follow-up period may be extended if new or worsening treatment-related AEs require longer observation. Similarly, the initial AE follow-up period may end early in the event of death, patient request to withdraw from follow-up, or initiation of new anti-cancer therapy.

After the initial AE follow-up period, patients who are not evaluable for objective response (see Section 10.1) are off study. Patients who are evaluable for objective response enter an extended follow-up period for progression and/or survival outcomes.

Patients who discontinue treatment with an ongoing response (PR or CR) or with ongoing stable disease (SD) are followed until the first evidence of progression after coming off treatment or until other anti-cancer therapy is initiated. At the onset of progression or

initiation of new therapy, whether this occurs during the initial or extended follow-up period, patients are followed only for survival.

The primary reasons for a patient's discontinuation from study treatment and from follow-up status are to be recorded in the source documents and the CRFs.

Certain late-occurring AEs may be subject to reporting during the extended follow-up period (eg, secondary malignancies).

8 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

8.1.2 Serious Adverse Event (SAE)

An AE is considered "serious" if in the view of the investigator, it results in any of the following outcomes:

- death,
- a life-threatening AE (An AE is consider "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.),
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment; they may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Unanticipated Problem (UP)

UPs include any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents; such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- related or possibly related to participation in the research (ie, there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the 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.

8.2 Adverse Event Characteristics

8.2.1 **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI CTCAE version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

8.2.2 **Expectedness**: AEs can be 'Unexpected' or 'Expected'.

Unexpected AEs are those AEs occurring in one or more subjects participating in the research protocol, the nature, severity, or frequency of which is not consistent with either:

- The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related document, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts;

  or

- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

See Sections 9.1.9 (sorafenib), 9.2.8 (valproic acid), and 9.3.10 (sildenafil).

8.2.3 **Attribution** of the AE:

- Definite – The AE *is clearly related* to the study treatment.

- Probable – The AE *is likely related* to the study treatment.

- Possible – The AE *may be related* to the study treatment.

- Unlikely – The AE *is doubtfully related* to the study treatment.

- Unrelated – The AE *is clearly NOT related* to the study treatment.

8.3 Known AE List

Expected AEs are those AEs, the specificity and severity of which is consistent with the listings for valproic acid, sorafenib or sildenafil in Section 9 or those documented in the informed consent document.

8.4 Time Period and Grade of AE Capture

All AEs, regardless of grade, will be recorded from the beginning of the study procedures through 30 days following the end of the study treatment.

8.5 Procedures for Recording AEs, SAEs, Qualifying Toxicities, and UPs

All AEs, SAEs, qualifying toxicities, and UPs will be recorded in MCC's OnCore database program.

In certain instances, it may be acceptable to record in OnCore only the highest grade of a toxicity occurring during a particular study segment when an event has serial fluctuations in grade over time.

SAE's will be entered into the OnCore SAE domain. UPs will be entered into the OnCore Deviations domain. An SAE that is both an SAE and a UP will be entered in both domains. For all SAEs, a corresponding entry should be made in the routine AE record to match the event entries in the SAE domain.

8.6 Expedited Reporting Procedures for SAEs, UPs, and Qualifying Toxicities

Table 5. Expedited Reporting Requirements (Events, Report Recipients, and Time Frames)

SAEs	**UPs**	**Qualifying Toxicities[1]**
Principal Investigator, Co-Investigator (as listed below), and Coordinating Study Team[2, 3]	Principal Investigator, Co-Investigator (as listed below), and Coordinating Study Team[2, 3]	Principal Investigator, Co-Investigator (as listed below), and Coordinating Study Team[2]
	DSMC[4]	DSMC[4]
	IRB[5]	

[1] See Section 6.4.2.

[2] Report event within 1 business day of becoming aware of the occurrence.

[3] A de-identified PDF of an OnCore SAE or deviation record may be used for expedited reporting purposes.

[4] Report event within 2 business days of becoming aware of the occurrence. A de-identified PDF of an OnCore SAE or deviation record may be used for expedited reporting purposes.

[5] Each UP must be reported to the VCU IRB within 5 business days of becoming aware of the occurrence.

Principal Investigator: Mark Malkin, MD [redacted]	[redacted]
Coordinating Study Team: [redacted]	**Massey Cancer Center DSMC:** [redacted]

