ECOG-ACRIN
cancer research group
Reshaping the future of patient care

November 10, 2022

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #31 to EAY131-V, *MATCH Treatment Subprotocol V: Phase II Study of Sunitinib in Patients with Tumors with cKIT Mutations (Excluding GIST, Renal Cell Carcinoma or Pancreatic Neuroendocrine Tumor).*

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

This addendum has been reviewed and approved by the Central IRB, which is the sole IRB of record for this study. Local IRB review and approval is unnecessary.

Implementation of this addendum must occur on the activation date. Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

The following revisions to the EAY131-V protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date and addendum number.
2.	Contact Page	Updated the phone number for the subprotocol chair, Dr. Lilian Gien.

The following revisions to the EAY131-V Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.

If you have any questions regarding this addendum, please contact eradomyshelsky@ecog-acrin.org or 857-504-2900.

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

We request review and approval of this addendum to EAY131-V so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAY131-V

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol V: Phase II Study of Sunitinib in Patients with Tumors with cKIT Mutations (Excluding GIST, Renal Cell Carcinoma or Pancreatic Neuroendocrine Tumor)

SUNITINIB TREATMENT SUBPROTOCOL CHAIR: Lilian T. Gien, MD
SUNITINIB TREATMENT SUBPROTOCOL CO-CHAIR: Andrew Poklepovic, MD
SUNITINIB TRANSLATIONAL CHAIR: Eric Collisson, MD

Version Date: November 10, 2022
NCI Update Date: August 12, 2015

NOTE: This subprotocol (EAY131-V) should be used in conjunction with the MATCH Master Protocol (EAY131).

Rev. Add13
Rev. Add19

NOTE: As of 11/17, all protocol changes will be noted by addendum number.

SUBPROTOCOL ACTIVATION DATE

August 12, 2015 (Incorporated in Addendum #1)
Update #2 – 8/15
Addendum #2 – 2/16
Addendum #3 – 5/16
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #13
Addendum #19
Addendum #21
Addendum #25
Addendum #31

Agent	IND#	NSC#	Supply
Sunitinib malate	IND Sponsor: DCTD, NCI IND #: 126200	736511	NCI Supplied

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Schema

Cycle = 42 days
Accrual Goal: 35

1. Introduction

1.1 Sunitinib Malate

Sunitinib malate (sunitinib; SU11248; SU011248; Sutent®) is an oral, multi-targeted, small molecule inhibitor of the receptor tyrosine kinases (RTKs) involved in tumor proliferation and angiogenesis, including vascular endothelial growth factor receptor-1 (VEGFR-1), -2, and -3, platelet-derived growth factor receptor (PDGFR) -α and -β, stem cell factor receptor (KIT), the tyrosine kinase (TK) receptor encoded by the *ret* proto-oncogene (RET; rearranged during transfection), fms-like tyrosine kinase 3 (Flt3), basic fibroblast growth factor (bFGF) and colony-stimulating factor (CSF)-1R (O'Farrell *et al.*, 2003a; Chow and Eckhardt, 2007; Faivre *et al.,* 2007; Gan *et al*., 2009; Mashkani *et al.*, 2010). Sunitinib selectively and potently inhibits the class III and class V split-domain RTKs (Mendel *et al*., 2003).

Sunitinib was granted regulatory approval on January 26, 2006 by Food and Drug Administration (FDA) for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerant to imatinib mesylate and accelerated approval for advanced renal cell carcinoma (RCC) (Goodman *et al.,* 2007; Izzedine *et al*., 2007; Rock *et al*., 2007), which was changed to regular approval on February 2, 2007.

Mechanism of Action

KIT-activating mutations

Although in renal cell carcinoma the main mechanism of action of sunitinib is the inhibition of VEGF driven angiogenesis, sunitinib also exerts direct antitumor activity on cells that express target RTKs associated with tumor cell proliferation, such as KIT, PDGFR, and RET.

KIT is a type III receptor tyrosine kinase that is important for the development of melanocytes, germ cells, mast cells, hematopoietic stem cells, and the interstitial cells of Cajal, the pacemaker cells of the gastrointestinal tract. Oncogenic KIT mutations result in ligand-independent kinase activation, leading to enhanced cell proliferation and survival [Hornick et al., 2007; Hoeben et al., 2008]. KIT-activating mutations are found in 85-90% of GISTs [Heinrich et al., 2003], and it is now established that mutant KIT is a clinically important therapeutic target for this malignancy.

KIT mutations have been found in several types of cancers. For example, KIT mutations occur in almost all cases of systemic mastocytosis [Yavuz et al., 2002]. In subsets of acute myeloid leukemia, KIT mutations occur in 37% of adult cases [Park et al., 2011]. KIT mutations have also been observed in germ cell cancers, reported in up to 26% of testicular seminomas [Kemmer et al., 2004], and in approximately 30% of unilateral ovarian dysgerminomas [Hoei-Hansen et al., 2007]. In melanoma, KIT mutations have been demonstrated in a small subset, mostly in those originating from mucosa, acral or chronic sun damaged sites [Beadling et al., 2008]. While KIT is also expressed in other tissues such as vascular endothelial cells, renal tubules, breast glandular epithelial cells, astrocytes, and sweat glands, recurrent mutations have not been described in these corresponding cancers, and early studies have failed to show efficacy of

KIT inhibitors in these entities, demonstrating the concept that a mutation or over-expression must be present in order for KIT to be a useful therapeutic target [Ashman et al., 2013].

There are multiple sites of KIT mutation in cancers. “Hot-spots” can correspond to the intracellular and extracellular juxtamembrane domains (exons 9, 11), the adenosine triphosphate (ATP) binding pocket of the receptor (exons 13, 14) and the activation loop of the kinase domain (exons 17, 18). Common sites of KIT mutation differ markedly between cancers. In GISTs, the most common region of KIT mutation is within exon 11 (65%), followed by exon 9 (15%), whereas mutations in exon 13 and 17 are uncommon (<5%) [Hornick et al., 2007]. In contrast, the most common KIT mutations in melanoma are within exons 11 and 13 [Beadling et al.,. 2008], whereas hematopoietic malignancies and germ cells mainly have mutations in exon 17. Figure X shows the mutation frequency across 80 cancer studies on the cBio portal http://bit.ly/1zCbcDi [PMID: 22588877]. Of note, GIST is not included in this dataset.

