Phase 2 Study of Pemetrexed and Sorafenib for Treatment of Recurrent or Metastatic Triple Negative Breast Cancer

NCT02624700

Version Date: 11/22/2017

Virginia Commonwealth University Massey Cancer Center

Protocol MCC-14-10790

Phase 2 Study of Pemetrexed and Sorafenib for Treatment of Recurrent or Metastatic Triple Negative Breast Cancer

Principal Investigator
Andrew Poklepovic, MD

Version #: 4

Version Date: 11/22/2017

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

TABLE OF CONTENTS

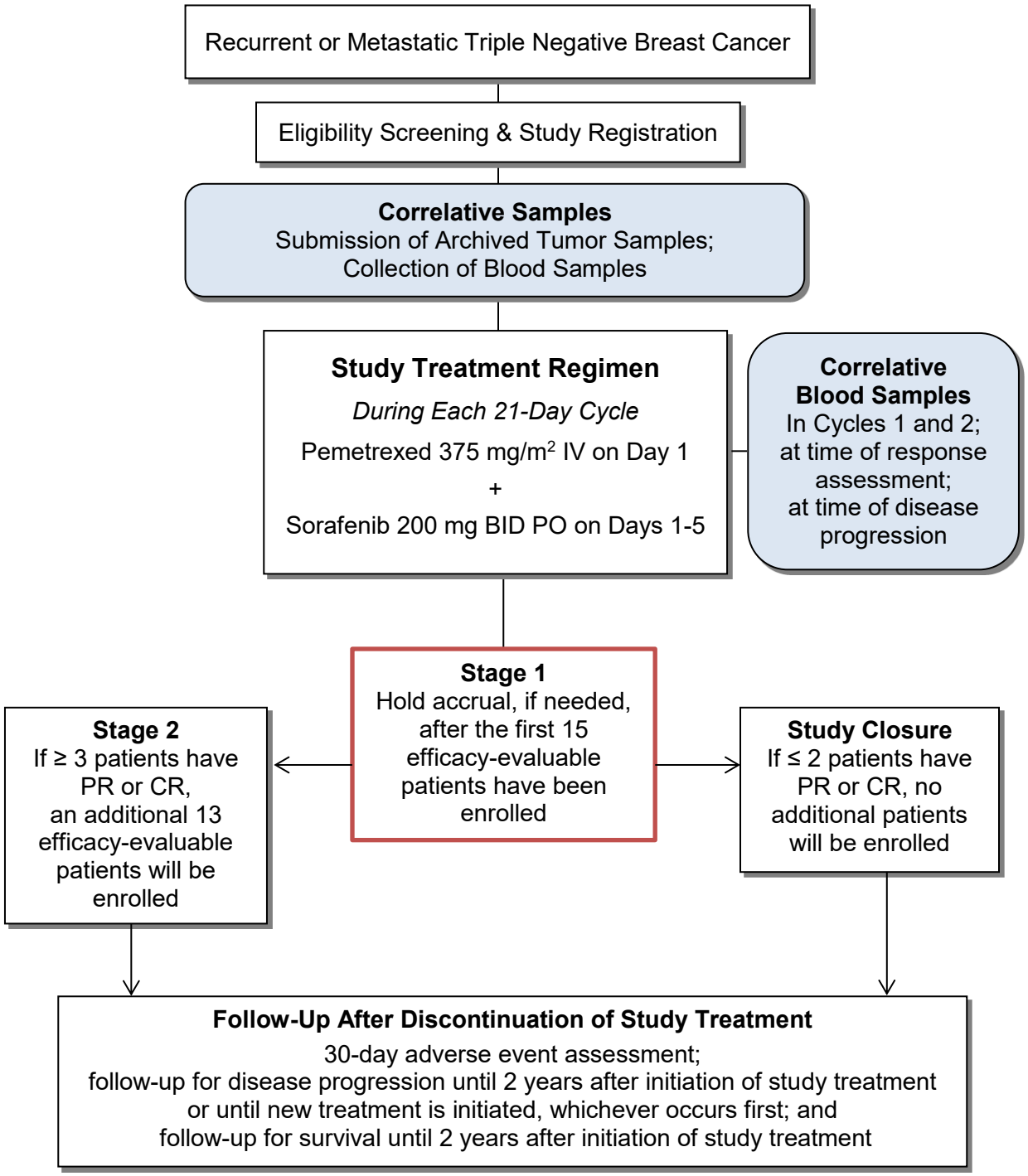
LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	adverse event
AICART	aminoimidazolecarboxamide ribonucleotide formyltransferase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice a day
CBC	complete blood count
CR	complete response
CrCL	creatinine clearance
CRF	case report form
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CTRL	Clinical and Translational Research Laboratory
DEPfff	dielectrophoretic field flow fractionation
DSMC	Data and Safety Monitoring Committee
EE	efficacy-evaluable
ER	estrogen receptor
FDA	Food and Drug Administration
HR	hormone receptor
IHC	immunohistochemistry
IM	intramuscular
INR	international normalized ratio
ITT	intent-to-treat
IV	intravenous
HER2	human epidermal growth factor receptor 2
IRB	Institutional Review Board
LLN	lower limit of normal
MCC	Massey Cancer Center
MMA	methylmalonic acid
MTD	maximum tolerated dose
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
PDGFR	platelet-derived growth factor receptor
PO	by mouth
PgR	progesterone receptor
PR	partial response
PRMC	Protocol Review and Monitoring Committee
QTc	QT interval, corrected
QTcF	QT interval with correction using Fridericia's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SIIT	solid tumor investigator-initiated trial
TNBC	triple negative breast cancer
TS	thymidylate synthase
UP	unanticipated problem
VCU	Virginia Commonwealth University
WCBP	woman of child-bearing potential

SCHEMA


Recurrent or Metastatic Triple Negative Breast Cancer
Eligibility Screening & Study Registration
Correlative Samples
Submission of Archived Tumor Samples;
Collection of Blood Samples
Study Treatment Regimen
During Each 21-Day Cycle
Pemetrexed 375 mg/m2 IV on Day 1
+
Sorafenib 200 mg BID PO on Days 1-5
Correlative Blood Samples
In Cycles 1 and 2;
at time of response assessment;
at time of disease progression
Stage 1
Hold accrual, if needed, after the first 15 efficacy-evaluable patients have been enrolled
Stage 2
If ≥ 3 patients have PR or CR, an additional 13 efficacy-evaluable patients will be enrolled
Study Closure
If ≤ 2 patients have PR or CR, no additional patients will be enrolled
Follow-Up After Discontinuation of Study Treatment
30-day adverse event assessment;
follow-up for disease progression until 2 years after initiation of study treatment or until new treatment is initiated, whichever occurs first; and
follow-up for survival until 2 years after initiation of study treatment

1 BACKGROUND

Most highly active cancer chemotherapy regimens combine agents with complementary activity. A treatment combination currently being studied in the phase 1 setting is pemetrexed, a folate analog metabolic inhibitor, and sorafenib, a tyrosine kinase inhibitor. Pemetrexed is approved by the Food and Drug Administration (FDA) for the treatment of non-squamous, non-small cell carcinoma of the lung and mesothelioma. Sorafenib is an FDA-approved agent for the treatment of differentiated thyroid cancer refractory to radioactive iodine treatment, renal cell carcinoma, and hepatocellular carcinoma.

Preclinical studies in both tumor cell lines and animal tumor models have shown promising anticancer effects of the combination of pemetrexed and sorafenib in diverse solid tumor types. These studies also suggest that the observed promising anticancer effects may be related to modulation of tumor cell autophagy. The results of the preclinical studies prompted evaluation of the combination in a phase 1 clinical trial which has identified an encouraging response pattern in patients with heavily pretreated breast cancer. The clinical responses seen in the breast cancer population of the phase 1 trial, coupled with the preclinical data, provide justification for further study of this therapeutic concept as a phase 2 clinical trial in breast cancer.

Patients with HER2-positive breast cancer generally remain on HER2-directed therapy as they advance through lines of therapy, and the combination of HER2-directed therapy with pemetrexed and sorafenib is beyond the scope of this trial. Therefore, patients with HER2-positive breast cancer will not be included. Recent advances in the treatment of hormone receptor (HR)-positive tumors have led to increasing differences in the way that clinicians treat HR-positive metastatic breast cancer, compared to triple negative breast cancer (TNBC). As such, inclusion of both HR-positive and HR-negative tumors could make it more difficult to determine clinical utility in each subgroup in a study of this size. Therefore, only patients with HR-negative breast cancer will be included in this study.

In summary, this phase 2 clinical trial will evaluate the efficacy of the combination of pemetrexed and sorafenib in patients with recurrent or metastatic TNBC. Candidate pharmacodynamic and predictive biomarkers will also be evaluated.

1.1 Autophagy

There are 2 main types of programmed cell death: Type I, also called apoptosis, refers specifically to an ATP energy-dependent process involving transcription of specific proteins and leading eventually to a cell's demise. Type II programmed cell death is known as autophagy, and is a ubiquitous process that occurs in all eukaryocytes (1, 2). Autophagy is a non-selective process in which cytoplasm and organelles are assorted into the autophagosome. After autophagosome formation, this structure fuses with an acidic endosome, where the contents are degraded. Based on the cell system and the drugs/stimulus being studied, autophagy can either act to protect cells from a toxic stress or can augment the toxicity of the stress. There is published evidence for both "protective" and "toxic" forms of autophagy based on the stimulus and cell type being examined (3-9).

Macroautophagy is one of the 3 main types of autophagy, and is regulated by 2 ubiquitin-like conjugation systems, ATG12-ATG5 and ATG8 (LC3A) (10-14). Apoptosis pathways have also been linked with autophagy, for example, knockdown of caspase 8 which can induce autophagic death (14). Beclin1 (autophagy-related gene 6 [ATG6])

contains a BH3 domain that binds to BCL-2/BCL-XL/MCL-1; release of Beclin1 from these proteins permits induction of autophagy (10-14).

The ser-thr kinase mTOR acts as one gatekeeper in the autophagy process, exerting an inhibitory effect. mTOR acts 1) in a signal transduction cascade that activates anti-autophagic transcription and translation and 2) by inhibiting the ATG proteins directly via their phosphorylation (15, 16). The PI3K class I/AKT pathway is involved in the down-regulation of autophagy by activation of mTOR, whereas Beclin1 and the class III type PI3K complex are positive regulators of autophagy (17).

1.2 Sorafenib

Sorafenib is a multitargeted protein kinase inhibitor that was originally developed as an inhibitor of RAF-1, a component of the ERK1/2 pathway, but which was subsequently found to inhibit multiple other kinases, including class III tyrosine kinase receptors such as platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), c-Kit, and FLT3 (3-7). Virginia Commonwealth University (VCU) investigator Paul Dent, PhD and collaborators have shown in vitro that sorafenib kills human leukemia cells through a mechanism involving down-regulation of MCL-1. In these studies, sorafenib-mediated down-regulation of MCL-1 occurred through a translational process that was mediated by endoplasmic reticulum stress signaling and the regulation of autophagy (18). More recently, his group has shown that sorafenib-mediated inhibition of PDGFRβ plays a key role in the ability of this agent to promote autophagy in tumor cells (7).

1.3 Pemetrexed

Pemetrexed, the first anti-folate cancer drug to be approved by the FDA in 20 years, is currently used for first-line therapy of mesothelioma and non-small cell lung cancer (NSCLC). It was originally developed as an inhibitor of thymidylate synthase (TS) (19-22). Pemetrexed also has at least one other target that becomes apparent from a continued antiproliferative effect of drug treatment in cell cultures exposed to exogenous thymidine, which prevents the cytotoxic effects of TS inhibition (19, 20). A secondary target is the downstream folate-dependent enzyme in *de novo* purine synthesis, aminoimidazolecarboxamide ribonucleotide formyltransferase (AICART). ZMP, the substrate of the AICART reaction, accumulates in intact pemetrexed-inhibited tumor cells, identifying AICART as the step in purine synthesis that becomes rate-limiting after drug treatment (19). The accumulating ZMP causes an activation of AMP-activated protein kinase with subsequent inhibition of the mammalian target of rapamycin (mTOR) and induction of autophagy. Inhibition of autophagy protects tumor cells from pemetrexed toxicity.

1.4 Preclinical Considerations of the Pemetrexed and Sorafenib Combination

In preclinical in vitro and in vivo models, sorafenib enhanced autophagy levels, and interacted in a greater than additive fashion with pemetrexed to kill tumor cells. Inhibition of autophagy blocked the toxic interaction between sorafenib and pemetrexed. Sorafenib and pemetrexed interacted in a greater than additive fashion to increase the number of autophagic vesicles in tumor cells, which was inhibited by knockdown of Beclin1, as shown in Figure 1.