9 PHARMACEUTICAL INFORMATION

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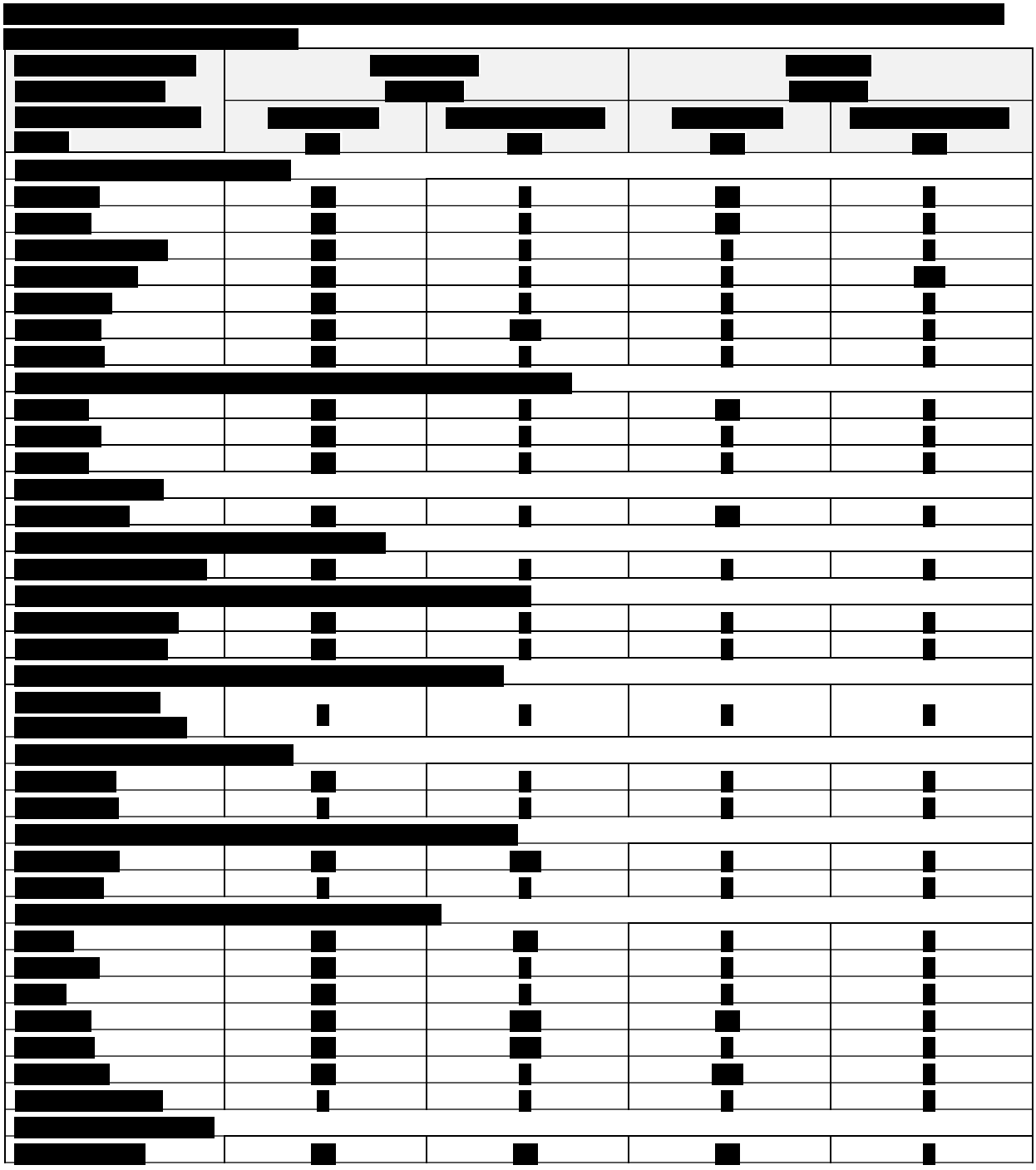

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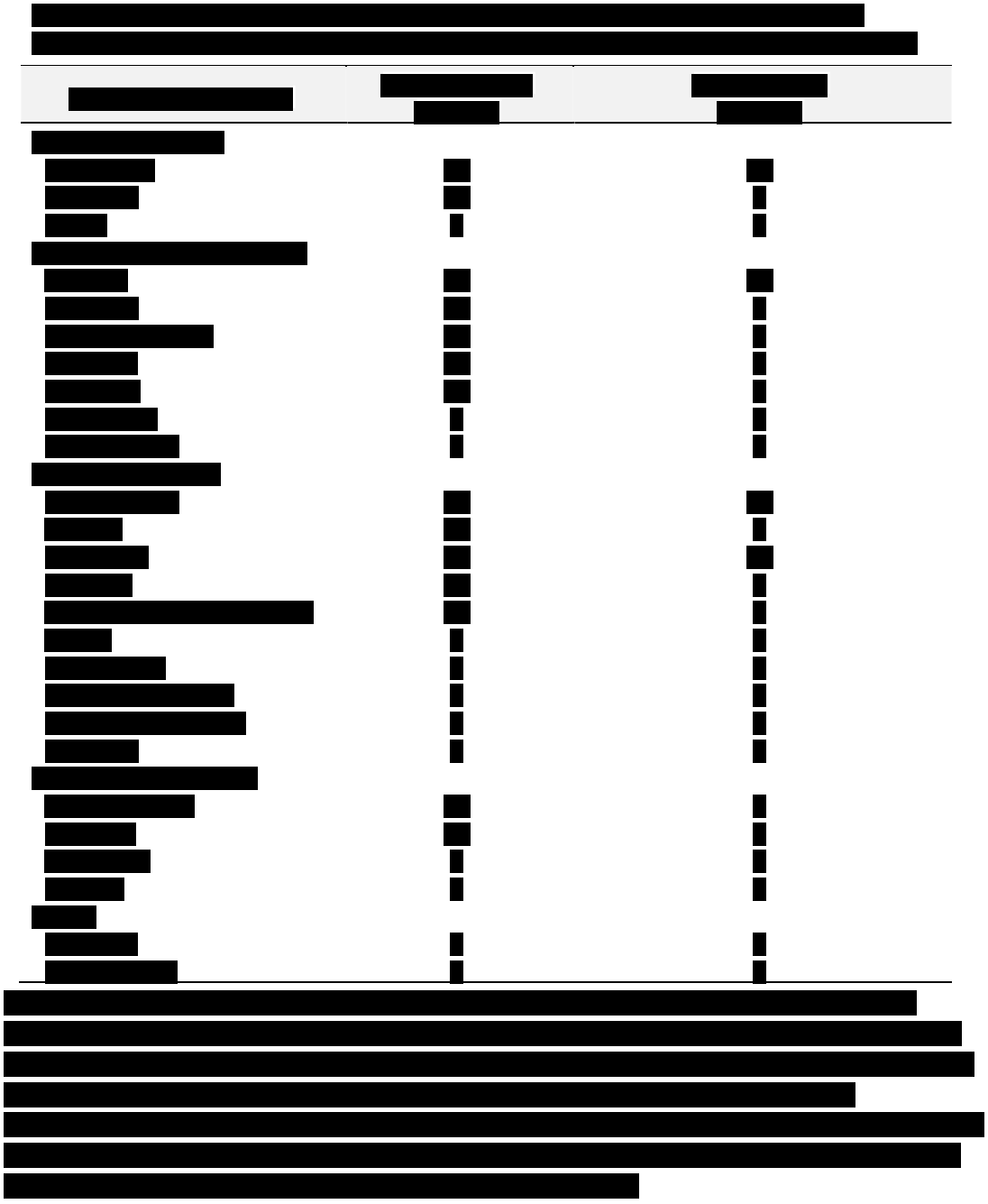