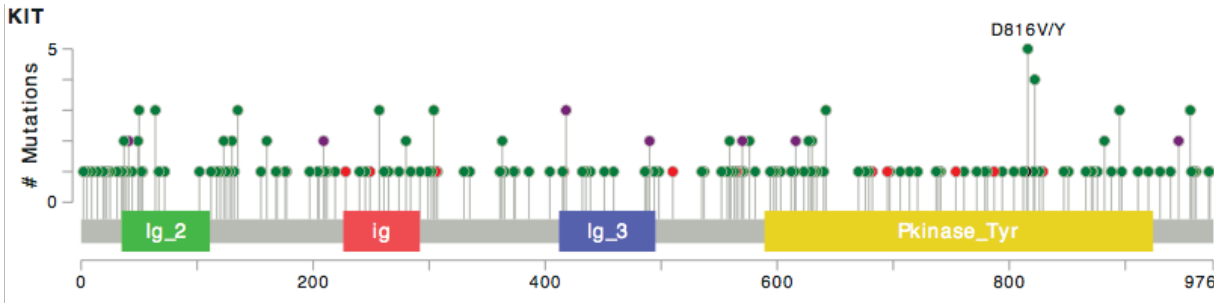

Figure 1:

Sunitinib selectively inhibits KIT, as demonstrated by the clinical activity of this agent in patients with advanced or metastatic GIST.

Nonclinical Specificity and Efficacy Studies

In vitro studies have demonstrated the specificity of sunitinib for inhibition of the Class 3 and Class 5 RTKs, including receptors for VEGF (VEGFR), KIT, Flt-3, and PDGFR (Investigator’s Brochure, 2014). Specifically, receptor phosphorylation inhibition studies have shown that sunitinib inhibits KIT-ligand-induced phosphotyrosine levels in a dose-dependent manner with IC_{50} values of 0.001-0.01 µM *in vitro* and reduced PDGFR-β phosphotyrosine levels *in vivo* (Abrams *et al*., 2003a). Sunitinib also selectively inhibited proliferation of human umbilical vein endothelial cells (HUVEC) stimulated with VEGF (IC_{50}=0.04 mcM) compared to FGF-stimulated proliferation (IC_{50}=0.7 mcM) (Mendel *et al*., 2003).

In animal efficacy studies, sunitinib showed broad antitumor activity in mouse xenograft models against a variety of human tumor cell lines including colorectal cancer (HT-29, Colo205), non-small cell lung cancer (H460), breast cancer (MDA-MB-435), melanoma (A375), epidermoid cancer (A431), and glioma (SF763T) (Mendel *et al.*, 2003). Sunitinib has also demonstrated antitumor activity against other breast cancer models (MMTV-v-Ha-ras transgenic mouse mammary carcinoma and dimethylbenzanthracene [DMBA]-induced rat mammary carcinomas) (Abrams *et al*., 2003b). In an animal model of KIT-expressing small cell lung cancer (SCLC; NCI-H526), sunitinib administration

resulted in greater tumor growth inhibition than did imatinib (Abrams *et al*., 2003a).

Additional nonclinical *in vitro* and *in vivo* studies are summarized in Chow and Eckhardt, 2007.

Clinical Pharmacokinetics

Orally-administered sunitinib is well absorbed in humans, with linear pharmacokinetics (PK) at doses of 50-150 mg/day (Sakamoto, 2004). Metabolism of sunitinib occurs primarily through the cytochrome P450 3A4 (CYP3A4) to N-deethyl sunitinib to form the metabolite SU012662. SU012662 undergoes further metabolism to an inactive metabolite SU014335.

The PK of sunitinib and SU012662 were measured in a phase 1 dose-escalation study in patients with advanced solid malignancies (Faivre *et al*., 2006). Twenty-eight patients received doses ranging from 15 mg/m^2 to 59 mg/m^2 (ranging from 50 mg every other day to 150 mg/day), on a 4 weeks on, 2 weeks off (4/2) schedule. Overall, sunitinib displayed a long half-life and a large volume of distribution with moderate interpatient variability. At the recommended dose, C_{max} occurred approximately 5 hours after administration and $t_{1/2}$ ranged from 41-86 hours. Doses of 50 mg daily led to plasma concentrations ranging from 50-100 ng/mL.

Fixed dosing on a milligram basis was considered appropriate for phase 2 studies (Faivre *et al*., 2006).

To determine the effect of food on the PK of sunitinib and its active metabolite SU012662, 16 healthy subjects received a single dose of sunitinib 50 mg under fasting conditions and 14 subjects received a single dose of sunitinib 50 mg under fed conditions. Sunitinib and SU012662 half-lives, and oral clearance of sunitinib, were not affected by food (Bello *et al*., 2006).

A study of sunitinib PK in patients with AML indicated that a plasma concentration of 50-100 ng/mL of combined sunitinib and SU012662 could be achieved on the first cycle of a 50 mg/day 4/2 regimen, similar to that achieved in studies with patients having other tumor types (Fiedler *et al*., 2005).

Population PK methods indicated that the covariates of weight, gender, race, ethnicity, ECOG score, and tumor type had no clinically significant effects on drug exposure, and that adjustments of starting doses based on these covariates were not required (Investigator's Brochure, 2014).

Concurrent administration of a single dose of sunitinib with ketoconazole (a strong CYP3A4 inhibitor) in healthy volunteers resulted in 49% and 51% increases in the combined (sunitinib + SU012662) C_{max} and $AUC_{0-\infty}$ values, respectively, compared with sunitinib alone (Washington *et al*., 2003). Concurrent administration of sunitinib and rifampin (a strong CYP3A4 inducer) in healthy subjects resulted in 23% and 46% reduction in combined C_{max} and $AUC_{0-\infty}$, respectively, compared with sunitinib alone (Bello *et al*., 2005). Thus, dose adjustments for sunitinib should be considered when coadministered with strong CYP3A4 inhibitors and inducers.