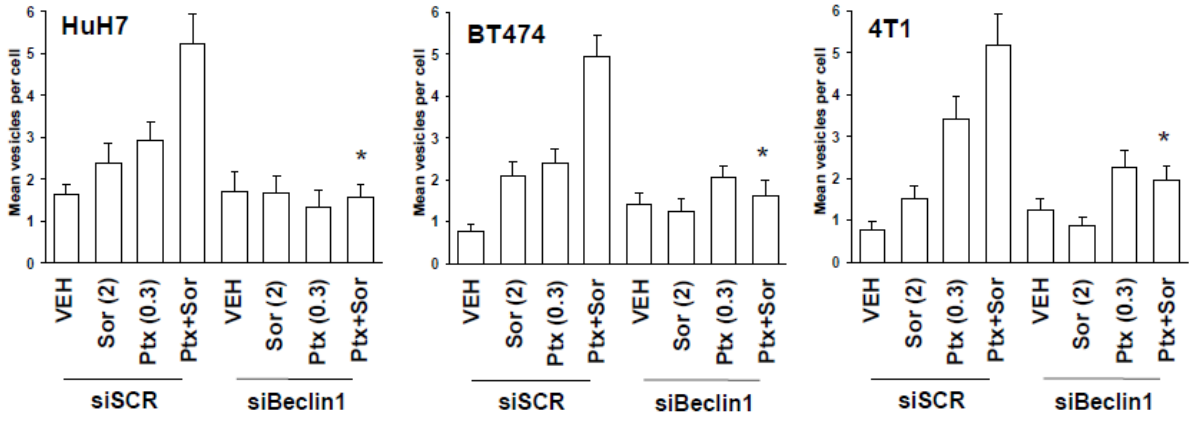


Figure 1. Additive Effect of Sorafenib and Pemetrexed in Increasing Number of Autophagic Vesicles in Tumor Cells

BT474, HuH7 and 4T1breast cancer cells indicated are transfected with siRNAs (si-scramble, siSCR; siBeclin1; 20 nM) and with a plasmid to express LC3-GFP (fluorescent protein tagged form of LC3). Twenty-four hours after transfection, cells were treated with vehicle (PBS) or pemetrexed (0.03-3.0 μM) and/or vehicle (DMSO) or sorafenib. Twelve hours after drug exposure cells were examined under a fluorescent microscope (40x) at the indicated times after drug exposure and the mean number of vesicles in 40 random cells calculated per experiment (n=2, 80 cells sampled, +/- SEM; * $p < 0.05$ less than corresponding siSCR value).

Additionally, evaluations were performed examining the relative phosphorylation and expression levels of signal transduction proteins whose expression and activity may correlate to pemetrexed + sorafenib sensitivity. Tumor cell types that displayed high levels of cell killing after pemetrexed + sorafenib exposure tended to exhibit elevated levels of ERK1/2, along with elevated expression levels of class III receptor tyrosine kinases such as PDGFRβ, FGFR1, and VEGFR1. Knockdown of PDGFRβ, p70S6K, or mTOR enhanced pemetrexed + sorafenib lethality.

Pemetrexed and sorafenib were also evaluated in murine tumor models. In orthotopic-established human mammary carcinoma tumors, sorafenib significantly reduced tumor growth, whereas pemetrexed had little impact on tumor mass (Figure 2).

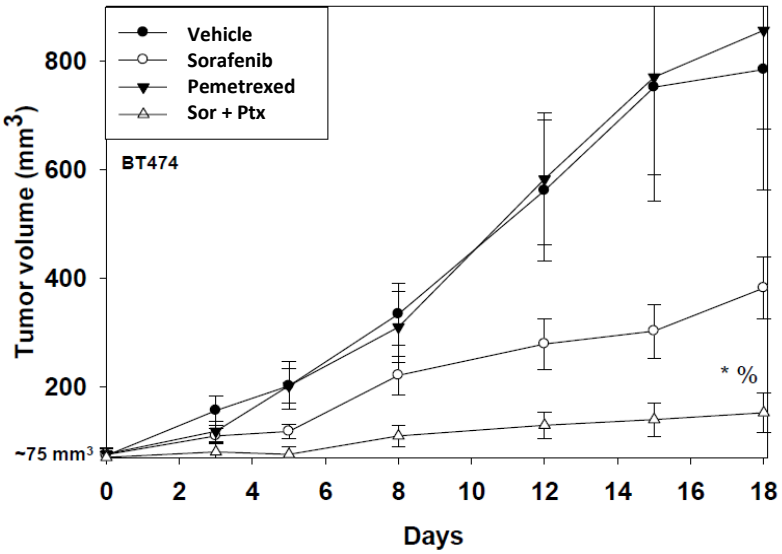


Figure 2. Reduction in Tumor Growth in HER2-positive BT474 Human Mammary Carcinoma Tumors Following Exposure to Sorafenib, Pemetrexed, and the Combination.

For studies with human mammary carcinoma cells, athymic Nu/Nu mice (8-week old, female) were injected, into the 4th mammary fat pad, with 1.0 x 10^7 BT474cells. Tumors of ~75 mm^3 grew over the following month. The animals were administered vehicle diluent (cremophore), sorafenib (25 mg/kg), pemetrexed (50 mg/kg), or the drug combination by oral gavage once every day for 5 days. Animals were treated for 5 days with drugs and tumor volumes measured every 2-3 days as indicated, and mean tumor volumes plotted (n=2 studies; 8 animals per group total +/- SEM; * $p < 0.05$ less than corresponding vehicle control value; % $p < 0.05$ less than corresponding sorafenib value).

Collectively, these data lead us to conclude that sustained inhibition of the p70S6k/mTOR-signaling module following pemetrexed and sorafenib exposure plays a central role in drug combination lethality through toxic forms of autophagy.

1.5 Phase 1 Results

In the phase 1 dose escalation study designed to find the maximum tolerated doses of pemetrexed and sorafenib, pemetrexed was administered every 2 weeks (ie, dose-dense schedule) with oral sorafenib on a continuous basis. While dose escalation continued through the initial cohorts based on lack of dose-limiting toxicities in the first cycle, it was difficult for patients to remain on continuous sorafenib when combined with dose-dense pemetrexed for more than a few cycles. Fatigue, hand-foot syndrome, and enhancement of pemetrexed-induced mucositis and cytopenias were problematic in subsequent cycles requiring dose delays and reductions.

However, in spite of the delayed toxicity issue, the combination demonstrated promising activity. Five out of 11 breast cancer patients in the phase 1 study, including 3 out of 5 patients with TNBC, demonstrated an objective response, with 4 partial responses (PRs) and one complete response (CR). In the TNBC population, there were one CR, 2 PRs, one stable disease, and one progressive disease as best response. One PR and the CR each had 10-month duration of response. All responding patients were heavily pretreated,

with a median of 6 previous lines of therapy and a mean of 6.6 previous lines. Cutaneous, nodal, and visceral metastases were all observed to respond to treatment (23). In the TNBC population, responses occurred after 2, 7, and 4 previous lines of cytotoxic therapy for metastatic disease. These tumor responses suggest that TNBC, even in heavily pretreated patients, can respond to pemetrexed and sorafenib treatment, supporting further development of this combination in pretreated patients with TNBC.

Based on the activity of the combination, the decision was made to move to an intermittent sorafenib dosing schedule for subsequent cohorts to allow continued dose escalation and dose maintenance. Intermittent dosing of sorafenib with dose-dense pemetrexed has been well tolerated, and tumor responses have continued to be observed, including in breast cancer.

The treatment doses initially selected for this phase 2 clinical trial were pemetrexed 500 mg/m^2 IV administered on day 1 with sorafenib 400 mg taken orally twice each day on days 1-5 of each 14-day cycle. This treatment regimen was well tolerated and below the highest tolerable dose of 750 mg/m^2 of pemetrexed with 400 mg PO BID of intermittent sorafenib tested in the phase 1 study. The lower dose of 500 mg/m^2 was selected for phase 2 study in breast cancer, because 4 of the 5 responding patients with breast cancer were treated at this dose during the phase 1 study. Additionally, intensification of dosing to higher doses was studied in lung cancer and high dose pemetrexed was not associated with improvements in response rate or median overall survival (24). The doses of both agents have been reduced effective with version 4 of the protocol. The new doses are pemetrexed 375 mg/m^2 IV administered on day 1 with sorafenib 200 mg taken orally twice each day on days 1-5 of each 21-day cycle.

1.6 Clinical Considerations

1.6.1 Vitamin Supplementation

Original dose-finding studies with pemetrexed were performed without folate and B_{12} supplementation. The maximum tolerated dose (MTD), without supplementation, was found to be 600 mg/m^2 dosed once every 3 weeks (25). Subsequently, it was determined that B_{12} and folate supplementation are required to mitigate pemetrexed-related hematologic toxicity. Therefore, pemetrexed will be supplemented with B_{12} and folate throughout study treatment.

1.6.2 Pemetrexed Dose-Dense Schedule

With vitamin supplementation, pemetrexed has been evaluated in multiple settings with various dosing schedules, and a variety of MTDs have been found. In a 3-week dosing schedule, single-agent pemetrexed has been reported to have a MTD of 1050 mg/m^2 (26). The MTD of pemetrexed has also been reported to be as high as 1800 mg/m^2 in combination with cyclophosphamide (27).

Pemetrexed has been studied in a dose-dense fashion, and, as a single agent, 1000 mg/m^2 was tolerated well on an every-2-week schedule (28). Much lower doses of pemetrexed demonstrated clinical activity when pemetrexed was given with sorafenib in the phase 1 study. A proposed mechanism of action of the combination of pemetrexed and sorafenib is through AICART inhibition during

pemetrexed exposure. Shortening the interval between dosing will increase the duration of AICART inhibition, which may be useful in defining the therapeutic index.

Pemetrexed was initially evaluated in the dose-dense setting for this study, but eligibility requirements were amended such that the extended (3-week) dosing schedule was thought to be more appropriate. These changes are explained further in Section 1.6.6.

1.6.3 Sorafenib Treatment Schedule

Pharmacokinetic data have demonstrated that once-daily dosing results in extremely low systemic concentrations compared to twice-daily dosing, eg, 800 mg once daily has significantly lower serum concentrations than 100 mg twice daily (29). Therefore, sorafenib will be taken by the patient on a twice-daily schedule in this phase 2 trial.

In the phase 1 study, *Pemetrexed Disodium and Sorafenib Tosylate in Treating Patients With Advanced Solid Tumors* (NCT01450384), it was identified during treatment of the initial cohort that it was difficult for patients to tolerate sorafenib on a continuous dosing schedule when combined with pemetrexed. Fatigue, hand-foot syndrome, and enhancement of pemetrexed-induced mucositis and cytopenias were observed. It is commonly recognized that single-agent sorafenib is difficult to tolerate when taken continuously at full dose. In the registration trial for sorafenib in hepatocellular carcinoma (SHARP Trial), dose reductions due to adverse events occurred in 26% of patients; dose interruptions due to adverse events occurred in 44% (30). In the phase 3 trial of sorafenib as a single agent in renal cell carcinoma, 13% of patients required dose reductions; 21% required dose omissions (31). Many patients in the continuously-dosed sorafenib cohort required both dose reductions and interruptions when combined with pemetrexed. As such, the treatment regimen in the phase 1 study was modified to implement an intermittent dosing strategy. Additionally, regorafenib, an analog of sorafenib which is FDA-approved for colorectal carcinoma and gastrointestinal stromal tumors (GIST), employs an intermittent dosing schedule, demonstrating that kinase inhibitors can be effective with intermittent dosing.

As the preclinical data suggest, combination therapy is the most effective approach for the induction of toxic autophagy. It was determined that 5 days of sorafenib dosing with each dose of pemetrexed will result in drug combination effects, and the days without therapy will allow continued dose intensity with repeated cycles. As anticipated, the intermittent dosing cohort of sorafenib has been observed to have significantly less toxicity than the continuous dosing cohort, and antitumor effects have been seen.

1.6.4 Assessment of ER, PgR, and HER2 Status in Recurrent or Metastatic Tumor

It is well known that breast cancers can undergo phenotypic shift altering expression of ER, PgR, and/or HER2 (32). Additionally, progressive cancers can acquire resistance to systemic treatment as a result of clonal evolution and selection. Therefore, eligibility will be based on the HER2, ER, and PgR reported following a biopsy or resection of recurrent or metastatic tumor. If recurrent or metastatic tumor

was not biopsied, the HER2, ER, and PgR status reported at the time of the initial diagnosis or resection will be used for eligibility screening.

1.6.5 Rationale for Modifying Eligibility Related to Previous Chemotherapy

Based on clinical experience with the initial patients referred for participation in this study, a treatment history that includes multiple previous lines of cytotoxic chemotherapy has been identified as a potential risk factor for increased hematologic toxicity related to study treatment. The decision was made to narrow eligibility to include only those who have had only one prior line of cytotoxic chemotherapy for metastatic disease and, if the patient had disease progression during or within 6 months following completion of adjuvant therapy, for first-line therapy. The related inclusion criterion was revised at the time of the first protocol amendment to reflect this decision (Section 4.1.4).

1.6.6 Rationale for Modifying Eligibility, Dose, Schedule, and Sample Size

Patients with TNBC are regularly treated with cytotoxic chemotherapy, as either single agents or doublet therapy. It was identified from the phase 1 study that patients previously treated with multiple lines of cytotoxic chemotherapy had an association with enhanced toxicity from this treatment regimen, as noted in Section 1.6.5. Accrual has been more difficult with restriction to the second line only setting, so the decision was made to re-expand to allow for patients to be more heavily pre-treated and remain eligible for study enrollment. As such, we determined that lowering the doses of both agents and treating on a 21-day cycle would be appropriate. The new dose and schedule fit with current patients on the protocol, who have found good tolerability at this dose and schedule, and with prior experience from the phase 1 study in which patients with breast cancer derived clinical benefit at doses below the recommended phase 2 dose.