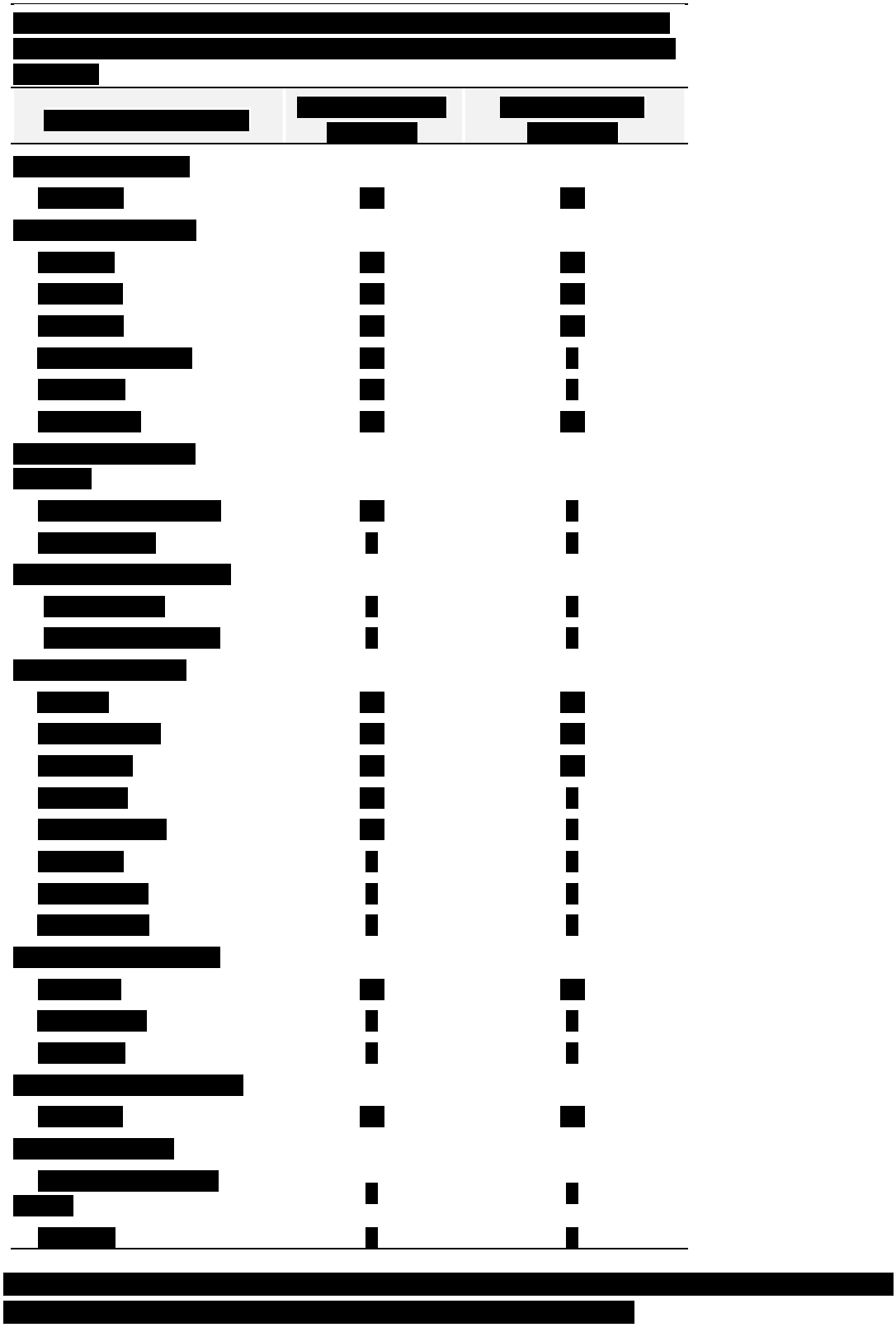

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10 MEASUREMENT OF EFFECT

10.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with sorafenib and/or valproic acid and/or sildenafil.