Proposed Dose and Schedule for Phase 2 Clinical Trials

Starting doses in multiple-dose studies were 25, 50, 75, and 100 mg administered orally once daily with the majority of patients receiving the 50-mg dose. Patients in sunitinib studies have been treated on four different schedules: schedules 4/1 and 4/2 comprised 4 consecutive weeks of daily dosing followed by a 1- or 2-week rest period, respectively, while schedules 2/1 and 2/2 comprised 2 consecutive weeks of daily dosing followed by a 1- or 2-week rest period, respectively. The majority of subjects were treated on schedules 4/2 or 2/2 in phase 1 studies. Schedule 4/2 has been well tolerated with generally mild to moderate adverse effects at a 50 mg daily dose. Alternate regimens of sunitinib are being explored; 50 mg of sunitinib daily for 2 weeks followed by a 1-week off-treatment period (sunitinib 2/1) (Britten *et al*., 2008), while another schedule is sunitinib 37.5 mg as a CDD (George *et al.,* 2008). Both schedules were well-tolerated, achieved therapeutic plasma concentrations and showed no significant accumulation of the drug. This study will use the most common dosing schedule of sunitinib, 50mg po daily for 4 weeks, followed by 2 weeks rest.

Safety Profile

Sunitinib is reasonably well tolerated, with asthenia, hypertension, dermatitis, and mild myelosuppression as the most common AEs (Stadler, 2006). The most common adverse reactions (≥ 20%) are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, plantar palmar erythrodysesthesia (PPE, hand-foot syndrome), skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding (Sutent Prescribing Information, 2014). Additionally, the inhibition of TK receptors by agents such as sunitinib can result in cutaneous AEs such as acral erythema, subungal splinter hemorrhages, modification of hair and skin pigmentation, mucositis, and (occasionally) periocular edema (Robert *et al*., 2005; Suwattee, 2008). PPE is characterized by inflammation, hyperkeratosis, blistering, and pain in the hands and/or feet of patients, usually bilaterally, which can occur in patients receiving sunitinib (Porta *et al*., 2007; Suwattee, 2008). A recent analysis of dermatological AEs in patients receiving sunitinib therapy has reported that all-grade PPE reactions occurred in 19% of patients (5% grades 3-4), skin discoloration in 28% (no grades 3-4), dry skin in 16% (1% grades 3-4), skin rash in 13% (1% grades 3-4), dermatitis in 8% (2% grades 3-4), hair color changes in 10% (no grades 3-4), alopecia in 6% (no grades 3-4), and phototoxicity in < 0.1% (no grades 3-4) (Rosenbaum *et al*., 2008).

Hepatotoxicity, which can lead to liver failure and possible death, has been associated with sunitinib. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience, leading to a boxed label warning. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. The incidence of low-grade and high-grade elevations of AST and ALT is reported to be 40-60%, and grade 3-4 elevations to be 2-5% [Shah et al., 2013]. It is recommended that liver function tests be monitored prior to initiating treatment, during each cycle, and as clinically indicated. Sunitinib should be interrupted for grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution.

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Cardiotoxicity, including congestive heart failure (3%-8%) and left ventricular dysfunction (12%-14%), has been reported in patients undergoing treatment with sunitinib (Chu *et al*., 2007; Khakoo *et al.*, 2008; Schmidinger *et al.*, 2008; Telli *et al.,* 2008). More subjects treated with sunitinib experienced decline in left ventricular ejection fraction (LVEF) than subjects receiving either placebo or IFN-α (Investigator's Brochure, 2014). In clinical trials, decreases in LVEF of ≥20% and below the lower limit of normal (LLN) occurred in approximately 2% of sunitinib-treated GIST patients, 4% of cytokine-refractory MRCC patients and 2% of placebo-treated patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued. In the treatment-naive MRCC study, 27% and 15% of subjects on sunitinib and IFN-α, respectively, had an LVEF value below the LLN. Two patients (< 1%) who received sunitinib were diagnosed with congestive heart failure (CHF). Among 461 patients enrolled in CDUS-monitored trials with sunitinib alone, 2% of patients experienced left ventricular systolic dysfunction (CDUS data). It is unknown whether patients with concurrent cardiac conditions may be at a higher risk for developing drug-related LVEF. Baseline and periodic evaluations of LVEF should be considered when clinically indicated while these patients are on sunitinib treatment. In patients without cardiac risk factors, a baseline evaluation of LVEF should be considered when clinically indicated.

Sunitinib has been shown to **prolong the QT interval** in a dose-dependent manner, which may lead to an increased risk for **ventricular arrhythmias,** including Torsade de Pointes. This condition has been reported in <0.1% of sunitinib-exposed patients. The DCTD, NCI, issued an IND AE Action Letter to all investigators using sunitinib describing the occurrence of QTc prolongation and Torsade de pointes (ventricular tachycardia) in patients on clinical trials utilizing sunitinib. As a result of this Action Letter, DCTD, NCI-sponsored sunitinib protocols were amended to include the requirement for a baseline EKG prior to study treatment, exclude patients with histories of serious ventricular arrhythmias or prolonged QTc, and exclude patients with certain cardiac conditions.

Treatment-related **hypertension** was reported in clinical trials in subjects with solid tumors, including primarily GIST and cytokine-refractory RCC. Sunitinib dosing was reduced or temporarily delayed in approximately 2.7% of this patient population. None of these patients were discontinued from treatment with sunitinib. Severe hypertension (> 200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of this patient population. Of subjects receiving sunitinib for treatment-naive MRCC, 33.9% receiving sunitinib experienced hypertension, compared with 3.6% on IFN-α. Severe hypertension occurred in 12% of treatment-naive patients on sunitinib compared to <1% on IFN-α. Hypertension was reported in 26.5% of patients receiving sunitinib in a Phase 3 pNET study, compared to 4.9% of patients receiving placebo. Severe hypertension occurred in 10% of pNET patients on sunitinib and 3% of patients on placebo (Investigator's Brochure, 2014). Among 516 patients enrolled in CDUS-monitored trials with sunitinib alone, 33.9% experienced hypertension (CDUS data). Patients should be screened for hypertension and controlled as appropriate. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