Effective with version 4 of the protocol, patients with at least one prior regimen of treatment for recurrent or metastatic disease may be eligible. The dose has been reduced as described in Section 1.5 and Section 6 to accommodate the potential for hematologic toxicity in patients who have received more than one previous treatment regimen. The change in cycle length from a dose-dense (every 14 days) schedule to a 21-day schedule changes the frequency at which patients are seen in later cycles. The schedules for physical exams, tumor response assessments, Vitamin B12 administration, and correlative sample collection have been adjusted to better fit the new patient visit intervals.

In order to accurately evaluate the efficacy of pemetrexed and sorafenib in combination at the new lower dose, it was determined that stage 1 of the two-stage design should include only patients treated at that lower dose. If that cohort meets the efficacy criteria to continue, patients previously treated at the higher dose will be included in the second stage for overall evaluation of efficacy. The percent non-evaluable estimate was adjusted based on the evaluability of patients who have already enrolled to the trial. The necessary sample sizes for stage 1 and 2 of the Simon's two-stage design were re-calculated. The new sample sizes and study design are described in Section 13.

1.7 Correlative Studies

1.7.1 Archived Tumor Samples

Serial analysis can identify potential new targets for therapy. This concept is being formally explored in trials such as the NCI Molecular Analysis for Therapy Choice (NCI MATCH) Trial, and several such potential pathways will be investigated in the MCC-14-10790 clinical trial.

Based on results reported for the phase 1 trial that evaluated the pemetrexed and sorafenib combination, the targets to be explored in this phase 2 study were revised at the time of the first protocol amendment. Expression of Beclin1 and other biomarkers evaluated in the phase 1 study that did not prove to be useful targets have been removed from the planned correlative studies for MCC-14-10790. Correlative data from the phase 1 study did suggest that the level of PTEN expression may be predictive of response to the pemetrexed/sorafenib combination, and evaluation of PTEN activity has been added to the plans for this phase 2 trial (33).

TS expression will also be evaluated. TS has previously been shown to be predictive of response to pemetrexed. The autophagy pathway will continue to be explored.

Because the expression of biomarkers can change during disease progression or in response to treatment, these biomarkers will be assessed using tumor samples from diagnostic specimens obtained at the time of initial diagnosis and tumor samples archived at the time of a diagnostic core biopsy or surgical resection of recurrent or metastatic tumor.

1.7.2 Blood Samples for Multiplex Assays

Blood samples will be collected on days 1 and 2 of cycle 1, day 1 of cycle 2, and at the time of each tumor response assessment (about every 9 weeks). Additionally, a blood sample will be collected, if possible, at time of disease progression (prior to starting new cancer therapy).

The plasma is isolated and stored for subsequent multiplex assays. Plasma from each patient will be subjected to multiplex assays to determine the expression of about 80 cytokines/growth factors.

1.7.3 Blood Samples for Collection and Analysis of Circulating Tumor Cells

The presence in the blood of circulating tumor cells (CTCs) derived from breast cancer provides an opportunity to study the in vivo response of tumor cells to drug treatment, with the advantage that samples can be obtained by a simple blood draw rather than by tumor biopsy.

LC3A (microtubule-associated protein 1 light chain 3) is a protein used in the detection of autophagic vesicles (34). Increases in autophagic vesicles were detected in tumor cell lines treated with the combination of pemetrexed and sorafenib (Figure 1). Immunohistochemical (IHC) analysis of autophagy in CTCs

has not been performed to date. The feasibility of testing for autophagic vesicle formation will be determined in CTCs using blood samples collected at baseline, about 24 hours after the first pemetrexed dose, and at the time of the first tumor response assessment.

2 OBJECTIVES

2.1 Primary Objective

To determine the objective response rate (ORR) in patients with recurrent or metastatic TNBC who have received the combination of pemetrexed and sorafenib

2.2 Secondary Objectives

In patients with recurrent or metastatic TNBC who have received a combination of pemetrexed and sorafenib:

2.2.1 To evaluate progression-free survival (PFS)

2.2.2 To determine the 2-year survival rate

2.2.3 To further characterize the safety and side effect profile of the combination

[redacted]

3 STUDY DESIGN

3.1 General Description

This study is a single-arm, open-label, phase 2 study of a regimen of dose-dense pemetrexed and sorafenib to determine the objective response rate in patients with recurrent or metastatic TNBC. Eligible patients will be those who have had disease progression during or after treatment for recurrent or metastatic disease with at least one previous regimen. Additionally, patients with disease progression or recurrence during or within 6 months of completion of adjuvant or neoadjuvant therapy are also eligible. Correlative studies will be conducted using blood samples and archived tumor samples.

Simon's two-stage design will be utilized in this study. In the first stage, if ≤ 2 patients of the first 15 efficacy-evaluable patients have a partial or complete response, then the trial will end for futility. If ≥ 3 patients have a partial or complete response, patient accrual will continue in the second stage. The patients enrolled and treated at the initial higher dose will count toward the second stage, and patients will continue to be enrolled and treated until the second stage contains 13 efficacy-evaluable patients.

The total sample size for the Simon's two-stage design is 37 patients. Based on enrollment of 2-3 patients per month, the expected enrollment period will be about 18-24 months.

3.2 Primary Endpoint

The proportion of patients with objective response defined as a complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

3.3 Secondary Endpoints

3.3.1 PFS defined as the time from initiation of study treatment until documented disease progression or death, whichever occurs first

3.3.2 Proportion of patients who are alive at 2 years following initiation of study treatment

3.3.3 Adverse events (AEs) reported using criteria in the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0)

4 PATIENT SELECTION

4.1 Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible for this study.

4.1.1 Unresectable adenocarcinoma of the breast involving chest wall, regional nodes, or distant site

4.1.2 Breast cancer determined to be ER-negative **and** PgR-negative defined for this study as < 10% tumor staining by IHC

Note: Eligibility should be based on the ER and PgR status reported at the time of the most recent biopsy or resection.

4.1.3 Breast cancer determined to be HER2-negative per current American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) HER2 Guidelines

Note: Eligibility should be based on the HER2 status reported at the time of the most recent biopsy or resection.

4.1.4 At least one prior regimen for treatment of recurrent or metastatic disease

Note: Prior regimen for recurrent or metastatic disease is not required if the patient had disease progression or recurrence during or within the first 6 months following completion of adjuvant or neoadjuvant chemotherapy.

4.1.5 Measurable disease per RECIST v1.1

4.1.6 Age ≥ 18 years

4.1.7 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 1)

4.1.8 Ability to swallow oral medications

4.1.9 Adequate bone marrow function as defined below:

- Absolute neutrophil count (ANC) ≥ 1,200/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin ≥ 9.0 g/dL, which must be stable in the opinion of the investigator without a history of transfusion dependence

4.1.10 Adequate renal function as defined below:

Calculated creatinine clearance ≥ 45 mL/min (see Appendix 2 for the Cockcroft-Gault formula for calculating creatinine clearance)

4.1.11 Adequate hepatic function as defined below:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for the laboratory
- Aspartate aminotransferase (AST) ≤ 3 x ULN for the laboratory, except in the presence of known hepatic metastasis, wherein the AST may be ≤ 5 x ULN
- Alanine aminotransferase (ALT) ≤ 3 x ULN for the laboratory, except in the presence of known hepatic metastasis, wherein the ALT may be ≤ 5 x ULN

4.1.12 Serum B_{12} and folate levels ≥ lower limit of normal (LLN) for the laboratory

Note: Patients may begin B_{12} and folic acid supplementation and be reconsidered for participation in the study when levels are ≥ LLN for the laboratory.

4.1.13 Ability to take folic acid, vitamin B_{12}, and dexamethasone according to the protocol instructions in Table 1 (Section 6.2)

4.1.14 Ability to interrupt chronic non-steroidal anti-inflammatory drugs (NSAIDs) beginning 2 days before (5 days before for long-acting NSAIDs) and continuing for 2 days following administration of each pemetrexed dose

4.1.15 Toxicities from previous cancer therapies resolved to ≤ grade 1 unless specified otherwise in the inclusion or exclusion criteria (Exceptions: Chronic residual toxicities that in the opinion of the investigator are not clinically relevant given the known safety/toxicity profiles of pemetrexed and sorafenib, such as alopecia, changes in pigmentation, stable endocrinopathies. Neuropathy related to previous chemotherapy must be resolved to ≤ grade 2.)

4.1.16 Women who are not postmenopausal or have not undergone hysterectomy must have a documented negative serum pregnancy test within 7 days prior to initiating study treatment. Note: Postmenopausal is defined as one or more of the following:

- Age ≥ 60 years
- Age < 60 years and amenorrheic for at least 1 year with follicle-stimulating hormone (FSH) and plasma estradiol levels in the postmenopausal range
- Bilateral oophorectomy

4.1.17 A woman of child-bearing potential (WCBP) and a male patient with partner who is a WCBP must agree to use a medically accepted method for preventing pregnancy for the duration of study treatment and for 2 months following completion of study treatment.

4.1.18 Ability to understand and willingness to sign the consent form written in English

4.2 Exclusion Criteria

4.2.1 Any investigational agent within 4 weeks prior to initiating study treatment

4.2.2 Anticancer therapy within 2 weeks prior to initiating study treatment

4.2.3 Plans for concurrent anticancer therapy except as permitted in Section 6.7.11

4.2.4 Known or presumed intolerance of pemetrexed or sorafenib

4.2.5 Known or suspected malabsorption condition or obstruction

4.2.6 Brain metastases meeting either of the following exclusion criteria:

- Untreated brain metastases
- After completion of brain-directed therapy, the patient has not been able to tolerate discontinuation of steroids or a decrease in steroid dose

4.2.7 Leptomeningeal metastasis

4.2.8 Any documented history of clinically identifiable thrombotic, embolic, venous, or arterial events such as cerebrovascular accident, transient ischemic attack, deep vein thrombosis, or pulmonary embolism within 6 months prior to initiating study treatment

Note: Patients with an asymptomatic catheter-related thrombus or a tumor-associated thrombus of locally-involved vessels or with incidental asymptomatic filling defects identified on imaging are not excluded.

4.2.9 Contraindication to antiangiogenic agents, including:

- Serious non-healing wound, non-healing ulcer, or bone fracture
- Major surgical procedure or significant traumatic injury within 4 weeks prior to initiating study treatment
- Pulmonary hemorrhage/bleeding event ≥ grade 2 (CTCAE v4.0) within 12 weeks prior to initiating study treatment
- Any other hemorrhage/bleeding event ≥ grade 3 (CTCAE v4.0) within 12 weeks prior to initiating study treatment

4.2.10 Systolic blood pressure (BP) > 160 mmHg or diastolic BP > 100 mmHg despite optimal medical management

4.2.11 QTc interval > 480 ms (≥ grade 2) on a 12-lead electrocardiogram (ECG)

- If baseline QTc on screening ECG is ≥ grade 2:
  - Check potassium and magnesium serum levels
  - Correct any identified hypokalemia and/or hypomagnesemia and repeat ECG to confirm exclusion of patient due to QTc

- For patients with heart rate < 60 bpm or > 100 bpm, manual read of the QT interval by a cardiologist is required, with Fridericia correction applied to determine QTcF which must be used to determine eligibility.

  Note: If heart rate is 60-100 bpm, manual read of the QT interval and correction to QTcF is not required.

4.2.12 Active or clinically significant cardiac disease including any of the following:

- Unstable angina (eg, anginal symptoms at rest) or onset of angina within 3 months prior to initiating study treatment
- Myocardial infarction within 6 months prior to initiating study treatment
- Ventricular arrhythmias requiring anti-arrhythmic therapy other than beta blockers
- New York Heart Association (NYHA) class III or IV congestive heart failure (see Appendix 3)

4.2.13 Serious (ie, ≥ grade 3) uncontrolled infection

4.2.14 Uncontrolled effusion eg, presence of third space fluid that, in the opinion of the investigator, cannot be successfully controlled by drainage

Note: Patients with small effusions remaining after pleurodesis are eligible. Determination of eligibility based on pleural size will be determined by the principal investigator.

4.2.15 Known human immunodeficiency virus (HIV) seropositivity

Note: HIV testing is not required.

4.2.16 Chronic or active hepatitis B or C infection requiring treatment with antiviral therapy

4.2.17 Seizure disorder requiring enzyme-inducing anti-epileptic drugs (EIAEDs)

Note: If the seizure disorder can be managed with agents that are not EIAEDs (eg, levetiracetam or valproate), the patient should not be excluded.

4.2.18 Planned ongoing treatment with other drugs thought to potentially have adverse interactions with either of the study drugs; if such drugs have been used, patients must have discontinued these agents at least 2 weeks (or as noted below) prior to initiating study treatment. Examples include:

- STRONG CYP3A4 inducers (see Section 6.7.12)

  Note: Examples of clinical inducers for cytochrome P450 (CYP) isozymes and classification of strong, moderate, and weak interactions are available through the FDA website (Table 3-3 of website):

  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

- Immunosuppressants (eg, tacrolimus, leflunomide, tofacitinib, roflumilast, pimecrolimus) (see Section 6.7.12)
- NSAIDs

  Note: NSAIDs must be discontinued within 5 days prior to initiating study treatment (see Section 6.7.10).