Evaluable for qualifying toxicities for the safety lead-in. Only those patients who have completed the first cycle of therapy (or have experienced a qualifying toxicity prior to the end of the first cycle) will be evaluable for the safety lead-in. Qualifying toxicities will be defined in the first cycle only. Patients must have completed twice-daily sorafenib dosing for at least 21 out of the first 28 days to be considered to have had sufficient exposure to the regimen for qualifying toxicity evaluation. Patients who are not evaluable for the qualifying toxicity assessment for the safety lead-in will be replaced.

Evaluable for qualifying toxicities for the early stopping rule after the safety lead-in. Patients who have initiated the first cycle of therapy will be considered evaluable for the early stopping rule. Qualifying toxicities will be defined in the first cycle only. Patients who are not evaluable for the qualifying toxicity assessment for the early stopping rule will not be replaced unless they were included in the safety-lead in.

Evaluable for objective response. Patients who have been treated with the combination of twice-daily sorafenib and valproic acid for a minimum of 28 days, 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. Patients who do not complete study dosing for at least 28 days, or those who do not have their disease re-evaluated following initiation of the combination of sorafenib and valproic acid, will be replaced to ensure that a sufficient number of patients will be available for response evaluation.

10.2 Response Criteria

The neurologic examination and the MRI or contrast-enhanced CT at each evaluation will be scored as follows:

10.2.1 Neurologic Exam Status

Table 12. Neurologic Exam Status as Compared to Pre-Treatment Exam

Status	Criteria
Better	No new neurologic deficits. Must be on stable or decreasing dose of steroids, with stable to improved ECOG performance status
Worse	New neurologic deficits, declining ECOG performance status, or requiring increasing dose of steroids to remain stable

10.2.2 MRI Assessment: Based on Response Assessment in Neuro-Oncology working group (RANO) criteria (37).

Table 13. RANO Criteria

Response	Criteria
Complete Response	Requires all of the following: Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; and with patient off corticosteroids or only on physiological replacement doses. Requires repeat MRI in 4 weeks for confirmation.
Partial Response	Requires all of the following: ≥ 50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of non-measurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared to baseline scan; and with patient on a dose corticosteroids not greater the dose at the time of baseline scan, and is stable or doing better clinically. Requires repeat MRI in 4 weeks for confirmation.
Stable Disease	Stable disease occurs if the patient does not qualify for complete response, partial response, or progression, and requires the following: Stable non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared with baseline scan and clinically stable status. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progressive Disease	Progression is defined as any of the following: ≥ 25% increase in the sum of the products of perpendicular diameters of enhancing lesions, on stable or increasing doses of steroids; a significant increase in non-enhancing (T2/FLAIR) on stable or increasing dose of steroids compared with baseline scan or best response after initiation of therapy; the appearance of new lesions; clear progression of non-measurable lesions; definite clinical deterioration not attributable to other causes apart from tumor or to decreases in corticosteroid dose.

10.2.3 Contrast-enhanced CT Assessment: Based on Macdonald Criteria (38).

Table 14. Macdonald Criteria

Response	Criteria
Complete Response	Requires all of the following: complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically.
Partial Response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically.
Stable Disease	Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically.
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration.

*Table from (37)

10.3 Considerations for Patients with Multifocal Disease

For patients with multifocal disease, progressive disease is defined as ≥ 25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurements after the initiation of therapy. The appearance of a new lesion or unequivocal, progression of non-target lesions will also be considered progression.

Partial response is defined as a ≥ 50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks, with stable or decreasing corticosteroid dose and with stable neurologic exam.

10.4 Timing of Imaging Studies

For the purposes of this study, patients will be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response (PR or CR).

Evaluation of neurologic imaging can be confounded by factors such as edema and subtle variances in imaging parameters. In the event that imaging meets objective progression criteria, but the patient‘s clinical status is stable or improving, with a stable or decreasing steroid dose, and, in the opinion of the investigator, the aggregate patient assessment is not definitive for progression, study therapy can continue at investigator’s discretion with repeat imaging at time of next scheduled assessment. If subsequent imaging again meets objective progression criteria, regardless of clinical and/or steroid dosing status, then progression criteria will have been met, and the date of progression will be noted as the earliest imaging date that was consistent with objective progression.

If clinical conditions raise the concern for progressive disease in between regularly scheduled interval scans, repeat imaging may be performed at the treating physician’s discretion.

10.4.1 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for a complete response or a partial response (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 complete response is measured from the time measurement criteria are first met for complete response 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.

10.4.2 PFS

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

11 CORRELATIVE STUDIES

11.1 PDGFRα Expression in Primary Tumor Samples

Analysis will take place on archived tissue. Patients being considered for enrollment onto this study will have had primary therapy for their high-grade glioma, which includes resection, when possible, with a minimum of a core needle biopsy of the tumor for patients with unresectable disease. Some patients will also have had a biopsy of recurrent disease. Other patients will have had progression from a lower grade glioma, and multiple biopsies will be available to choose from. The preferred tumor specimen is from the primary resection specimen at the time of initial treatment for high-grade glioma.

11.2 Timing of Sample Collection and Analysis

In the initial PDGFRα-unselected cohort, archived samples may be obtained and submitted for initial processing any time after study consent is obtained, preferably within the first few weeks of study therapy. Analysis/interpretation of these samples may be done without regard to participant initiation of study treatment. Samples may be held for batch processing, staining, and analysis until such time as it is determined whether the study will proceed to enrollment of only patients known to have PDGFRα-positive tumors.