In subjects receiving sunitinib for treatment-naive MRCC, 39% had **bleeding events** compared with 11% receiving IFN-α (Investigator's Brochure, 2014). Treatment emergent bleeding events occurred in 18% of patients receiving sunitinib in the double-blind treatment phase of the GIST phase 3 study, compared with 17% receiving placebo. Seventeen (4.5%) patients on sunitinib versus 5 (1.7%) patients on IFN-α experienced Grade 3 or greater treatment-related bleeding events. Of patients receiving sunitinib for cytokine-refractory MRCC (C-R MRCC), 26% experienced bleeding. Bleeding events, excluding epistaxis, occurred in 21.7% of patients receiving sunitinib in the Phase 3 pNET study compared to 9.85% of patients receiving placebo. Routine assessment of this event should include complete blood counts and physical examination. Among 516 patients enrolled in CDUS-monitored trials with sunitinib alone or in combination with other agents, there were 123 reported bleeding events (CDUS data). Epistaxis was the most common hemorrhagic AE reported. Tumor-related hemorrhage can occur with sunitinib and in the case of pulmonary tumors, may present as severe and life-threatening hemoptysis or pulmonary hemorrhage.

Thyroid dysfunction has been reported with sunitinib. **Hypothyroidism** has been reported in 71% patients with RCC (Rini et al., 2007) and in 36% of those with GIST (Desai et al, 2006) treated with sunitinib. Acquired hypothyroidism was noted in 6.2% of GIST patients on sunitinib versus 1% on placebo. Hypothyroidism was reported as an adverse event in 16% of patients on sunitinib in the treatment-naive MRCC study and three patients (< 1%) in the IFN-α arm, and in 4% of patients across the two cytokine-refractory MRCC studies. Additionally, TSH elevations were reported in 2% of cytokine-refractory MRCC patients. Overall, 7% of the cytokine-refractory MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. In the Phase 3 pNET study, treatment-related hypothyroidism was reported in 6 patients (7.2%) receiving sunitinib and in one patient (1.2%) on placebo. Cases of hyperthyroidism have been reported in clinical trials and through post-marketing experience (Investigator's Brochure, 2014). Baseline measurement of thyroid function is recommended, and patients with thyroid dysfunction should be treated appropriately prior to starting sunitinib therapy. All patients should be observed closely for signs and symptoms of thyroid dysfunction on sunitinib treatment. Patients with signs and/or symptoms suggestive of hypothyroidism or hyperthyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Hypoglycemia has also been reported with sunitinib therapy. General guidelines recommend checking blood glucose levels regularly and assessment if anti-diabetic drug dose modifications are required (Sutent Prescribing Information, 2014).

Nonclinical evidence of **adrenal toxicity** following sunitinib exposure led the company to perform specialized safety assessments in clinical studies, including computed tomography or MRI in 336 subjects to specifically identify any change in adrenal gland structure or the presence of adrenal gland hemorrhage (Investigator's Brochure, 2014). Neither event was observed. Adrenocorticotropic hormone (ACTH) stimulation testing was done in 400 patients across multiple sunitinib trials. One subject developed consistently abnormal test results during treatment that were unexplained and may be related to sunitinib treatment. Eleven additional subjects had abnormalities in the final

test, with low peak cortisol levels. None of these patients had clinical evidence of adrenal insufficiency. However, based on the nonclinical findings, patients receiving sunitinib should be clinically followed for signs and symptoms of adrenal insufficiency, especially in (1) patients with comorbidities associated with adrenal dysfunction, (2) patients with preexisting adrenal insufficiency (primary or secondary), and (3) patients with concomitant stress (e.g., fever, infection, bleeding, serious accident, surgery) that may precipitate overt adrenal insufficiency in the presence of subclinical sunitinib-induced adrenal toxicity.

Serum chemistries including phosphate should be performed at the beginning of each treatment cycle. Supportive care may include anti-emetic premedication, supportive oral care products, and analgesics. Serious complications due to degeneration or shrinkage of tumors, including tumor lysis syndrome, gastrointestinal perforation and tracheoesophageal fistula, have occurred rarely in patients with abdominal, head and neck, thyroid, and other malignancies treated with sunitinib, believed to be the result of the antitumor effect of sunitinib. Other serious effects include thromboembolic events, rare reversible posterior leukoencephalopathy syndrome (RPLS), proteinuria with rare nephrotic syndrome, and rare microangiopathic hemolytic anemia.

Management of treatment related adverse events is discussed in greater detail in Section 3.4.

1.2 Supporting Preliminary Data

Clinical Experience

As of 01 October 2012, 13026 subjects with solid malignant tumors had received at least one dose of sunitinib in multiple-dose studies, and for 12801 of these 13026 (98.3%) subjects, safety data is available (Investigator's Brochure, 2014). In phase 1 studies, sunitinib demonstrated single-agent activity in patients with RCC, GIST, non-GIST sarcomas, non-small cell lung cancer (NSCLC), colorectal cancer, neuroendocrine tumors (NET), melanoma, prostate cancer, and thyroid cancer. Sunitinib has also been studied in the phase 1 setting in patients with acute myeloid leukemia (AML). Pivotal trials of sunitinib in imatinib-resistant GIST (a placebo-controlled phase 3 trial), and metastatic RCC (MRCC) (single-arm, non-randomized, multicenter, open-label trial) and supporting trials in each disease were completed and submitted in support of the New Drug Application (NDA). In addition, there are several ongoing company-sponsored single agent and combination clinical trials for a variety of other indications.