4.2.19 Pregnancy or breastfeeding

4.2.20 Previous malignancy with the following exceptions: adequately treated basal cell carcinoma or squamous cell carcinoma of the skin; any in situ malignancy; adequately treated Stage 1 or Stage 2 cancer from which the patient is currently in remission; any other cancer from which the patient has been disease-free for 3 years

4.2.21 Medical, psychological, or social condition that, in the opinion of the investigator, may increase the patient's risk or limit the patient's adherence with study requirements

5 STUDY ENTRY AND WITHDRAWAL PROCEDURES

5.1 Study Entry Procedures

5.1.1 Required Pre-Registration Screening Tests and Procedures

5.1.2 Refer to the study calendars in Section 12 (Table 10) for the screening tests and procedures that are required prior to registration and/or treatment and for the timing of these events relative to the start of treatment.

5.1.3 Registration Process

To register a patient, the following documents must be provided to the registrar at VCU Massey Cancer Center [redacted]

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

The registrar will complete the registration process by assigning a study identification (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 the patient's initial enrollment data (eg, demographics, consent, eligibility, on study) into the OnCore database within 24 hours following study registration and before treatment begins.

5.2 Study Withdrawal

A patient may decide to withdraw from study participation at any time. Patients must be withdrawn from the study when any of the following occurs:

- Consent withdrawal for study treatment and study procedures
- If, in the investigator's opinion, continuation of the study requirements would be harmful to the patient's well-being
- Patient is lost to follow-up

The reason for and date associated with study withdrawal or removal from the study must be documented in the source documents and OnCore database.

6 STUDY TREATMENT

6.1 Baseline Tests and Procedures

Patients who are eligible and enrolled in the study but do not immediately initiate study treatment are expected to meet eligibility criteria until the time when treatment is initiated. For example, if an enrolled patient's post-enrollment (pretreatment) liver function tests no longer meet eligibility criteria, treatment should be held until the investigator can provide guidance to the study team.

6.2 Administration of Study Treatment

Pharmaceutical information and instructions for pemetrexed and sorafenib are included in Sections 9.1 and 9.2, respectively. The study treatment regimen is outlined on Table 1.

Table 1. Study Treatment Regimen

Study Medication	Dose	Route of Administration	Treatment Schedule
Study Treatment			
Pemetrexed	375 mg/m^2	Intravenous infusion over 10 minutes[A]	Administered on **day 1** of each 21-day cycle[B]
Sorafenib	200 mg	Oral	Taken **twice daily** on an empty stomach on **days 1-5** of each 21-day cycle[C]
Supplementation and Premedication Regimen[D]			
Folic acid	1 mg	Oral	Taken **once daily** as follows: • On at least 5 days during the 7-day period preceding the first dose of pemetrexed • Throughout treatment with pemetrexed • Continued for 21 days after the last dose of pemetrexed
Vitamin B_{12}	1000 mcg	Intramuscular	Administered **once at each time point** as follows: • 1-2 weeks prior to the first dose of pemetrexed[E] • Approximately every 9 weeks during pemetrexed treatment[F] • Continuing through approximately 8 weeks following the last dose of pemetrexed
Dexamethasone[G]	4 mg	Oral	Taken **twice daily** on the: • Day before pemetrexed treatment • Day of pemetrexed treatment • Day after pemetrexed treatment

A. If necessary, the duration of the pemetrexed infusion may be extended to a maximum of 20 minutes.

B. **The following criteria must be met for each pemetrexed treatment**: ANC must be ≥ 1,200/mm^3; platelet count must be ≥ 100,000/mm^3; and calculated creatinine clearance must be ≥ 45 mL/min (see Appendix 2 for Cockcroft-Gault equation).

C. Instruct patient to take sorafenib on an empty stomach (ie, at least 1 hour before or 2 hours after eating) starting the morning of each pemetrexed dose.

D. Refer to Section 9.1.6 for supplementation rationale.

E. The time period required for the initial B_{12} injection may be extended to 15 days prior to initiating pemetrexed. If the B_{12} level prior to study registration was < LLN for the lab, a second B_{12} injection should be administered, preferably prior to initiation of pemetrexed but no later than prior to the third dose of pemetrexed.

F. After the initial dose (given prior to initiation of pemetrexed therapy), vitamin B_{12} injections may be administered on the same day as the pemetrexed treatment.

G. At the investigator's discretion, patients who do not develop pemetrexed-associated drug rash and who have difficulty tolerating dexamethasone may omit or reduce the dexamethasone dose.

6.3 Missed Sorafenib Doses

If a sorafenib dose is missed, the patient will be instructed to omit the dose and to not take more than 2 doses of sorafenib on the same day to make up for doses that were missed on the previous day.

6.4 Monitoring Patient Adherence with Oral Medications

Patients will be instructed to record the doses of sorafenib they have taken in the study medication diary that will be provided. Also, concurrent medication assessments will be used to capture B_{12} and folic acid supplementation, dexamethasone, and supportive care medications.

Patients will be instructed to bring their diary and any unused sorafenib to each visit with their study team. The diary will be reviewed by the study team periodically (see study calendar [Table 11]). Patient reports of self-administration, review of medication diary, and pill counts will be used to assess patient adherence with the sorafenib regimen.

6.5 Duration of Therapy

Study treatment will continue until one of the following occurs (also see Study Withdrawal, Section 5.2):

- More than 3 consecutive weeks of treatment delay due to unresolved toxicity
- AE that requires discontinuation of study treatment (see Section 7)
- Pregnancy
- Determination by the investigator that discontinuation is in the patient's best medical interest
- Disease progression
- Patient decision to discontinue study treatment
- Withdrawal of study sponsor support

The reason for discontinuation of study treatment must be documented in the source documents and in the OnCore database.

6.6 QT Prolongation Considerations

6.6.1 Any time the QT interval is evaluated, follow the guidelines listed below:

- When HR < 60 bpm or >100 bpm, manual read of the QT interval by a cardiologist using Fridericia correction is required.
- When HR is within the range of 60 bpm -100 bpm, a manual read of the QT interval is **not** required.

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

6.6.2 To the extent possible, concurrent use of sorafenib with 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).

Note: 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 Torsade 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."

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

- Grade 0 (< 450 ms), a follow-up 12-lead ECG with QTc evaluation should be done at the next scheduled visit.
- Grade 1 (450-480 ms), a follow-up 12-lead ECG with QTc evaluation should be done within 8 days after concurrent use starts.
- Grade 2 (481-500 ms), withhold study treatment until a follow-up 12-lead ECG at the next possible opportunity shows QTc ≤ grade 1 (≤ 480 ms); evaluate QTc within 8 days after reintroduction of study treatment.

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

6.6.5 Refer to Table 5 (Section 7.8) for instructions regarding any episode of syncope (grade 3) or near-syncope (pre-syncope grade 2) and for prolonged QTc interval grade 3 or 4.

6.7 General Concomitant Medication and Supportive Care Guidelines

6.7.1 Hypertension

Hypertension is commonly encountered; rarely, dangerous levels of hypertension are associated with sorafenib therapy. BP will be monitored on day 1 of each treatment cycle and as clinically indicated throughout study treatment. Clinically significant hypertension should be managed aggressively by the investigator to prevent complications.

6.7.2 Nausea/Vomiting

Anti-emetics should be prescribed, per the investigator's discretion, as clinically indicated.

6.7.3 Diarrhea

Clinically significant diarrhea should be managed aggressively to prevent electrolyte abnormalities and dehydration. Diarrhea can be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea-free for 12 hours.

6.7.4 Management of Dyspepsia/Gastrointestinal Reflux

Consider the addition of proton pump inhibitors for prophylaxis or treatment of dyspepsia/GI reflux, especially in those who have known history of either condition.

6.7.5 Fluid and Electrolyte Abnormalities

- Patients who develop diarrhea, mucositis, anorexia, or other toxicity that can contribute to fluid loss or inadequate fluid intake should be carefully monitored and rehydrated, as clinically necessary, to minimize the risk of postural hypotension and renal failure.

- Fluids should be administered, as indicated, to prevent and/or treat dehydration. Maintain appropriate electrolyte balance including correction of hypokalemia, hypophosphatemia, and hypomagnesemia, if possible, prior to and during study treatment. Oral supplementation of magnesium, potassium, and phosphorus should be considered to be standard supportive measures in those patients who demonstrate electrolyte abnormalities.

6.7.6 Palmar-Plantar Erythrodysesthesia

Palmar-plantar erythrodysesthesia (PPE), also known as hand-foot skin reaction, is a common adverse reaction associated with sorafenib. Biopsy specimens of patients with PPE secondary to tyrosine kinase inhibition show hyperkeratosis, keratinocyte necrosis, and dermal inflammation. Sorafenib dose modification instructions are provided on Table 6 in Section 7.8; recommended management strategies for skin toxicities consistent with PPE are summarized in this section of the protocol.

PPE Prevention

- Before initiating sorafenib treatment, 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 each day throughout treatment.

PPE Treatment

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

- Instruct the patient to protect tender areas as follows:
  - Use socks/gloves to cover moisturizing creams
  - Wear well-padded footwear; use insole cushions or inserts.
  - Soak feet in 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 twice each day. Approximately 5% to 8% strength provides gentle chemical exfoliation.
  - Topical analgesics (eg, lidocaine 2%) may be used for pain control.
  - Topical corticosteroids (eg, clobetasol 0.05%) should be considered for patients with grade 2 or 3 PPE.
- Systemic steroids (except the dexamethasone doses on the day before, the day of, and the day after each pemetrexed dose) should be avoided.

6.7.7 Third Space Fluid

For patients who develop clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) before or during initiation of pemetrexed therapy, consideration should be given to draining the effusion prior to dosing. However, if in the investigator's opinion, the effusion represents progression of disease, study treatment will be discontinued.

6.7.8 Blood Product Support and Growth Factors

Transfusions and hematopoietic growth factors are permitted at the investigator's discretion.

6.7.9 Leucovorin for Management of Severe Neutropenia, Thrombocytopenia, and Mucositis

Because folic acid and vitamin B_{12} supplementation has significantly reduced the number of episodes of grade 4 hematologic and grades 3 and 4 non-hematologic toxicities associated with pemetrexed therapy, the need for leucovorin as a rescue agent is not anticipated.

However, if necessary, leucovorin is permitted, but not required, for any of the following:

- Grade 4 neutropenia lasting > 3 days
- Grade 4 leukopenia lasting > 3 days
- Grade 4 thrombocytopenia (leucovorin should be administered immediately)
- Grade 3 thrombocytopenia associated with bleeding
- Grade 3 or 4 mucositis

The recommended doses and schedule for leucovorin rescue are as follows: Leucovorin 100 mg/m^2 IV once, followed by leucovorin 50 mg/m^2 IV every 6 hours for up to 8 days.

6.7.10 Use of NSAIDs

Use of NSAIDs during study treatment should be avoided. However, if the investigator determines that NSAID use is required, the guidelines below should be followed:

- *Patients with normal renal function (ie, creatinine clearance ≥ 80 mL/min)*

  Although ibuprofen can decrease the clearance of pemetrexed, up to 400 mg 4 times a day can be administered with pemetrexed in patients with normal renal function.

- *Patients with mild to moderate renal insufficiency (creatinine clearance from 45 mL/min to 79 mL/min)*

  Caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency. Patients with mild to moderate renal insufficiency, should avoid taking NSAIDs with short elimination half-lives beginning 2 days before and continuing until 2 days following administration of pemetrexed.

- *All patients*

  In the absence of data regarding potential interaction between pemetrexed and **NSAIDs with longer half-lives**, all patients taking these NSAIDs should interrupt dosing beginning 5 days before and continuing until 2 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal toxicity, and gastrointestinal toxicity.

6.7.11 Other Cancer Therapy

Cancer treatment, other than the treatment specified in the protocol, is not permitted with the **following exceptions**:

- Palliative radiation therapy as long as the target lesion(s) is not included in the treatment field and no more than 10% of bone marrow is irradiated
- Bisphosphonates
- Receptor activator of nuclear factor-kappa B ligand (RANKL)-inhibitors (eg, denosumab)

6.7.12 Prohibited/Discouraged Medications

- Non-prescription nutritional and dietary supplements are discouraged but not prohibited unless known to have drug interactions or modulation of drug metabolism pathways. If nutritional and/or dietary supplements are used, dose and schedule of the supplements should be documented.
- Hepatotoxicity from sorafenib is a known toxicity, and acetaminophen may confound interpretation of toxicity. Therefore, acetaminophen should be avoided, if possible, in patients with ≥ grade 2 elevation of AST, ALT, or total bilirubin.

- Patients may not receive medications in the following classes during study treatment. If such medications have been used, the patient must have discontinued these agents ≥ 2 weeks before starting/resuming study treatment.
  - Immunosuppressants such as tacrolimus, leflunomide or tofacitinib, roflumilast, pimecrolimus
  - Strong CYP3A4 inducers (refer to Section 4.2.18).

6.8 Study Pocket Card for Patients

A pocket card identifying the name of the study, the names of the study medications, and contact information including the study team and a 24-hour on-call study physician will be provided to each patient. The purpose of this card is to facilitate communication between the study team and the patient's health care providers not involved with the study. Patients will be encouraged to carry the card with them at all times and to show it to their health care providers so that potential interactions with the study medications can be identified before initiating new medications.