If the study continues to enrollment of a PDGFRα-positive cohort, archived samples will need to be collected, processed, and scored as part of the screening process to determine eligibility.

After the first interim analysis for 6-month PFS:

- If the study continues with enrollment of PDGFRα-unselected patients only, tissue collection, processing, and analysis may continue, with the understanding that samples may be processed and/or analyzed for PDGFRα status in a non-CLIA-certified setting. In

this case, samples will be deparaffinized in VCU Anatomic Pathology, immunostained in the VCU Massey Cancer Center Clinical and Translational Research Laboratory (VCU MCC CTRL) and scored in VCU Anatomic Pathology.

- If the study continues with enrollment of PDGFRα-selected patients (only those who have PDGFRα-positive tumors), results of PDGFRα immunostaining will need to be available PRIOR TO enrollment. Immunostaining for the PDGFRα-positive cohort will be performed in a CLIA-certified setting. In this case, for consistency, all previously collected samples from the PDGFRα-unselected patient cohort will also undergo staining and analysis in the CLIA-certified setting.

11.3 Collection of Specimens

A total of 5 unstained slides, each with specimen 4-microns thick, should be obtained. All slides will have PHI removed before submission for correlative testing and will be labeled with:

- Study Number
- Subject ID#
- Surgical pathology accession #

VCU MCC CTRL and VCU Anatomic Pathology will maintain logs of samples handled for correlative testing keyed by those 3 identifiers.

To obtain a biopsy specimen from VCU archives, contact VCU Anatomic Pathology [redacted] and reference surgical pathology specimen number and block number. Provide a copy of protocol specifications for sample collection and signed informed consent.

- For the PDGFRα-unselected cohort, make arrangements for de-identified slides to be obtained and submitted to the VCU MCC CTRL to be stored until a determination is made about where the slides will be processed and analyzed.

- For the PDGFRα-selected cohort, make arrangements for de-identified slides to be obtained and submitted to the VCU Anatomic Pathology for pre-enrollment processing and analysis to determine PDGFRα-status

VCU Anatomic Pathology [redacted]

To obtain an archived biopsy specimen from outside hospital, request that a tissue block be sent to Anatomic Pathology at the above address, Attention [redacted] and

notify [redacted] to expect the specimen for research testing. The study team should coordinate with [redacted] to transfer the prepared slides from outside tissue blocks to the VCU MCC CTRL.

If the outside hospital does not transfer blocks of tissue, request delivery of 5 unstained slides, each with specimen 4-microns thick, directly to the study team. Blank slides from an outside hospital do not need to be sent to pathology for preparation, and may be submitted directly to the VCU MCC CTRL for immunostaining.

11.4 Handling of Specimens

Five unstained slides, each with specimens 4 microns thick, will be submitted for immunostaining.

11.5 Immunostaining of Specimens

Immunostaining and analysis will be done in either the VCU MCC CTRL or in a CLIA-certified setting, per Section 11.2.

11.6 Interpretation of Correlative Study

[redacted]

11.7 Other Potential Pharmacodynamic Markers

The laboratory of [redacted] at MCC will analyze the samples for the pharmacodynamic marker studies.

12 STUDY CALENDAR

Table 15. Study Calendar

Event	Baseline[A]	On Treatment[B]									Follow Up[C]	
		Cycle 1				Cycle 2				Cycle 3+	Initial 30-Day Period	Extended Period
		D1	D8	D15	D22	D1	D8	D15	D22	D1		
Informed Consent	X[D]											
Demographics, Height	X[D]											
History and Physical Exam including Performance Status, Dermatologic and Neurologic Assessments	X	X[E]	X[F]	X	X[F]	X		X		X		
Vital Signs, Weight	X	X	X[F]	X	X[F]	X		X		X		
Baseline Symptoms	X											
Adverse Event Assessment		X	X[F]	X	X[F]	X		X		X	X[C]	
Concurrent Medications, Including Steroid Dosing Review	X	X	X[F]	X	X[F]	X		X		X		
Study Medication Diary Review and Pill Count		X	X[F]	X	X[F]	X		X		X		
Pregnancy Test, Counseling	X[G]											
ECG	X		X[H]							X[H]		
Tumor Imaging	X[I]	X[J]										
Survival, Alternative Therapies											X[C]	X[K]
Archived Tumor Tissue	X[L]											
CBC with Differential, Platelets	X	X[B]	X[F]	X	X[F]	X		X		X		
Basic Metabolic Panel,[M,N] Hepatic Panel,[O] Magnesium,[N] Phosphorus[N]	X	X[B]	X[F]	X	X[F]	X		X		X		
PT, INR[P]	X	X										
Serum Valproic Acid Level[Q]	X	X										
Serum Ammonia	X											
Valproic Acid	Initiate, titrate, and/or maintain level ≥ LLN for the laboratory and dose per Sections 6 and 9.											
Sorafenib		Initiate on C1D1, provided valproic acid level is ≥ LLN for the laboratory; continue dosing per Sections 6 and 9.										
Sildenafil												