Sunitinib as a therapy for tumors with KIT-mutations

The majority of data supporting the use of sunitinib for KIT mutations has been studied in GISTs. The tyrosine-kinase inhibitor (TKI) imatinib is established as the standard therapy for metastatic GIST, and has been associated with substantial improvements in overall survival. However, after an initial benefit from imatinib, the vast majority of patients eventually develop disease progression or secondary resistance. Sunitinib, which also selectively inhibits KIT, has demonstrated clinical benefit for patients who progress on imatinib therapy. In a phase III trial of sunitinib vs. placebo, 312 GIST patients with confirmed progression on previous imatinib therapy were randomized in a 2:1 ratio to receive sunitinib (n=207) or placebo (n=105); the trial was unblinded early when a planned interim analysis showed significantly longer time to tumor progression

with sunitinib. Median time to tumor progression was 27.3 weeks (95% CI 16.0–32.1) in patients receiving sunitinib and 6.4 weeks (4.4–10.0) in those on placebo (hazard ratio 0.33; p<0.0001). Therapy was reasonably well tolerated; the most common adverse events were fatigue, diarrhea, skin discoloration and nausea [Demetri et al., 2006]. This trial led to FDA-approval of sunitinib as a treatment option for patients with imatinib resistant tumors.

Recent studies have shown that sunitinib may have activity in patients with other tumors that have c-KIT mutations, such as melanoma. There are three phase II studies demonstrating response to imatinib for melanomas harboring KIT mutations of approximately 20-29% [Carvajal et al., 2011, Guo et al., 2011, Hodi et al., 2013]. In a phase II study of sunitinib in melanoma patients, of the four evaluable patients with KIT mutations, 1 had a complete remission for 15 months and 2 had partial responses (1- and 7-month duration) [Minor et al., 2012]. The tolerability and toxicity of sunitinib was similar to that reported in renal cell cancer and GISTs.

Efficacy according to genotype

It is known that GIST responsiveness to imatinib varies by primary KIT genotype; exon 11-mutant GISTs are more sensitive to imatinib than exon 9-mutant GISTs. Heinrich et al. (2008) conducted a study which evaluated the clinical activity of sunitinib based on GIST kinase genotype. When evaluating primary tumor genotype, the objective response to sunitinib was more common in patients with KIT exon 9 than exon 11 mutant GISTs (37% vs 5%, p=0.002), and the median progression-free survival (PFS) was significantly longer for patients with exon 9 mutations compared to those with exon 11 mutations (19.4 months vs 5.1 months, p=0.0005). Median overall survival was also significantly longer for patients with exon 9 mutations (26.9 months vs 12.3 months, p=0.012). Among those with secondary tumor genotype, clusters of mutations occurred in exons 13 and 14, as well as exon 17. The median PFS with sunitinib was significantly longer for those with secondary KIT exon 13 or 14 mutations, than for those with exon 17 or 18 mutations (7.8 months vs 2.3 months, p=0.016). Furthermore, Gajiwala et al. (2009) demonstrated biochemically that GISTs with exon 17 mutations are strongly resistant to sunitinib. These mutants bind sunitinib in the inactivated form but are then converted to the active drug-resistant form. We will exclude patients with exon 17 and 18 cKIT mutations from this trial.

KIT inhibitors in other malignancies

Other than in GIST and melanoma, sunitinib has not been studied systematically as a therapy against the KIT mutation in other malignancies. Early trials of imatinib in unselected cases of acute myeloid leukemia (AML) have been unsuccessful, likely due to the low rate of KIT mutations of 7%, and the frequency of resistant mutations on the activation loop of the kinase domain [Piccaluga et al., 2007]. However, small studies have suggested that identification of particular mutations in AML may select a subgroup of patients who are more likely to respond [Cairoli et al., 2005]. Imatinib has also been used in cases of systemic mastocytosis, but the heterogeneous group of patients leads to difficulty in adequately evaluating response to therapy. Additionally, activation loop mutations are found in the majority of patients with systemic mastocytosis. Use of imatinib may be more effective in those cases negative for the activation loop mutations [Orfao et al., 2007]. Imatinib has also been tested in breast

cancer cell lines and testicular seminoma cell lines with encouraging results [Roussidis et al., 2007; Kemmer et al., 2004].

1.3 Rationale

Although sunitinib has anti-angiogenic properties and has activity against several kinases, Sunitinib has been approved for patients with metastatic GIST who are resistant to imatinib. Few studies have evaluated sunitinib in melanomas with cKIT mutations, but response has been observed, and otherwise this agent has not been evaluated in other malignancies with cKIT mutations. The numbers of patients with a cKIT mutation in each type of malignancy is relatively small, making it difficult to establish response among specific types of malignancies.

The MATCH trial aims to establish whether patients whose tumors harbor mutations in specific pathways of interest benefit (as defined as objective response) from agents targeting that pathway, irrespective of tumor type. This trial will allow detection of a sufficient cohort of patients to determine the effect of sunitinib on tumors with cKIT mutations, and allow investigation of whether agents likely to have activity against a molecular alteration in one disease will exhibit similar activity in other diseases with the same molecular alterations.

1.4 Objectives

Primary:

a) Observe response rate in patients with c-KIT mutations treated with sunitinib

Secondary:

a) Observe 6-month progression free survival of patients with c-KIT mutations treated with sunitinib
b) Observe time to progression of patients with c-KIT mutations treated with sunitinib
c) Document toxicities in patients with c-KIT mutations treated with sunitinib

2. Selection of Patients

Each of the criteria in the checklist that follows must be met, along with the eligibility in the MATCH Master Protocol, in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 2 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 2 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.Execofficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: All patients must have signed the relevant treatment consent form

2.1 Eligibility Criteria

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_____ 2.1.1 Patients must fulfill all eligibility criteria outlined in Section 3.1 of MATCH Master Protocol (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

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_____ 2.1.2 Patients must have a somatic cKIT mutation in exon 9, 11, 13 or 14, excluding exon 17 or 18 mutations, activating PDGFRA or PDGFRB variants and fusions, or another aberration, as identified via the MATCH Master Protocol and described in Appendix II. See Appendix II

Actionable Mutations of Interest (aMOIs)for information on the inclusion and exclusion mutations, along with the corresponding Levels of Evidence (LOE).

_____ 2.1.3 Patient must have normal organ and marrow function as defined below:

- Total bilirubin must be within normal institutional limits.
- Creatinine must be within normal institutional limits.

OR

Creatinine clearance ≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

Creatinine Clearance: _____

- Serum Calcium must be ≤ 12.0 mg/dL.