6.9 Follow-Up Period

6.9.1 Required Monitoring of Vitamin B_{12} and Folate Supplementation

All patients who have received pemetrexed will be monitored to ensure that vitamin B_{12} and folic acid supplementation continue after the last pemetrexed dose as described in Table 1 (Section 6.2).

6.9.2 30-Day Evaluation of AEs

Patients who discontinue treatment for any reason other than consent withdrawal remain on study in follow-up status for a 30-day evaluation period following the last dose of study treatment. During this 30-day post-treatment period, resolution or stabilization of ongoing treatment-related AEs, and evolution of new treatment-related AEs will be reported.

6.9.3 Disease Progression and Survival Follow-Up Requirements

- All patients who have discontinued study treatment due to toxicity or reason other than disease progression will continue to have assessments for tumor response until 2 years after initiation of study therapy or until new cancer therapy is initiated or until disease progression, whichever occurs first.

- All patients will be followed for survival following discontinuation of study therapy until 2 years after initiation of study therapy or death, whichever occurs first.

The patient's follow-up status will be recorded in the source documents and the CRFs.

7 DOSING DELAYS/DOSING MODIFICATIONS

7.1 Recording Dose Modifications

All dosing interruptions and modifications will be recorded in the source documents and captured in the OnCore database.

7.2 Toxicity Assessment

Dose reduction should be limited to management of toxicity related to study treatment and not for management of adverse effects determined by the investigator to be related to underlying disease or other medical condition or concomitant treatment.

If a patient experiences more than one toxicity:

- Dose reduction should be according to the instructions for the clinically significant toxicity with the higher grade.
- In the case of 2 or more toxicities of the same grade, the investigator may dose reduce according to the toxicity determined to be the most likely to be related to study treatment.

7.3 Toxicity Grading

AEs will be characterized and graded according to NCI CTCAE v4.0.

7.4 General Instructions and Guidelines

7.4.1 Cycle Delays

- The following criteria **must be met** before administration of pemetrexed on day 1 of each cycle:
  - ANC must be ≥ 1,200/mm^3
  - platelet count must be ≥ 100,000/mm^3
  - calculated creatinine clearance must be ≥ 45 mL/min (see Appendix 2 for Cockcroft-Gault equation)
- If treatment has been held due to toxicity, all toxicity must have recovered to meet the criteria outlined in the dose modification tables and other instructions outlined in Section 7 before resuming study treatment.
- If pemetrexed must be held on cycle day 1, sorafenib must also be held until pemetrexed can be administered.
- If sorafenib must be held for sorafenib-related toxicity, administration of pemetrexed should also be delayed for **up to 1 week**. If sorafenib treatment cannot be resumed after 1 week of treatment delay, pemetrexed should be resumed.
- With permission from the principal investigator, a treatment cycle may be delayed for up to 2 weeks for scheduling purposes.

7.4.2 Dose Escalation

If the dose of either of the study medications has been reduced, the dose may be re-escalated at the investigator's discretion to no higher than the starting dose, unless the patient has had a grade 4 AE related to the agent being considered for re-escalation.

7.4.3 Required Discontinuation of Study Treatment

- If treatment has been held due to toxicity and recovery has not been sufficient to resume treatment after 3 weeks of treatment **delay**, study treatment must be discontinued.

7.4.4 Dose Modification Guidelines

- Unless specified otherwise in the dose modification protocol instructions, the sorafenib dose should only be reduced for sorafenib-related toxicity and the pemetrexed dose should only be reduced for pemetrexed-related toxicity.
- If a toxicity requiring interruption of sorafenib occurs early during the treatment cycle, the remaining sorafenib dose(s) in the cycle will be **omitted** (ie, these doses will not be made up).
- Study treatment should be modified in response to clinically significant toxicities attributed to study treatment. If a specific toxicity is not covered in the dose modification tables in Sections 7.6 and 7.8, follow the instructions listed below. (Refer to Appendix 4 for a list of hematologic toxicities using CTCAE v4.0 terminology.)
  - Grade 1 non-hematologic toxicity: Maintain dose
  - Grade 2 non-hematologic toxicity: Option to modify dose
  - Grade 3 non-hematologic toxicity: Requirement to modify dose

    Exceptions: Dose reduction is not required for alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity, and laboratory abnormalities that are asymptomatic and/or not clinically significant in the opinion of the investigator.
  - Grade 4 non-hematologic toxicity: Discontinue study treatment
  - Grade 4 hematologic toxicity: Requirement to modify the **pemetrexed** dose; recommendation to modify the sorafenib dose

    Exception: Dose reduction is not required for grade 4 decrease in lymphocyte count.

7.5 Dose Reduction Steps for Pemetrexed

The dose reduction steps to be used for pemetrexed are listed in the table below. (Dose reduction steps for sorafenib are listed in Table 4.)

Table 2. Dose Reduction Steps for Pemetrexed

Dose Reduction Step	Pemetrexed
Full Dose	375 mg/m^2 on day 1 of each 21-day cycle
If reduction from previous step is indicated:	275 mg/m^2 on day 1 of each 21-day cycle
If reduction from previous step is indicated:	200 mg/m^2 on day 1 of each 21-day cycle
If reduction from previous step is indicated:	Discontinue study treatment

7.6 Dose Modification Instructions for Pemetrexed

In addition to the dose modification instructions in Section 7.4, instructions for specific pemetrexed-related toxicities are listed in Table 3.

Table 3. Dose Modification Instructions for Pemetrexed

Toxicity	Pemetrexed Dose Modifications *(Refer to Table 2 for pemetrexed dose reduction steps)*
Investigations (Hematologic)	
Nadir ANC < 500/mm^3 **and** nadir platelets ≥ 50,000/mm^3	• Hold study treatment until criteria for treatment are met.* • When resuming treatment, decrease pemetrexed dose by one dose reduction step.
Nadir platelets < 50,000/mm^3 without bleeding regardless of nadir ANC	
Nadir platelets < 50,000/mm^3 with bleeding regardless of nadir ANC	• Hold study treatment until criteria for treatment are met.* • When resuming treatment, decrease pemetrexed dose by one dose reduction step.
Gastrointestinal Disorders	
Grade 3 or 4 mucositis	• Hold study treatment until resolution to ≤ grade 1. • When restarting study treatment, decrease the dose of pemetrexed by one dose reduction step.
Other Pemetrexed-Related Non-Hematologic Toxicities	
Grade 2 non-hematologic toxicity that is persistent, intolerable, or unresponsive to optimal management	At the investigator's discretion, reduce the dose of pemetrexed by one dose reduction step.
Grade 3	Hold study treatment until resolution to ≤ grade 1, tolerable grade 2, or baseline. • When resuming study treatment, decrease the pemetrexed dose by one dose reduction step. Exceptions: Pemetrexed dose reduction is not required for alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity, and laboratory abnormalities that are asymptomatic and/or not clinically significant in the opinion of the investigator. • If toxicity persists for more than 3 weeks of delay, discontinue study treatment. • For bleeding that requires more than minor medical intervention, consider discontinuing study treatment.
Grade 4	Discontinue study treatment.
*Laboratory criteria that must be met before each pemetrexed dose are: - ANC must be ≥ 1,200/mm^3 - platelet count must be ≥ 100,000/mm^3 - calculated creatinine clearance must be ≥ 45 mL/min (see Appendix 2 for Cockcroft-Gault equation)	

7.7 Dose Reduction Steps for Sorafenib

The dose reduction steps to be used for sorafenib are listed in Table 4. (Dose reduction steps for pemetrexed are listed in Table 2.)

Table 4. Dose Reduction Steps for Sorafenib

Dose Reduction Step	Sorafenib *(In Each Cycle)*
Full Dose	200 mg BID on days 1-5
If reduction from previous step is indicated:	200 mg BID on days 1-3
If reduction from previous step is indicated:	200 mg BID on day 1 only
If reduction from previous step is indicated:	Discontinue Sorafenib

7.8 Dose Modification Instructions for Sorafenib

In addition to the dose modification instructions in Section 7.4, dose modification instructions for specific sorafenib-related toxicities are listed in Table 5 and Table 6.

Table 5. Sorafenib Dose Modification Guidelines

Toxicity	Sorafenib Modification *(Refer to Table 4 for sorafenib dose reduction steps)*
Cardiac	
Grade 3 or 4 myocardial infarction	Discontinue sorafenib
Gastrointestinal Disorders	
Perforation (esophageal, gastric, colonic, duodenal, ileal, jejunal, rectal, or small intestine)	Discontinue sorafenib
Investigations	
Grade 3 or 4 AST or ALT increased	Hold sorafenib: • *If ≤ grade 1 elevation in AST and/or ALT at baseline:* - If no alternative explanation for transaminitis can be determined (such as viral hepatitis, progressive underlying hepatic metastasis), discontinue sorafenib - Otherwise, upon resolution to ≤ grade 1, resume sorafenib with a decrease in sorafenib dose of one dose reduction step • *If grade 2 elevation in AST and/or ALT secondary to hepatic metastasis at baseline*: - If ≥ 50% increase from baseline and no alternative explanation for transaminitis can be determined (such as viral hepatitis, progressive underlying hepatic metastasis), discontinue sorafenib - If < 50% increase from baseline, upon resolution to ≤ grade 2, resume sorafenib with a decrease in sorafenib dose of one dose reduction step
Grade 3 ECG QTc interval prolonged *See Section 6.6 for additional instructions*	Hold sorafenib: • Check and immediately administer potassium and/or magnesium to achieve potassium level of ≥ 4 mEq and magnesium level of ≥ 2 mEq • Consider chronic oral potassium and/or magnesium supplementation • Review with investigator prior to patient's next scheduled treatment, considering the following options: - Hold sorafenib until QTc recovers to pre-study treatment baseline (≤ grade 1 [≤ 480ms]) - When QTc returns to baseline, resume sorafenib cautiously with additional QTc monitoring at earliest opportunity within 8 days after resuming sorafenib - If QTc prolongation is thought to be related to sorafenib, decrease sorafenib dose by one dose reduction step when resuming sorafenib - For recurrent grade 3 QTc thought to be related to sorafenib despite dose reduction, consider discontinuation of sorafenib
Grade 4 ECG QTc interval prolonged	Discontinue sorafenib

Table 5 continued on the next 2 pages

Table 5. Sorafenib Dose Modification Guidelines

Toxicity	Sorafenib Modification *(Refer to Table 4 for sorafenib dose reduction steps)*
Nervous System Disorders	
Grade 2 pre-syncope or grade 3 syncope *(potentially reflecting cardiotoxicity)*	• Obtain 12-lead ECG for cardiology review/consultation • Check magnesium and/or potassium levels; promptly administer potassium and magnesium to achieve a potassium level of ≥ 4 mEq and magnesium level ≥ 2 mEq • IF ECG shows new dysrhythmia or QTc ≥ grade 2 (> 480ms), hospitalize for monitoring with cardiology consultation • Hold sorafenib until any potassium and magnesium abnormalities are corrected, symptoms resolved, and QTc improved to ≤ grade 1 (≤ 480ms) • Reintroduce sorafenib cautiously, with input from cardiology and with additional QTc evaluation, either concurrent with reintroduction or at earliest possible opportunity within 8 days from reintroduction • If event is thought to be related to sorafenib, consider reducing the sorafenib dose by one dose reduction step when resuming sorafenib • Consider chronic oral supplementation of potassium and/or magnesium • For recurrent syncope or near-syncope thought to be related to sorafenib, consider discontinuation of sorafenib
Skin and Subcutaneous Disorders	
PPE (hand-foot syndrome)	See Table 6 for instructions related to PPE
Grade 3 or 4 rash acneiform	Hold sorafenib: • Re-evaluate at least weekly until resolution to ≤ grade 1 or tolerable grade 2 • When resuming sorafenib, decrease sorafenib dose by one dose reduction step • If rash persists for more than 3 weeks of treatment delay, discontinue sorafenib • If grade 4 acneiform rash (related to sorafenib), sorafenib may be discontinued at investigator's discretion
Stevens-Johnson syndrome or toxic epidermal necrolysis	Discontinue sorafenib if Stevens-Johnson Syndrome or toxic epidermal necrolysis are suspected
Vascular Disorders	
Hypertension defined as systolic BP > 160 mmHg **and** diastolic BP > 100 mm/Hg	Hold sorafenib until resolution to ≤ grade 2 When resuming sorafenib, decrease sorafenib dose by one dose reduction step; **monitor BP weekly for 4 weeks**
Grade 4 hypertension	Discontinue sorafenib

Table 5 continued on the next page

Table 5. Sorafenib Dose Modification Guidelines	
Toxicity	**Sorafenib Modification** *(Refer to Table 4 for sorafenib dose reduction steps)*
Other Sorafenib-Related Non-Hematologic Toxicities	
Any grade 2 non-hematologic toxicity that is persistent, intolerable, or unresponsive to optimal management	At the investigator's discretion, reduce by one dose reduction step
Grade 3	Hold sorafenib until resolution to ≤ grade 1, tolerable grade 2, or baseline: • When resuming sorafenib, decrease the sorafenib dose by one dose reduction step Exceptions: Sorafenib dose reduction is not required for alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity, and laboratory abnormalities that are asymptomatic and/or not clinically significant in the opinion of the investigator • If toxicity persists for more than 3 weeks of treatment delay, discontinue sorafenib • For bleeding that requires more than minor medical intervention, consider discontinuing sorafenib
Grade 4	Discontinue sorafenib

Table 6. Sorafenib Dose Reduction Guidelines for PPE

Grade	Occurrence	Action *(Refer to Table 4 for sorafenib dose reduction steps)*
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 or 2nd occurrence	• Continue sorafenib and institute supportive measures for symptomatic relief.* • If no improvement during the remainder of the cycle, see below.
	3rd occurrence or persistence of grade 2 toxicity through the remainder of the cycle	• Stop sorafenib treatment until toxicity resolves to ≤ grade 1. • When resuming treatment (next cycle), decrease sorafenib dose by one dose reduction step. • 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 1. • When resuming treatment, decrease sorafenib by one dose reduction step. • Institute or continue supportive measures for symptomatic relief.*
	3rd occurrence or persistence of grade 3 toxicity through the remainder of the cycle	Discontinue sorafenib.
* See Section 6.7.6 for prevention and management guidelines for PPE.		