A. Within 2 weeks prior to enrollment unless otherwise noted.
B. C1D1 labs do not need to be repeated on C1D1 if done within 7 days prior to initiation of study treatment. Other C1D1 assessments may be performed within 3 days prior to day 1 dosing. In cycle 1, weekly assessments must be done within +/- 1 day of required time point. In cycle 3 and subsequent cycles, assessments must be done within +/- 3 days of scheduled time point; greater variations in timing may be permitted after cycle 2, with prior principal investigator/designee notification. For patients who are still on study for longer than 36 months, assessments may be done every other cycle (approximately every 8 weeks).
C. See Section 7.8: The 30-day post-treatment follow-up period is meant to capture resolution or stabilization of ongoing treatment-related AEs or evolution of new treatment-related AEs.
D. Within 4 weeks prior to initiation of study treatment.
E. If baseline history and physical exam is performed on a day other than C1D1, a brief visit to determine neurologic stability on current dose of steroids is also required on day 1 or day before.
F. Only patients in the safety lead-in cohort.
G. For women capable of pregnancy: pregnancy test at baseline; subsequently, review pregnancy risks and offer pregnancy test
H. First “on-treatment” ECG is done approximately C1D8-C1D15 to evaluate acute changes relative to the study drug combination; the second is done approximately C3D1 to evaluate changes after a more chronic dosing of study drug combination.
I. MRI or contrast-enhanced CT within 3 weeks prior to enrollment. An MRI is the preferred modality in all patients without a contraindication to MRI. Baseline and follow-up scans must be performed using the same modality.
J. Imaging to be done to assess response every 2 months from initiation of treatment until off-study due to patient withdrawal, progression, or death. If MRI or contrast-enhanced CT shows response then repeat after 1 month to confirm response and then follow every 2 months from time of confirmatory MRI or CT. Patients with symptoms suggestive of progression may have imaging done between regularly scheduled scans, any time there is clinical concern for progressive disease. See also Section 10.4.
K. See Section 7.8: After stopping study treatment, capture initiation of new therapy, first new progression date, and/or survival status since last observation approximately every 2 months during extended follow-up.
L. Obtain and analyze archived tumor tissue per Section 11. During enrollment of the initial PDGFRα-unselected subgroup (prior to first interim analysis), archived tumor tissue must be obtained and analyzed, but analysis does not need to be performed prior to enrollment. After the first interim analysis, if the study proceeds to include only PDGFRα-positive patients, archived specimen analysis for PDGFRα will be required, and results must be known, prior to enrollment.
M. Sodium, potassium, carbonate, chloride, glucose, calcium, BUN, creatinine.
N. Additional assessments may be done at investigator discretion in patients with congestive heart failure, bradyarrhythmias, those on drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities.
O. ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, total protein.
P. In patients taking warfarin: at baseline and then as clinically indicated.

Q. Initial level approximately 5 days after starting valproic acid. Once on study treatment, check level at least every 2 weeks, or more frequently if clinically indicated, through the end of cycle 2. After cycle 2, check only as clinically indicated.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a single-arm phase 2 study of sorafenib, valproic acid, and sildenafil in the treatment of patients with recurrent high-grade glioma. The primary objective is to determine the efficacy of the drug combination in terms of 6-month PFS. This study will be conducted through an adaptive design potentially including 2 Simon's two-stage mini-max designs. Initially, recurrent high-grade glioma patients will be enrolled, regardless of tumor molecular subtype, to determine the efficacy of the drug combination. If efficacy criteria are not met in patients inclusive of all molecular subtypes, then only patients with tumors that express PDGFRα will be enrolled. Therefore, 2 Simon's designs may be included; the first is for patients in the entire cohort and the second is for patients with PDGFRα expressing tumors only if efficacy criteria are not met in the entire cohort. Details on the rationale of the adaptive design can be found in Section 1.9.

The total expected sample size is estimated to be 44, with a range from 32 to 66 patients.

Both a safety lead-in and a safety stopping rule are provided to monitor whether there are "too many" unexpected toxicities related to the drug combination, as patients continue being enrolled in the study. To ensure safety with respect to any interaction toxicity effects among the 3 drugs, we provide a safety lead-in rule for the first 6 qualifying toxicity-evaluable patients—like a "3+3" phase 1 design. Once a dose has been identified wherein < 2 of 6 qualifying toxicity-evaluable patients develop a qualifying toxicity during the first 4 weeks of therapy, then that dose will be used for expansion. Qualifying toxicities are defined in Section 6.4.2.

Once the dose for expansion to the full cohort is identified, then an early sequential safety stopping rule which is based on the occurrence rate of qualifying grade 3 or greater toxicities is provided to monitor safety for any toxicities in the expansion. The safety lead-in rule is designed for a "3+3" study and is used to enhance safety analysis for the first 6 qualifying toxicity-evaluable patients on the study, whereas the sequential stopping rule for subsequent enrollment has considered the variability of toxicity rate by confidence intervals based on observed data and scenarios where unacceptable toxicity could occur prior to study suspension. More details on the clinical rationale are in Section 1.7. Details on the safety lead-in and safety stopping rule are in Section 13.6.