_____ 2.1.4 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have no clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g. complete left bundle branch block, third degree heart block):

Date of ECG: _____

Rev. 2/16 _____ 2.1.5 Patients with known left ventricular dysfunction must have ECHO or a nuclear study (MUGA or First Pass) within 4 weeks prior to registration to treatment and must not have left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN). If the LLN is not defined at a site, the LVEF must be > 50% for the patient to be eligible.

2.1.5.1 The following groups of patients are eligible provided they have New York Heart Association Class II cardiac function on baseline ECHO/nuclear study:

- Patients with a history of Class II heart failure who are asymptomatic on treatment
- Patients with prior anthracycline exposure
- Patients who have received central thoracic radiation that included the heart in the radiotherapy port

Date of ECHO/nuclear study: _____

NOTE: Pre-treatment LVEF determination in patients without known left ventricular dysfunction (or per Section 2.1.5.1) is NOT otherwise required.

_____ 2.1.6 Patients with any of the following conditions are excluded:

- Serious or non-healing wound, ulcer, or bone fracture
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment
- Any history of cerebrovascular accident (CVA) or transient ischemic attack within 12 months prior to study entry
- History of myocardial infarction, cardiac arrhythmia, stable/unstable angina, symptomatic congestive heart failure, or coronary/peripheral artery bypass graft or stenting within 12 months prior to study entry
- History of pulmonary embolism within the past 12 months

_____ 2.1.7 Patients must not have known hypersensitivity or excess toxicity from sunitinib or compounds of similar chemical composition or biologic effect. This list includes, but is not limited to, patients with significant cardiac or hepatic toxicity from multikinase inhibitors with similar kinase inhibitory profiles (sorafenib, regorafenib, pazopanib).

Questions regarding a significant intolerance to a prior therapy should be directed to the sub-protocol PI.

_____2.1.8 Patients must not have had prior therapy with sunitinib.

_____2.1.9 Patients must not have planned ongoing administration of STRONG and MODERATE CYP3A4 inhibitors or inducers. See Appendix V (and Appendix VI of the MATCH Master Protocol). The reference list of cytochrome p450 (CYP) isozymes and classification of strong, moderate, and weak interactions is available through the FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

- Strong CYP3A4 inhibitors are not permitted within 7 days before dosing and should be avoided throughout the study.
- Strong CYP3A4 inducers are not permitted within 12 days before dosing and should be avoided throughout the study.

_____2.1.10 Patients must not have GIST, renal cell carcinoma, or pancreatic neuroendocrine tumor

_____2.1.11 Patients must not have a NCI CTCAE version 4 grade 3 hemorrhage within 4 weeks of starting study treatment

_____2.1.12 Patients must not have hypertension that cannot be controlled by medications (> 140/90 mmHg despite optimal medical therapy)

_____2.1.13 Patients must not have pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication

_____2.1.14 Participants may not have a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to starting sunitinib.

_____2.1.15 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

_____2.1.16 Patients who require therapeutic doses of coumarin derivative anticoagulants such as warfarin are excluded, although doses up to 2 mg daily are permitted for prophylaxis of thrombosis.

NOTE: Low molecular weight heparin is permitted provided that the patient's PT INR is < 1.5.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3. Sunitinib Treatment Plan

3.1 Administration Schedule

Sunitinib is dosed at 50mg po, daily, regardless of ideal or actual body weight.

3.1.1 Sunitinib

50mg po, daily, for 4 weeks continuously, followed by 2 weeks of rest.

Repeat at 6 week cycles until progression or patient is withdrawn from study, as outlined in Section 3.6.

3.1.2

Dose interruptions and modifications will be performed according to guidelines outlined in Section 3.4

3.2 Adverse Event Reporting Requirements

The Adverse Event Reporting Requirements for all EAY131 subprotocols are outlined in the MATCH MASTER protocol. Please refer to those guidelines when determining if an event qualifies as a Serious Adverse Event (SAE) and requires expedited reporting via CTEP's Adverse Event Reporting System (CTEP-AERS).

In addition, the following section outlines agent specific requirements and must be followed to ensure all reporting requirements are met.

3.2.1 Additional instructions, requirements and exceptions for protocol EAY131 – Subprotocol V

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

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EAY131 – Subprotocol V specific expedited reporting requirements:

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on Sunitinib, or within 28 days of the female patient's last dose of Sunitinib, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in MATCH Master Protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EAY131 – Subprotocol V specific expedited reporting exceptions:

For Subprotocol V, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event

3.2.2 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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Rev. 3/17
Rev. Add21

3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Sunitinib malate (SU011248 L-malate, NSC 736511).

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 7115 patients.* Below is the CAEPR for Sunitinib malate (SU011248 L-malate).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Version 2.14, February 15, 2019[1]

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
ENDOCRINE DISORDERS			
		Endocrine disorders - Other (thyroiditis)	
		Hyperthyroidism	
	Hypothyroidism		***Hypothyroidism (Gr 2)***
EYE DISORDERS			
		Eye disorders - Other (macular edema)	***Eye disorders - Other (macular edema) (Gr 2)***
	Papilledema		***Papilledema (Gr 2)***
		Vision decreased	***Vision decreased (Gr 2)***