8 ADVERSE EVENT: 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 AE (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 the investigator, its occurrence places the patient or patient 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,

  Planned inpatient hospitalizations, eg, for planned surgery, or those that occur for logistical reasons, eg, to complete a therapy that cannot be completed due to outpatient clinic business hours, are exempt from SAE reporting. Events that prolong such hospitalizations and otherwise meet reporting criteria are, however, still subject to SAE reporting requirements.
- a persistent or significant 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 jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Unanticipated Problem (UP)

Unanticipated problems 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 research protocol and informed consent document approved by the institutional review board (IRB); and (b) the characteristics of the patient population being studied;

- related or possibly related to participation in the research (possibly related means 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 patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.4 AE Description and Grade

The descriptions and grading scales found in the revised CTCAE v4.0 will be utilized for AE reporting.

8.1.5 AE Expectedness

AEs can be 'Unexpected' or 'Expected'. Expected AEs are those AEs, the specificity and severity of which are consistent with the listings for pemetrexed and sorafenib found in protocol Sections 9.1 and 9.2, respectively, or in the most current version of the FDA-approved prescribing information for each drug.

Unexpected AEs are those AEs occurring in one or more patients participating in the study, 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 patient(s) experiencing the AE and the patient's predisposing risk factor profile for the AE.

8.1.6 AE Attribution

- 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.

8.2 Known AEs

The expected AEs for pemetrexed can be found in protocol Section 9.1 and in the pemetrexed (Alimta) prescribing information. The known AEs for sorafenib can be found in protocol Section 9.2 and in the sorafenib (Nexavar) prescribing information.

8.3 Secondary Malignancy

A secondary malignancy is a cancer caused by previous treatment for a malignancy (eg, treatment with investigational agent/intervention, radiation therapy, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. Any secondary malignancy should be reported via expedited reporting mechanisms.

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, and UPs

All AEs, SAEs, and UPs will be recorded in MCC's OnCore Clinical Trials Management System. In most cases, it is 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 and UPs

Refer to Table 7 for expedited reporting requirements and instructions. Also, refer to Section 8.7 for requirements and instructions for expedited reporting to Eli Lilly and Company and to Section 8.8 for requirements and instructions for expedited reporting to Bayer HealthCare Pharmaceuticals, Inc.

Table 7. Expedited Reporting Requirements

SAEs	UPs
Principal Investigator[A] Andrew Poklepovic [redacted]	**Principal Investigator[A]** Andrew Poklepovic [redacted]
Study Team[A] [redacted]	**Study Team[A]** [redacted]
Eli Lilly and Company[B]	**DSMC[C]** [redacted]
Bayer HealthCare Pharmaceuticals, Inc[D]	**IRB[E]**
	Eli Lilly and Company[B]
	Bayer HealthCare Pharmaceuticals, Inc[D]

A. Report event within 1 business day of becoming aware of the occurrence. A PDF of a de-identified OnCore SAE or Deviation record may be used for expedited event reporting purposes.

B. Refer to Section 8.7 for requirements and instructions for expedited reporting to Lilly.

C. Report each UP within 24 hours of becoming aware of the occurrence. A PDF of a de-identified OnCore SAE or Deviation record may be used for expedited event reporting purposes.

D. Refer to Section 8.8 for requirements and instructions for expedited reporting to Bayer.

E. Report each UP to the VCU IRB within 24 hours of becoming aware of the occurrence.

8.7 Requirements for Expedited Reporting to Eli Lilly and Company

8.7.1 SAEs

- All SAEs possibly, probably, or definitely related to pemetrexed must be reported to Lilly within 24 hours of the principal investigator's awareness.
- The written SAE report should be completed using a Council for International Organization for Medical Sciences (CIOMS) Suspect Adverse Reaction Report Form. This form is available on the CIOMS website

8.7.2 Other Events Requiring Expedited Reporting to Lilly

In addition to an event determined to be an UP, any event that the principal investigator determines is new and important and possibly, probably, or definitely related to pemetrexed will be reported to Lilly within 24 hours of the investigator's awareness.

8.7.3 Reporting Method

Fax completed forms and reports to Lilly using either of the following numbers:

[redacted]

8.8 Requirements for Expedited Reporting to Bayer HealthCare Pharmaceuticals, Inc

8.8.1 SAEs

All SAEs must be reported to Bayer within 24 hours of the principal investigator's awareness and must include the following minimum information:

- Name and contact information of the reporter
- Name of the study drug(s)
- Description of the reported SAE
- Patient identified by one or more of the following:
  - Patient initials
  - Patient identification number for the study
  - Knowledge that a patient who experienced the AE exists
  - Age
  - Sex
- Investigator assessment of study drug causality; a separate causality assessment should be provided for each study drug.

Additional data that would aid the review and causality assessment of the case include but are not limited to:

- Date of onset
- Severity
- Time from administration of study drug(s) to start of the event
- Duration and outcome of the event
- Any possible etiology for the event
- Final diagnosis or syndrome, if known
- Actions taken, if any

8.8.2 Other Events Requiring Expedited Reporting to Bayer

The investigator will report to Bayer within 24 hours of the investigator's awareness of other events such as:

- UPs or any other new and important event related to treatment with the study medications
- Any pregnancy during which a female patient was exposed to sorafenib

8.8.3 Form to be Used for Expedited Reporting of SAEs to Bayer

The written SAE report should be completed using a CIOMS form. This form is available on the CIOMS website.

8.8.4 Reporting Methods

All reports will be sent to Bayer by either of the following methods:

- [redacted]
- [redacted]

9 PHARMACEUTICAL INFORMATION

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

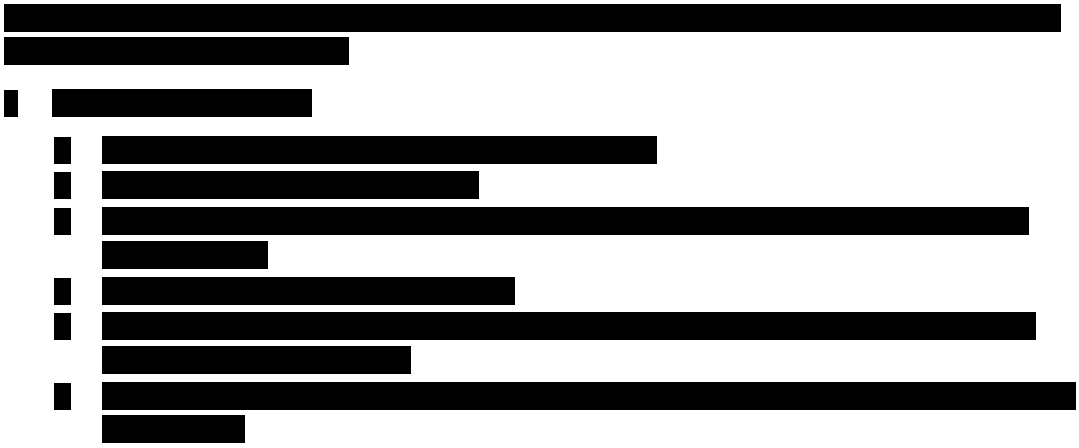
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]			[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

10 MEASUREMENT OF EFFECT

10.1 Criteria for Tumor Response

Tumor response will be evaluated and recorded using RECIST v1.1 (35).

10.2 Tumor Response Requirements

10.2.1 Time Points for Assessment of Tumor Response

Tumor response will be assessed at the following time points:

- At baseline
- At the end of cycle 3 and then every 9 weeks (+/- 1 week)

At the investigator's discretion, additional assessments may be performed when clinically indicated.

10.2.2 Imaging

Only imaging of the initial sites of disease is required at subsequent time points to provide tumor measurements for assessment of antitumor effect. The same type of imaging used at baseline should be used at each scheduled assessment.

10.2.3 Clinical Examination

- Per RECIST v1.1 criteria (35), imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but can be assessed by clinical exam.
- Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (eg, skin nodules).

10.3 Confirmation of Response

In the event of a PR or CR, the method used when the response was first documented must be repeated at the time of the next scheduled evaluation (ie, in about 10 weeks) to confirm the tumor response. (At the investigator's discretion, confirmatory assessments can be performed sooner, but no less than 4 weeks following the assessment [imaging or clinical examination] indicating the PR or CR.)

10.4 Central Review for Imaging Interpretation

Centralized radiologic review for evaluation of tumor response will be conducted.

11 CORRELATIVE STUDIES

11.1 Participation in Correlative Studies

Section 1.7 outlines the plans and rationale for the correlative studies.

Participation in the correlative studies using collected blood samples and samples from archived tumor tissue, **if available**, is mandatory.

11.2 Collection, Processing, and Distribution of Samples

- The study team will coordinate collection of all correlative samples.
- Tumor and blood samples will be de-identified prior to distribution to the laboratories performing the correlative studies.
- Massey Cancer Center Clinical and Translational Research Lab (CTRL) will receive, process, store, and/or distribute all correlative blood samples to the laboratories that will be performing the correlative studies.
- Questions regarding study requirements should be directed to the study team. The principal investigator should be contacted in the event that a correlative sample must be missed or is found to be inadequate for submission.

11.3 Archived Tumor Samples

Expression of PTEN, TS, and additional cellular proteins (see Section 1.7.1) will be analyzed by IHC methods using samples from tumor archived at the time of: 1) the initial breast cancer diagnosis, and 2) disease progression, ie, biopsy of recurrent or metastatic tumor performed prior to study registration.

11.3.1 Archived Diagnostic Tumor Samples

- A tumor block or a total of 20 unstained slides (as tissue quantity permits), each with specimen 5 microns thick, should be requested from the archived initial diagnostic samples.
- A tumor block or a total of up to 20 unstained slides (as tissue quantity permits), each with specimen 5 microns thick, should be requested from samples archived following a biopsy of recurrent or metastatic tumor.

11.3.2 Requesting Tumor Samples from Outside Hospitals

To obtain an archived biopsy specimen from an outside hospital:

- Request that a tissue block be sent to the study team; the study team will coordinate with VCU Anatomic Pathology for slide preparation and for return of the block to the outside hospital.
- If the outside hospital does not transfer blocks of tissue, request delivery of 20 unstained slides (if from the initial diagnostic biopsy) or up to 20 unstained slides

(if from a biopsy of recurrent or metastatic tumor), each with specimen 5 microns thick.

11.3.3 Tumor Sample Slide Labeling

The tumor sample slides should be labeled with the following information before transfer to the CTRL:

- Study number
- Patient study identification number
- Date of tumor sample collection

11.3.4 Immunostaining of Unstained Slides

All unstained slides will be de-identified by labeling as in Section 11.3.3 and delivered to the CTRL where immunostains for expression of PTEN, TS, and other proteins of interest will be performed.

11.3.5 Interpretation of Immunostaining Results

After staining, slides stained with validated antibodies for standard IHC will be returned to the VCU Anatomic Pathology for interpretation by a clinical pathologist. Results will be communicated to the CTRL and the study team.

11.4 Correlative Blood Samples for Multiplex Assays

11.4.1 Time Points for Blood Sample Collection for Multiplex Assays

A blood sample to be used for the multiplex assays will be collected at the following time points:

- Prior to initiation of study treatment (after study registration)
- Approximately 24 hours after the first dose of pemetrexed (cycle 1, day 2)

  Note: If collection is not possible on day 2, this sample may be collected on day 3 or day 4.
- Cycle 2, day 1
- At approximately the time of each tumor response assessment prior to disease progression
- If possible, at time of disease progression

11.4.2 Instructions for Blood Sample Collection for Multiplex Assays

- At each time point for the multiplex assays:
  - Collect 5 mL of blood in a purple top EDTA blood collection tube.
  - Invert 8-10 times after collection and deliver at ambient temperature within 2 hours of collection to the Massey CTRL.

- The CTRL will:
  - Spin sample for 10 minutes at 1200 ×g.
  - Collect 0.25 mL aliquots of supernatant into approximately fifteen (15) 1.0 mL cryovials.
  - Collect the “buffy coat” into a 1.0 mL cryovial using care to not contaminate with red blood cells (RBCs).
  - Freeze the vials at - 80°C.
  - Resuspend the RBC/WBC pellet in 1.0 mL ice cold phosphate buffered saline (PBS).
  - Place 0.1 mL of the resuspension onto 10 glass microscope slides.
  - Using another slide, streak the blood across each slide to create a film.
  - Permit the slides to air dry.
  - Label the slides “RBC”; refer to Section 11.6 for additional information to be included.
  - Store the slides at 4°C.
  - Email Dr. Paul Dent that the slides are ready for pick-up.