13.2 Sample Size/Accrual Rates

The sample size and power are calculated based on Simon's two-stage mini-max design which minimizes the expected maximum sample size (35). The primary outcome, 6-month PFS, is considered as a binary variable, ie, a patient either has 6-month PFS or not. Per the previous studies of second-line therapy in GBM, we assume that the null hypothesis, the proportion of patients who have 6-month PFS, is ≤ 20%, ie, $p0 \leq 0.2$, which is unacceptably low, and the true proportion is p1=0.4. With a one-sided type I error of 5% and power of at least 80%, the first stage will enroll 16 response-evaluable patients. If there are 3 or less response-evaluable patients who have 6-month PFS, then the trial in the unselected patient population will end. If 4 or more response-evaluable patients have 6-month PFS, then the trial will enroll an additional 17 response-evaluable patients into the second stage. If 11 or more out of the total of 33 response-evaluable patients have 6-

month PFS, the drug combination meets efficacy criteria and further studies can be pursued.

As mentioned in Section 13.1, the study will be conducted through an adaptive design possibly with 2 Simon's two-stage designs. Both of these Simon's designs will share the same parameters/settings, assumptions for sample size, and power calculations. The total sample size may range from 32 to 66. We expect that it is very likely that the study will enroll 16 response-evaluable patients inclusive of all molecular subtypes, and then a total of 16 response-evaluable patients with PDGFRα-expressing tumors in the first stage (inclusive of patients with PDGFRα-positive tumors in the first interim analysis), and an additional 17 response-evaluable patients with PDGFRα-expressing tumors in the second stage. Per previous studies, PDGFRα is the third most common gene event identified in GBM, and about 30-40% patients have positive PDGFRα expression among all GBM patients , with a higher percentage in patients with transformed GBM from lower grade glioma (39). Therefore, we expect that the total sample size for the adaptive design is about 44 response-evaluable patients. Based on previous recruitment at the Massey Cancer Center, it is estimated that 8-12 patients will be enrolled per year, and therefore, it is estimated that the study will complete enrollment in approximately 4 years and be closed in approximately 5 years. It is likely that the accrual rate for the PDGFRα expression cohort will be slower than for the entire population and the study team will invite more clinical sites to increase the accrual rate.

13.3 General Statistical Analysis

Patient demographics, AEs and SAEs, disease status, treatment dosing level, treatment status, clinical response, time-to-event intervals etc. will be recorded and summary descriptive statistics will be calculated. The clinical response rates will also be summarized using descriptive statistics for each cohort, along with their corresponding 95% confidence intervals.

13.4 Analysis of Primary Endpoints

The primary endpoint is whether a patient has a 6-month PFS or not. The proportion of response-evaluable patients who have 6-month PFS in the entire cohort and in PDGFRα expressing tumor and their confidence intervals will be calculated, respectively. The Kaplan-Meier method will be used to describe the time to progression and the median time to progression will be estimated, along with its 95% confidence intervals (40), for the entire population and for PDGFRα expression, respectively. Cox regression analysis will be used to evaluate baseline characteristics and any potential covariates.

13.5 Analysis of Secondary Endpoints

The overall best response rate to the drug combination will be estimated for the entire study population and for the PDGFRα-expressing high-grade glioma cohort, along with the 95% confidence intervals.

The Kaplan-Meier method will be used to describe the time to overall survival and the median time to overall survival will be estimated, and along with its 95% confidence intervals, for the entire population and for PDGFRα expression, respectively. Cox regression analysis will be used to evaluate baseline characteristics and any potential covariates.

13.6 Safety Lead-in, and Safety Stopping Rule

13.6.1 Safety Lead-in

The first 6 patients will be treated as a single dose-level safety lead-in prior to continuation of accrual of the entire study cohort. The lead-in rule is designed for a “3+3” study and is used to enhance safety analysis for the first 6 patients on the study, wherein the sequential stopping rule has considered the variability of toxicity rate by confidence intervals based on observed data and scenarios where unacceptable toxicity could occur prior to study suspension. Patients will be evaluated for qualifying toxicities as defined in Section 6.4.2. If < 2 of 6 qualifying toxicity-evaluable patients complete the first 4 weeks of therapy without a qualifying toxicity, then the dose is considered safe for expansion to the remainder of the entire study cohort. If ≥ 2 of 6 qualifying toxicity-evaluable patients experience a qualifying toxicity during the first 4 weeks of therapy, doses will be modified and an additional 6 patients enrolled for qualifying toxicity evaluation. In this case, the protocol will be placed on hold until the protocol is amended to specify the modified doses. Once a dose has been identified wherein < 2 of 6 patients develop a qualifying toxicity during the first 4 weeks of therapy, then that dose will be used for enrollment of the entire study cohort. In the event that toxicity develops late, the stopping rule below will remain in effect to trigger review by the DSMC.

13.6.2 Sequential Safety Stopping Rule after the Safety Lead-in

In addition to the safety lead-in described above, a formal sequential stopping guideline, which is based on the occurrence rate of qualifying toxicities, is designed for a phase 2 study, with a relatively looser threshold than the safety lead-in rule. If the stopping guideline is reached, accrual is stopped and a thorough review of the safety data is completed by the DSMC. The stopping guideline indicates a level of concern based on the occurrence rate of qualifying toxicities. However, the stopping guideline is not an indicator that an insurmountable safety problem exists. Likewise, the fact that a stopping guideline is not reached does not provide assurance that the drug combination is safe. Qualifying toxicity is defined in Section 6.4.2.

Previous studies of sorafenib have shown the acceptable occurrence rate for grade 3 or greater toxicities is ≤ 35% (41). Using a binomial probability calculation, values of “m” (number of patients with qualifying toxicities) and "n" (number of qualifying toxicity-evaluable patients that have been treated) are selected such that the two-sided 95% confidence interval of the sequential observed occurrence toxicity rate keeps containing the prefixed acceptable occurrence rate ≤ 35%.