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension (Gr 2)***
Abdominal pain			***Abdominal pain (Gr 3)***
Anal mucositis			***Anal mucositis (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
Dyspepsia			***Dyspepsia (Gr 2)***
		Esophagitis	
	Flatulence		***Flatulence (Gr 2)***
	Gastritis		***Gastritis (Gr 2)***
	Gastroesophageal reflux disease		
		Gastrointestinal perforation[2]	
Mucositis oral			***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
		Pancreatitis	
Rectal mucositis			***Rectal mucositis (Gr 2)***
Small intestinal mucositis			***Small intestinal mucositis (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Flu like symptoms		
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
HEPATOBILIARY DISORDERS			
		Cholecystitis	
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (necrotizing fasciitis)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	CPK increased		
	Creatinine increased		***Creatinine increased (Gr 3)***
		Electrocardiogram QT corrected interval prolonged	
	Lipase increased		***Lipase increased (Gr 4)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Serum amylase increased		***Serum amylase increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperuricemia		***Hyperuricemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		
		Hypoglycemia	
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
		Musculoskeletal and connective tissue disorder - Other (fistula formation)	
	Myalgia		***Myalgia (Gr 2)***
		Osteonecrosis of jaw	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Pain in extremity		***Pain in extremity (Gr 2)***
		Rhabdomyolysis	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Leukoencephalopathy	
		Nervous system disorders - Other (cerebral infarction)	
	Paresthesia		
		Reversible posterior leukoencephalopathy syndrome	
		Transient ischemic attacks	
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Nephrotic syndrome	
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		***Epistaxis (Gr 2)***
Laryngeal mucositis			***Laryngeal mucositis (Gr 2)***
Pharyngeal mucositis			***Pharyngeal mucositis (Gr 2)***
Tracheal mucositis			***Tracheal mucositis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
	Hair color changes		***Hair color changes (Gr 2)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Pruritus		
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event	
	Vascular disorders - Other (hemorrhage)[4]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[3]Allergic reactions observed include anaphylaxis and angioedema.

[4]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI tract, GU system, respiratory tract, nervous system [including fatal intracranial hemorrhage, and cerebrovascular accident], and tumor site) have been reported.

Adverse events reported on Sunitinib malate (SU011248 L-malate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Sunitinib malate (SU011248 L-malate) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Pericardial effusion

GASTROINTESTINAL DISORDERS - Ascites; Dysphagia; Gastrointestinal disorders - Other (enteritis); Hemorrhoids; Ileus; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Pain

INVESTIGATIONS - GGT increased; INR increased

METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypokalemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain

NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Peripheral sensory neuropathy; Seizure; Spinal cord compression; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion

RENAL AND URINARY DISORDERS - Hematuria; Urinary retention

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pharyngolaryngeal pain; Pleural effusion; Pneumothorax

VASCULAR DISORDERS - Flushing; Hypotension

Rev.2/16 **NOTE**: Sunitinib malate (SU011248 L-malate) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

3.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Dose interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability.

The acceptable dose levels for sunitinib therapy are listed below in the following table. Treatment is initiated at dose level 0, if a dose reduction occurs for grade II or III toxicity, and a patient tolerates the dose reduction well, and is deriving clinical benefit, a dose level escalation back to the prior dose may be considered after 1 cycle.

Dose Level	Dose and Administration Schedule
0	50mg po daily for 4 weeks, 2 weeks rest
-1	37.5 mg po daily for 4 weeks, 2 weeks rest
-2	25 mg po daily for 4 weeks, 2 weeks rest
-3	Discontinue therapy

If the drug is held longer than 2 weeks (excluding 2 week rest period), discontinue sunitinib.

Specific dose modification criteria and management in response to specific toxicities are listed in the table below:

Table 1. Sunitinib Dose-Reduction Guidelines

Toxicity	Sunitinib Modification
Skin and Subcutaneous Disorders	
Palmar-plantar erythrodysesthesia syndrome (PPE) (hand-foot syndrome)	See table 2 below 'Sunitinib Dose Reductions for PPE (Hand-Foot Syndrome)'
Grade 3 or 4 rash acneiform	Hold sunitinib • Re-evaluate at least weekly until resolution to ≤ grade 1 or tolerable grade 2 • Re-start sunitinib at one dose-reduction step • If AE persists > 14 days, discontinue sunitinib • If grade 4 acneiform rash (related to sunitinib), sunitinib may be discontinued at investigator's discretion
Stevens-Johnson syndrome or toxic epidermal necrolysis	Discontinue sunitinib if Stevens-Johnson syndrome or toxic epidermal necrolysis are suspected
Gastrointestinal Disorders	
Perforation (esophageal, gastric, colonic, duodenal, ileal, jejunal, rectal, or small intestine)	Discontinue sunitinib
Investigations	
Grade 3 or 4 AST or ALT increase	Hold sunitinib • If no alternative explanation for transaminitis can be determined (such as viral hepatitis, progressive underlying hepatic malignancy), discontinue sunitinib • Otherwise, upon resolution to ≤ grade 1 or baseline, re-start sunitinib at one dose-reduction step • If patient develops ≥ grade 3 hepatic failure, discontinue sunitinib.
Grade 3 or 4 electrocardiogram QT corrected interval prolonged	See also Section 3.5.4. Hold sunitinib • Check and immediately administer potassium to achieve levels of ≥ 4 mmol/L and magnesium to levels of ≥ 2 mg/dL • Consider chronic oral supplementation of potassium and/or magnesium • Review with the subprotocol principal investigator and consult with a cardiologist prior to patient's next scheduled treatment, considering the following options: - HOLD sunitinib until QTc recovers to pre-study treatment baseline (grade 1 or less, or ≤ 480ms) - When QTc returns to baseline, reinitiate sunitinib cautiously, with additional QTc monitoring at earliest possible follow-up opportunity, but no more than 8 days from reintroduction of sunitinib - If QTc prolongation event felt attributable to sunitinib, follow protocol dose-reduction-step guidelines (see table above in Section 3.4) when re-introduced - For recurrent QTc grade 3 felt attributable to sunitinib despite dose-step reduction, discontinue sunitinib