11.4.3 Testing and Analysis

Multiplex assay testing and analysis using blood samples will be performed by Paul Dent, PhD. Frozen plasma samples from each time point for each patient will be stored at - 80°C until the trial is completed. Using commercially-available characterized multiplex beads of the same lot purchased from Bio-Rad, the levels of approximately 100 cytokines and growth factors in the plasma will be determined. Changes during study treatment will be assessed. Refer to Section 1.7.2 for a description of the planned research.

11.5 Correlative Blood Samples for CTC Analysis

11.5.1 Time Points for Blood Sample Collection for CTCs

A blood sample to be used for CTC analysis will be collected at the following time points:

- Prior to initiation of study treatment (after study registration)
- Approximately 24 hours after the first dose of pemetrexed (cycle 1, day 2)

  Note: If collection is not possible on day 2, this sample may be collected on day 3 or day 4.
- At approximately the time of the first tumor response assessment

11.5.2 Blood Sample Collection Instructions for CTC

- For all patients:

  At each time point, collect at least 9 mL of blood in each of two 10-mL green top heparin blood collection tubes.

- For a subset of 17 patients:

  Collect at least 9 mL of blood in a 10-mL purple top EDTA blood collection tube for provision to ApoCell (a molecular diagnostics and profiling company) at the following 2 time points:

  - Prior to initiation of study treatment (after study registration)
  - About 24 hours after the first dose of pemetrexed (cycle 1, day 2)

  Note: If collection is not possible on day 2, this sample may be collected on day 3 or day 4.

- Each tube collected will be inverted 8-10 times after collection and then delivered at ambient temperature within 2 hours of collection to the CTRL for further processing, labeling, and storage.

11.5.3 CTC Processing and Analysis

The Massey CTRL staff will:

- Receive, process, and analyze samples per standard CTRL procedures for CTC isolation.

  Note: Specimens cannot be analyzed unless, at a minimum, the pretreatment sample AND at least one post-treatment sample have been collected.

- For the subset of patients who have a second blood sample collected for CTC analysis (see Section 11.5.2), coordinate the provision of samples to ApoCell for CTC isolation using the ApoStream DEPff device and analysis.

Refer to Section 1.7.3 for a description of the planned research

11.6 Blood Sample Labeling

Each collected blood sample and processed end product should be labeled as follows:

- Study number
- Patient study identification number
- Date of sample collection
- Time of sample collection
- Study time point

11.7 Tracking for All Samples

Collection and distribution of all samples will be logged by the study team in OnCore on the appropriate eCRF(s).

12 STUDY CALENDAR

The schedule of tests, exams, disease assessments, collection of samples for correlative studies, and administration of study medications are listed on 2 tables: requirements during screening and after registration (before treatment begins) on Table 10; requirements during treatment and study follow-up on Table 11.

Table 10. Study Calendar – Screening/Pretreatment Requirements

Tests, Exams, Procedures, and Other Requirements	Prior to Initiation of Study Treatment
Informed Consent	Prior to study-specific procedures
Imaging[A]	Within 28 days
Disease Assessment[B]	
Medical/Surgical History	
Demographics	
Height	
12-Lead ECG[C]	
Concurrent Medications[D]	Within 14 days
Baseline Conditions and Symptoms	
Physical Exam	
Weight	
Vital Signs	
Blood Pressure	
Performance Status[E]	
CBC with Differential	
Serum Chemistry[F]	
Serum B_{12}, Folate, MMA, Homocysteine	
INR	
Serum Pregnancy Test[G]	Within 7 days
Correlative Blood Sample Collection	After study registration[H]
Folic Acid[I]	On at least 5 out of the 7 days before the 1st dose of pemetrexed
Vitamin B_{12}[I]	7-14 days before the 1st dose of pemetrexed
Dexamethasone[I]	One day before the 1st dose of pemetrexed

Table 10 Footnotes:

A. Baseline imaging **must be contrast-enhanced** and include the following:

- Chest CT, CT or MRI of abdomen and pelvis, and all other suspected sites of disease within 28 days prior to initiation of study treatment (pemetrexed or sorafenib); for patients with a CT contrast allergy, the chest CT may be performed without contrast or, if the chest is not a known site of disease, a chest x-ray may be used.
- Brain (CT or MRI) **within 8 weeks** prior to initiation of study treatment to screen for brain metastasis.

The imaging used at baseline will be used at each subsequent imaging time point.

B. Disease assessment by imaging or clinical examination; see Section 10.

C. 12-Lead ECG with rhythm strip and determination of QTc interval; see Section 4.2.11 for related exclusion criteria.

D. Include over-the-counter medications.

E. Refer to Appendix 1 for ECOG criteria.

F. Chemistry includes the following panels and tests: basic metabolic panel (sodium, potassium, carbonate, chloride, glucose, calcium, BUN, and creatinine); hepatic panel (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, and total protein); magnesium; and phosphorous.

G. Only required for WCBP; see Section 4.1.16 for the definition of WCBP. (Note: FSH and plasma estradiol levels may be required to determine if a patient is postmenopausal which may be needed to determine if the patient is a WCBP.)

H. Baseline blood samples for multiplex assays and samples for CTC analysis can be collected any time following study registration (including on cycle 1, day 1) but must be collected prior to initiation of study treatment; see Sections 11.1, 11.4, and 11.5.

I. Refer to Table 1 (Section 6.2) for instructions regarding the required supplementation and premedication regimen which begins prior to cycle 1, day 1.

Table 11. Study Calendar – During Treatment and Follow-Up

	Cycle 1 and Cycle 2[A] (21 days)			Cycle 3 and Ongoing[A] (21 Days)			Every 9 Weeks (+/- 1 week)	End of Treatment	Follow-Up[B]	
	Day 1	Day 2	Days 3-5	Day 1	Day 2	Days 3-5			30-Day	Ongoing
Weight	X			X				X		
Vital Signs	X			X				X		
Blood Pressure	X			X				X		
Performance Status[C]	X			X				X		
Adverse Events[D]	X			X				X	X	
Concurrent Medications[E]	X			X				X		
Physical Exam	X			X[F]				X		
CBC with Differential	X			X				X		
Serum Chemistry[G]	X			X				X		
INR	X[H]			X[H]						
Imaging/Clinical Examination and Disease Assessment[I]							X[I]	X[J]		
Correlative Blood Samples (Multiplex Assays)	X[K] *(cycles 1, 2)*	X[K] *(only cycle1)*					X[K]	X[K]		
Correlative Blood Samples for CTCs	X[L] *(only cycle1)*	X[L] *(only cycle1)*					X[L] *(at 1st tumor assessment)*			
Submission of Archived Tumor	X *(request samples by end of cycle 2)*[M]									
Folic Acid PO[N]	Daily doses for the duration of treatment and for 21 days after the last pemetrexed dose									
Vitamin B_{12} IM[N]							X	X[O]		
Dexamethasone PO[N]	On days -1, 1, 2			On days -1, 1, 2						
Pemetrexed IV [N]	X			X						
Sorafenib PO BID [N]	X	X	X	X	X	X				
Diary Review/Pill Count	X			X				X		
Survival Status										X[P]

Table 11 Footnotes:

A. Cycle 1, day 1 assessments do not need to be repeated if done within 7 days prior to initiation of study treatment. Subsequent day 1 assessments may be done up to 3 days prior to day 1 of each cycle.

B. See Section 6.9 for information regarding the duration of follow-up.

C. See Appendix 1 for ECOG criteria.

D. Assessment and reporting of AEs based on the NCI CTCAE v4.0.

E. Include over-the-counter medications.

F. Physical exam is required on day 1 of each of the first 3 cycles. **Beginning with cycle 4**, physical exam is required on day 1 of every other cycle, ie, cycles 4, 6, 8, etc.

G. Chemistry includes the following panels and tests: basic metabolic panel (sodium, potassium, carbonate, chloride, glucose, calcium, BUN, and creatinine); the hepatic panel (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, and total protein); magnesium; and phosphorous.

H. If the patient is taking warfarin.

I. Only imaging of initial sites of disease is required at each scheduled time point (ie, at the end of cycle 3 and then every 9 weeks [+/- 1 week]). The same method used at baseline should be used at each subsequent time point. (Refer to Section 10 regarding centralized radiologic review, the timing of confirmatory scans, and assessments by clinical examination.)

J. For patients who discontinued study treatment in the absence of disease progression, assessment of tumor response every 10 weeks (+/- 1 week) continues to be required for 2 years following initiation of study treatment or until disease progression or initiation of new cancer treatment, whichever occurs first.

K. Blood samples for the multiplex assays will be collected in cycle 1 on day 1 before initiation of treatment (if not collected previously), on day 2 (if day 2 is not possible, collect samples on day 3 or 4), on day 1 of cycle 2, at approximately the time of each tumor response assessment, and, if possible, at the time of disease progression (before initiation of new cancer therapy); see Section 11.4.

L. Blood samples for CTC analysis will be in cycle 1 on day 1 before initiation of treatment (if not collected previously), on day 2 (about 24 hours after initiation of treatment; if 24 hours is not possible, collect samples on day 3 or 4), and at the time of the first tumor response assessment; see Section 11.5.

M. Samples from recurrent or metastatic tumor (archived following a biopsy or surgical resection performed prior to study registration) **and** samples from tumor archived at time of initial breast cancer diagnosis (see Section 11.3).

N. Refer to Table 1 in Section 6.2 for a summary of the treatment regimen.

O. Continuing approximately every 9 weeks until approximately 8 weeks following the last dose of pemetrexed.

P. All patients will be followed for survival about every 2 months after discontinuation of study therapy until 2 years after the initiation of study therapy or until death, whichever occurs first. If the patient is unable to return for a study visit, the study team may contact the patient, family member, and/or other members of the patient's health care team to determine the patient's vital status.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a single-arm phase 2 study of pemetrexed and sorafenib in the treatment of patients with recurrent or metastatic TNBC. The primary objective is to determine the efficacy of the combination therapy in terms of the objective response rate.

13.2 Sample Size and Accrual Rate

The sample size and power are calculated based on Simon's two-stage minimax design which minimizes the expected maximum sample size under the alternative hypothesis. The primary endpoint will be determined by objective radiologic criteria (RECIST v1.1). In the phase 1 trial of pemetrexed and sorafenib, 5 of 11 patients with breast cancer had a clinical response (CR or PR). We assume that the null hypothesis, the proportion of patients who have responses, is ≤ 15%, ie, $p0 \leq 0.15$, which is unacceptably low, and the promising response rate is $p1 \geq 0.35$.

With a one-sided type I error of 5% and power of at least 80%, by Simon's two-stage minimax method, the first stage needs to enroll 15 efficacy-evaluable patients at the lower doses of pemetrexed and sorafenib effective with version 4 of the protocol. If there are ≤ 2 patients who have a response, then the trial will end for futility. If 3 or more patients have a response, then the trial will move into the second stage. Efficacy-evaluable patients enrolled at the previous higher dose level will be counted toward the second stage. Patients will continue to be enrolled until there are 13 efficacy-evaluable patients in the second stage. If 8 or more out of the total of 28 efficacy-evaluable patients have a CR or PR, the intervention meets efficacy criteria and further study can be pursued.

To account for about 25% of patients not being evaluable for response, the total sample size for the Simon's two-stage design is 37 patients. Based on previous recruiting history, we anticipate that 2-3 patients will be enrolled per month and the expected enrollment period will be about 18-24 months.

13.3 Analysis Populations

There will be 2 efficacy populations and 1 safety population used for statistical analysis of the primary and secondary endpoints.

13.3.1 Intent-to-treat (ITT) Population

The ITT population includes all patients who have received at least one dose of pemetrexed and one dose of sorafenib.

13.3.2 Efficacy-Evaluable (EE) Population

The EE population includes all patients who initiated a minimum of 2 cycles of study treatment and have undergone at least one assessment of response after receiving study treatment.

13.3.3 Safety Population

The safety population includes all patients who have received at least one dose of pemetrexed and one dose of sorafenib.

13.4 Statistical Analysis Plan

All efficacy analyses will be conducted both the EE population and the ITT population. Only the EE population analyses will be used to determine if the number of responses met the criteria for the study to proceed from Stage 1 to Stage 2 and if the study meets pre-specified criteria for activity of interest.

13.4.1 Analysis of the Primary Endpoint

The primary endpoint is the percentage of patients with HER2-negative metastatic breast cancer achieving an objective response (either PR or CR). In the first stage (n=15), if ≤ 2 EE patients have a response, then the trial will end for futility. If 3 or more patients have a response, an additional 13 patients (including those enrolled at the previous higher dose) will be enrolled in the second stage. If 8 or more of the total of 28 EE patients have a response, the intervention meets efficacy criteria, shows promising evidence, and allows further study to be pursued. The proportion of patients who have a response will be calculated along with its 95% confidence interval by the biased-reduced estimation method by Chang et al (36), recommended by Porcher and Desseaux (37).

13.4.2 Analysis of Secondary Endpoints

Patients' demographics, AEs and SAEs, disease status, treatment status, clinical

response, time-to-event intervals, etc will be listed and summary descriptive statistics will be calculated.

The Kaplan-Meier method will be used to describe the time to death or disease progression; the median time to death or progression will be estimated, along with 95% confidence intervals. A Cox regression model may be used to model the time to death or progression, adjusting for any effects of potential covariates (such as tumor size, tumor stage, biomarker, and age).