More specifically, the following values of m/n apply to those patients who are qualifying toxicity evaluable: 5/7, 6/8-9, 7/10-11, 8/12-13, 9/14-15, 10/16-17, 11/18-19, 12/20-21, 13/22-23, 14/24-25, 15/26-28, 16/29-30, 17/31-32, 18/33-34, 19/35-37, 20/38-39, 21/40-41, 22/42-44, 23/45-46, 24/47-48, 25/49-51, 26/52-53, 27/54-56, 28/57-58, 29/59-61, 30/62-63, 31/64-65, 32/66. If, at any time, m/n reaches the values shown, accrual to the study protocol is stopped and the accumulated safety data is submitted to the DSMC for evaluation. Please refer to Section 6.4.2 for a list of qualifying toxicities.

13.6.3 Summary of Safety Monitoring Plan

As mentioned in Section 13.6.1, once a dose has been identified wherein < 2 of 6 patients develop a qualifying toxicity during the first 4 weeks of therapy, then the study will be conducted through a Simon's two-stage design (Section 13.1) at that dose for the entire population first and then for the PDGFRα-expressing population. As mentioned in Sections 13.1-13.2, 16 patients will be enrolled for the first stage for the entire population. The monitoring plan for the 16 patients is summarized in the table below. Subsequent patients will be monitored as described in Section 13.6.2.

Table 16. Summary of Safety Monitoring Plan

Number of qualifying toxicity-evaluable patients	**Cumulative safety monitoring plan**
The first 6 patients	Must have < 2/6 qualifying toxicity-evaluable patients as indicated by the safety lead-in rule in Section 13.6.1
The next 6 patients	Of the 7-12 qualifying toxicity-evaluable patients, must have < 5-8 patients who develop qualifying toxicities, as indicated in the sequential safety stopping rule in Section 13.6.2
The next 4 patients	Of the 13-16 qualifying toxicity-evaluable patients, must have < 8-10 patients who develop qualifying toxicities, as indicated in the sequential safety stopping rule in Section 13.6.2
Further patients	Continue monitoring of qualifying toxicity-evaluable patients as in Section 13.6.2

13.7 Evaluability for Qualifying Toxicity, Toxicity, Response

Each registered patient will be deemed as evaluable for toxicity, qualifying toxicities and response as per Section 10.1:

For response evaluability, the patients are coded as having a response or not.

- Responders - Best response assessment is complete response or partial response
- Non-Responders - Best response assessment is stable disease or progressive disease or those patients who were not assessed or not evaluable
- The coding of patients as responders or non-responders will be made by the study team with the concurrence of the biostatistician.

14 DATA AND SAFETY MONITORING PLAN (DSMP)

14.1 Study Team

The study team, consisting of physicians, research nurses, clinical research associates, study statistician, and regulatory personnel, will have primary responsibility for study conduct. The study team will maintain a study summary and meet at least monthly while patients are on study treatment. The study statistician will meet with the study team at least quarterly. Meetings will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study

schema. The appropriateness of further patient enrollment and the specific intervention for a next patient enrollment are addressed. All meetings including attendance are documented.

14.2 Monitoring and Auditing

14.2.1 MCC Compliance Office

Compliance specialists in the MCC Compliance Office will provide ongoing monitoring and auditing for this trial.

14.2.2 Data and Safety Monitoring Committee

The study will be reviewed by the MCC Data and Safety Monitoring Committee (DSMC) initially according to the risk level specified by the MCC Protocol Review and Monitoring Committee (PRMC) and then according to a schedule based on study status and quality indicators. The DSMC reviews reports of the sponsor-investigator/study team and the MCC Compliance Office focusing on data integrity and patient safety.

15 REGULATORY COMPLIANCE AND ETHICS

15.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979).

15.2 Regulatory Compliance

This study will be conducted in compliance with the protocol and applicable regulatory requirements.

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the patients and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the patient and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. The patient will sign the informed consent document prior to any procedures being done specifically for the study. The patients should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The patients may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.4 Patient Confidentiality

Patient confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biologic samples and genetic tests in addition to the clinical information relating to participating patients.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor-investigator.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

16 DATA COLLECTION AND MANAGEMENT

16.1 CRFs and Data Collection

Data Massey Cancer Center OnCore data management will provide standard CRFs and create study-specific CRFs to be able to capture all information required by the protocol. The CRFs will be approved by the study team to ensure the most effective data acquisition.

The investigator(s) and study coordinator(s) must maintain source documents for each patient in the study. All information on CRFs will be traceable to these source documents, which are generally maintained in the patient's file.

All CRFs should be completed and available for collection within a timely manner, preferably no more than 14 days after the patient's visit.

16.2 Study Record Retention

The investigator will maintain all study records according to applicable regulatory requirement(s).

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APPENDIX 1. PERFORMANCE STATUS CRITERIA

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

Appendix 2. Cockcroft-Gault Equation

Calculated Creatinine Clearance (Cockcroft and Gault)
Creatinine Clearance (mL/min) = {(140 - Age) × Wt in kg × G} / (Creat × 72) G = 1 (males); G=0.85 (females)

Appendix 3. NYHA Classification of Heart Failure

Class	Description
I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
III	Symptoms with less than ordinary physical activity. Walking 1 to 2 blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.