13.5 Definitions for Responders and Non-Responders

Response status will be reported in OnCore at the time of each scheduled response evaluation. The OnCore entry, in the Follow-up tab, supported by source documents and related CRFs, will capture the "best response" experienced by a patient for the duration of study participation.

The coding of patients as responders or non-responders will be made by the principal investigator with the concurrence of the biostatistician.

- Responders are defined as patients whose best response is PR or CR.
- Non-Responders are defined as patients whose best response is stable disease or progressive disease. Non-responders will also include patients who were not evaluable for response for the ITT analyses.

[redacted]

[redacted]

[redacted]

14 DATA AND SAFETY MONITORING

14.1 Study Team

The study team minimally consists of the principal investigator, the research nurse, the clinical research associate, and the study biostatistician. While patients are on treatment, the principal investigator, the research nurse, and the clinical research associate will meet at least monthly to review study status; quarterly meetings will be held with the study biostatistician. This review 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. 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 study.

14.2.2 Data Safety and Monitoring Committee

The study will be reviewed by the MCC Data Safety and 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 provided by the principal 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 Patients of Research (US National Commission for the Protection of Human Patients of Biomedical and Behavioral Research, April 18, 1979).

15.2 Regulatory Compliance

This study will be conducted in compliance with the clinical trial protocol and with federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Patients/Informed Consent); 21 CFR 56 (Institutional Review Boards); 21 CFR 312 (IND Application); and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children).

15.3 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the Office for Human Research Protections (OHRP). Any amendments to the protocol or consent materials must also be approved. Only institutions holding a current US Federalwide Assurance issued by OHRP may participate.

15.4 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 patients and their families. Consent forms describing in detail the study interventions/, 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. Patients should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Patients may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to patients for their records; the original consent form will be maintained in the research records. The rights and welfare of 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.

15.5 Patient Confidentiality

Patient confidentiality is strictly held in trust by the participating investigators and their staff. This confidentiality includes the clinical information relating to participating patients, as well as any genetic or biological testing.

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 principal investigator.

The study monitor or other authorized representatives of the principal investigator 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

MCC OnCore data management will provide standard electronic CRFs (eCRFs) and create study-specific eCRFs to be able to capture all information required by the protocol. The eCRFs 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 eCRFs will be traceable to these source documents, which are generally maintained in the patient's file.

All eCRFs 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

As applicable, study records will be maintained a minimum of 5 years beyond the publication of any abstract or manuscript reporting the results of the protocol or submission of a final report to clinicaltrials.gov.

17 REFERENCES

1. Dice JF. 2007. Chaperone-mediated autophagy. *Autophagy* 3: 295-9
2. Levine B, Kroemer G. 2008. Autophagy in the pathogenesis of disease. *Cell* 132: 27-42
3. Yacoub A, Hamed HA, Allegood J, Mitchell C, Spiegel S, Lesniak MS, Ogretmen B, Dash R, Sarkar D, Broaddus WC, Grant S, Curiel DT, Fisher PB, Dent P. 2010. PERK-dependent regulation of ceramide synthase 6 and thioredoxin play a key role in mda-7/IL-24-induced killing of primary human glioblastoma multiforme cells. *Cancer Res* 70: 1120-9
4. Yacoub A, Park MA, Gupta P, Rahmani M, Zhang G, Hamed H, Hanna D, Sarkar D, Lebedeva IV, Emdad L, Sauane M, Vozhilla N, Spiegel S, Koumenis C, Graf M, Curiel DT, Grant S, Fisher PB, Dent P. 2008. Caspase-, cathepsin-, and PERK-dependent regulation of MDA-7/IL-24-induced cell killing in primary human glioma cells. *Mol Cancer Ther* 7: 297-313
5. Walker T, Mitchell C, Park MA, Yacoub A, Graf M, Rahmani M, Houghton PJ, Voelkel-Johnson C, Grant S, Dent P. 2009. Sorafenib and vorinostat kill colon cancer cells by CD95-dependent and -independent mechanisms. *Mol Pharmacol* 76: 342-55
6. Martin AP, Park MA, Mitchell C, Walker T, Rahmani M, Thorburn A, Haussinger D, Reinehr R, Grant S, Dent P. 2009. BCL-2 family inhibitors enhance histone deacetylase inhibitor and sorafenib lethality via autophagy and overcome blockade of the extrinsic pathway to facilitate killing. *Mol Pharmacol* 76: 327-41
7. Park MA, Reinehr R, Haussinger D, Voelkel-Johnson C, Ogretmen B, Yacoub A, Grant S, Dent P. 2010. Sorafenib activates CD95 and promotes autophagy and cell death via Src family kinases in gastrointestinal tumor cells. *Mol Cancer Ther* 9: 2220-31
8. Martin AP, Mitchell C, Rahmani M, Nephew KP, Grant S, Dent P. 2009. Inhibition of MCL-1 enhances lapatinib toxicity and overcomes lapatinib resistance via BAK-dependent autophagy. *Cancer Biol Ther* 8: 2084-96
9. Yacoub A, Park MA, Hanna D, Hong Y, Mitchell C, Pandya AP, Harada H, Powis G, Chen CS, Koumenis C, Grant S, Dent P. 2006. OSU-03012 promotes caspase-independent but PERK-, cathepsin B-, BID-, and AIF-dependent killing of transformed cells. *Mol Pharmacol* 70: 589-603
10. Ravikumar B, Sarkar S, Davies JE, Futter M, Garcia-Arencibia M, Green-Thompson ZW, Jimenez-Sanchez M, Korolchuk VI, Lichtenberg M, Luo S, Massey DC, Menzies FM, Moreau K, Narayanan U, Renna M, Siddiqi FH, Underwood BR, Winslow AR, Rubinsztein DC. 2010. Regulation of mammalian autophagy in physiology and pathophysiology. *Physiol Rev* 90: 1383-435
11. Mizushima N, Levine B. 2010. Autophagy in mammalian development and differentiation. *Nat Cell Biol* 12: 823-30
12. Yang Z, Klionsky DJ. 2010. Eaten alive: a history of macroautophagy. *Nat Cell Biol* 12: 814-22
13. Tooze SA, Jefferies HB, Kalie E, Longatti A, McAlpine FE, McKnight NC, Orsi A, Polson HE, Razi M, Robinson DJ, Webber JL. 2010. Trafficking and signaling in mammalian autophagy. *IUBMB Life* 62: 503-8

14. Yu L, Alva A, Su H, Dutt P, Freundt E, Welsh S, Baehrecke EH, Lenardo MJ. 2004. Regulation of an ATG7-beclin 1 program of autophagic cell death by caspase-8. *Science* 304: 1500-2

15. Paglin S, Lee NY, Nakar C, Fitzgerald M, Plotkin J, Deuel B, Hackett N, McMahill M, Sphicas E, Lampen N, Yahalom J. 2005. Rapamycin-sensitive pathway regulates mitochondrial membrane potential, autophagy, and survival in irradiated MCF-7 cells. *Cancer Res* 65: 11061-70

16. Sini P, James D, Chresta C, Guichard S. 2010. Simultaneous inhibition of mTORC1 and mTORC2 by mTOR kinase inhibitor AZD8055 induces autophagy and cell death in cancer cells. *Autophagy* 6

17. Funderburk SF, Wang QJ, Yue Z. 2010. The Beclin 1-VPS34 complex--at the crossroads of autophagy and beyond. *Trends Cell Biol* 20: 355-62

18. Dokmanovic M, Clarke C, Marks PA. 2007. Histone deacetylase inhibitors: overview and perspectives. *Mol Cancer Res* 5: 981-9

19. Racanelli AC, Rothbart SB, Heyer CL, Moran RG. 2009. Therapeutics by cytotoxic metabolite accumulation: pemetrexed causes ZMP accumulation, AMPK activation, and mammalian target of rapamycin inhibition. *Cancer Res* 69: 5467-74

20. Rothbart SB, Racanelli AC, Moran RG. 2010. Pemetrexed indirectly activates the metabolic kinase AMPK in human carcinomas. *Cancer Res* 70: 10299-309

21. Jarmula A. 2010. Antifolate inhibitors of thymidylate synthase as anticancer drugs. *Mini Rev Med Chem* 10: 1211-22

22. Fleeman N, Bagust A, McLeod C, Greenhalgh J, Boland A, Dundar Y, Dickson R, Tudur Smith C, Davis H, Green J, Pearson M. 2010. Pemetrexed for the first-line treatment of locally advanced or metastatic non-small cell lung cancer. *Health Technol Assess* 14 Suppl 1: 47-53

23. Poklepovic AS, Shafer DA, Roberts JD, Geyer CE, Dent P, Moran R, Tombes MB, Shrader E, Strickler K, Wan W. 2015. Phase I study of pemetrexed and sorafenib in advanced solid tumors. *ASCO Meeting Abstracts* 33: 2586

24. Cullen MH, Zatloukal P, Sorenson S, Novello S, Fischer JR, Joy AA, Zereu M, Peterson P, Visseren-Grul CM, Iscoe N. 2008. A randomized phase III trial comparing standard and high-dose pemetrexed as second-line treatment in patients with locally advanced or metastatic non-small-cell lung cancer. *Ann Oncol* 19: 939-45

25. Rinaldi DA, Kuhn JG, Burris HA, Dorr FA, Rodriguez G, Eckhardt SG, Jones S, Woodworth JR, Baker S, Langley C, Mascorro D, Abrahams T, Von Hoff DD. 1999. A phase I evaluation of multitargeted antifolate (MTA, LY231514), administered every 21 days, utilizing the modified continual reassessment method for dose escalation. *Cancer Chemother Pharmacol* 44: 372-80

26. Takimoto CH, Hammond-Thelin LA, Latz JE, Forero L, Beeram M, Forouzesh B, de Bono J, Tolcher AW, Patnaik A, Monroe P, Wood L, Schneck KB, Clark R, Rowinsky EK. 2007. Phase I and pharmacokinetic study of pemetrexed with high-dose folic acid supplementation or multivitamin supplementation in patients with locally advanced or metastatic cancer. *Clin Cancer Res* 13: 2675-83

27. Dittrich C, Petruzelka L, Vodvarka P, Gneist M, Janku F, Kysela T, Melemed A, Latz J, Simms L, Krejcy K. 2006. A phase I study of pemetrexed (ALIMTA) and

cyclophosphamide in patients with locally advanced or metastatic breast cancer. *Clin Cancer Res* 12: 7071-8

28. Emmanouilides C, Yermetaki T, Serpanou A, Sapountzi E, Mantziari P, Titopoulos I, Filippou D. 2010. Feasibility study of dose-dense biweekly administered pemetrexed in patients with non-small cell lung cancer. *Hematol Oncol Stem Cell Ther* 3: 34-8
29. Strumberg D, Richly H, Hilger RA, Schleucher N, Korfee S, Tewes M, Faghih M, Brendel E, Voliotis D, Haase CG, Schwartz B, Awada A, Voigtmann R, Scheulen ME, Seeber S. 2005. Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. *J Clin Oncol* 23: 965-72
30. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Haussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J, Group SIS. 2008. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 359: 378-90
31. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM, Group TS. 2007. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 356: 125-34
32. Kuukasjarvi T, Kononen J, Helin H, Holli K, Isola J. 1996. Loss of estrogen receptor in recurrent breast cancer is associated with poor response to endocrine therapy. *J Clin Oncol* 14: 2584-9
33. Poklepovic A, Gordon S, Shafer DA, Roberts JD, Bose P, Geyer CE, Jr., McGuire WP, Tombes MB, Shrader E, Strickler K, Quigley M, Wan W, Kmieciak M, Massey HD, Booth L, Moran RG, Dent P. 2016. Phase I study of pemetrexed with sorafenib in advanced solid tumors. *Oncotarget*
34. Sivridis E, Koukourakis MI, Zois CE, Ledaki I, Ferguson DJ, Harris AL, Gatter KC, Giatromanolaki A. 2010. LC3A-positive light microscopy detected patterns of autophagy and prognosis in operable breast carcinomas. *Am J Pathol* 176: 2477-89
35. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. 2009. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-47
36. Chang MN, Wieand HS, Chang VT. 1989. The bias of the sample proportion following a group sequential phase II clinical trial. *Stat Med* 8: 563-70
37. Porcher R, Desseaux K. 2012. What inference for two-stage phase II trials? *BMC Med Res Methodol* 12: 117

APPENDIX 1. PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (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 > 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 > 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 FORMULA

Calculated Creatinine Clearance (Cockcroft-Gault)
Creatinine clearance (mL/min) = [(140 - Age) × Weight in kg ×G] / (Creatinine × 72) G=1 (males); G=0.85 (females)

APPENDIX 3. NEW YORK HEART ASSOCIATION CLASSIFICATION

New York Heart Association Classification of Heart Failure	
Class I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
Class 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.
Class III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
Class IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

APPENDIX 4. HEMATOLOGIC ADVERSE EVENTS

For the purposes of this study, the following CTCAE v4.0 AE terms qualify as “Hematologic” AEs.

From the Blood and Lymphatic system disorders category:

- Anemia
- Febrile neutropenia
- Leukocytosis

From the Investigations category:

- Hemoglobin increased
- Lymphocyte count decreased
- Lymphocyte count increased
- Neutrophil count decreased
- White blood cell decreased