Proteinuria	Monitor urine protein once every cycle with urinalysis. If protein excretion positive on urinalysis, obtain 24-hour urine protein. Interrupt treatment for 24-hour urine protein ≥ 3 grams. Discontinue for repeat episodes of protein ≥ 3 grams despite dose reductions or nephrotic syndrome.
Nervous System Disorders *(potentially reflective of cardio-toxicity)*	
Grade 2 pre-syncope or grade 3 syncope	See also Section 3.5.2. • Obtain ECG for cardiology review/consultation • Check magnesium and potassium and promptly administer potassium to achieve level of ≥ 4 mmol/L and magnesium to level ≥ 2 mg/dL • IF ECG shows new dysrhythmia or QTc ≥ grade 2 (> 480ms), hospitalize for monitoring with cardiology consultation • HOLD sunitinib until any potassium and magnesium abnormalities are corrected, symptoms resolved and QTc returns to grade 1 or less (≤ 480ms) • Reintroduce sunitinib cautiously, with input from cardiology and with additional QTc evaluation, either concurrent with reintroduction or at earliest possible follow-up opportunity and no more than 8 days from reintroduction • If event felt attributable to sunitinib consider dose modification of sunitinib when re-introduced • Consider chronic oral supplementation of potassium and/or magnesium • For recurrent syncope or near-syncope felt attributable to sunitinib consider permanent discontinuation
All Other Non-Hematologic Toxicities Attributable to sunitinib	
Any grade 2 non-hematologic toxicity that is persistent, intolerable, or unresponsive to optimal management	At the treating investigator's discretion, reduce to the next lower dose-reduction step
Grade 3 or 4	Omit sunitinib until resolution to ≤ grade 1, baseline or tolerable grade 2 • Re-start sunitinib at one dose-reduction step • If AE persists > 14 days, discontinue sunitinib In addition, at investigator discretion: • For bleeding that requires more than minor medical intervention, consider discontinuing sunitinib • For severe persistent hypertension or hypertensive crisis despite optimal antihypertensive management, consider discontinuing sunitinib • For evidence of cardiac ischemia or myocardial infarction, consider discontinuing sunitinib • For grade 4 AEs related to sunitinib, consider discontinuing sunitinib

Dose reduction guideline table for Plantar Palmar Erythrodysesthesia

Table 2. Sunitinib Dose-Reduction Guidelines and Management for PPE

Grade	Occurrence	Action
Grade 1	1st occurrence or recurrence	Continue sunitinib 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 sunitinib and institute supportive measures for symptomatic relief.* If no improvement within 7 days, see below.
	No improvement within 7 days or recurrence beyond 2nd occurrence	Stop sunitinib treatment until toxicity resolves to grade 0-1. When resuming treatment, decrease sunitinib dose by 1 dose-reduction step. Institute 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 sunitinib treatment until toxicity resolves to grade 0-1. When resuming treatment, decrease s sunitinib by 1 dose-reduction step. Institute supportive measures for symptomatic relief.*
	3rd occurrence	Discontinue sunitinib treatment.

*See section 3.5.3 for PPE management

Table 3. Other Hematologic and Non-Hematologic Adverse Events

Event	AE Grade or Observation	Dose modification
Neutropenia	Grades 1 and 2	Maintain dose
	Grade 3*	Hold sunitinib until ≤ grade 2, then resume at same dose level
	Grade 4	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment
Thrombocytopenia	Grades 1 and 2	Maintain dose
	Grade 3* and severe grade 2, at investigator discretion	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment
	Grade 4	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment

*Recurrent grade 3 events require dose reduction.

3.5 General Concomitant Medications & Supportive Care Guidelines

3.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

3.5.2 Hypertension

3.5.2.1 Hypertension is common during sunitinib therapy. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe or symptomatic hypertension, temporary suspension of sunitinib is recommended until hypertension is controlled. If hypertension is associated with neurologic or cardiac symptoms, institute dose reduction or consider discontinuation as per table 1, in Section 3.4

3.5.3 Plantar Palmar Erythrodysesthesia (PPE)

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

3.5.3.1 PPE Prevention

- Before initiating treatment with sunitinib, 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 sunitinib treatment, instruct patients to avoid pressure points and items that rub, pinch, or create friction.
- Instruct the patient to apply moisturizing lotions to their hands and feet twice a day throughout treatment.

3.5.3.2 PPE Treatment

- Treatment may begin at the first clinical signs of PPE. At first occurrence, independent of grade, supportive measures should be promptly initiated. Tender areas should be protected as follows:
- Use socks/gloves to cover moisturizing creams
- Wear well-padded footwear; use insole cushions or inserts.
- Foot soaks with tepid water and Epson salts.
- Creams may be used as follows:
- Non-urea based creams may be applied liberally.
- Keratolytic creams (eg, urea-based creams, salicylic acid 6%) may be used sparingly and only to affected hyperkeratotic areas.

- Alpha hydroxyl acids (AHA)-based creams may be applied liberally 2 times a day. Approximately 5% to 8% provides gentle chemical exfoliation.
- Topical analgesics (eg, lidocaine 2%) may be used for pain control.
- Topical corticosteroids like clobetasol 0.05% should be considered for patients with grade 2 or 3 PPE. Systemic steroids should be avoided.
- Use of celecoxib: A meta-analysis of PPE prevention strategies concluded that celecoxib, with statistically significant results, was the most promising agent. Therefore, celecoxib can be considered to reduce the severity of PPE as follows: Celecoxib 200 mg once daily should begin at the first clinical signs or symptoms of grade 2 or greater PPE.

3.5.4 QT Prolongation Considerations During Therapy

3.5.4.1 Any time QTc is evaluated:

- When HR is between 60-100 bpm, no manual read of QTc required
- When HR < 60 or >100 bpm, manual read of QTc by member of the study team is required, using Fridericia correction

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

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

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

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

3.5.4.5 For any episode of syncope (grade 3) or near-syncope (pre-syncope grade 2) or QTc grade 3 or 4 (> 500 ms on 2 ECGs), see Table 1 in section 3.4

3.5.5 Hypothyroidism

3.5.5.1 Sunitinib is associated with thyroid dysfunction. Monitor thyroid function once every cycle, and as part of investigations for fatigue or tremor. Thyroid dysfunction should be managed as part of routine standard of care.

3.6 Duration of Agent-specific treatment

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the MATCH Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease progression

3.7 Duration of Follow-Up

Refer to the MATCH Master Protocol for specifics on the duration of follow-up.

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4. Study Parameters

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4.1 Therapeutic Parameters for Sunitinib Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving sunitinib treatment.

NOTE: All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration to Steps 1, 3, 5, 7, excluding the radiologic evaluation and electrocardiogram (ECG).

Test/Assessment	Prior to Registration to Treatment	Treatment				End of Treatment	Follow Up[F]
		Every Cycle, prior to treatment	For Cycle 1, Week 1-4 and 6	For Cycles 1 and 2, Day 21 (± 3 days)[O]	Every 2 Cycles		
H&P, Weight, Vital signs[A]	X	X[J]	X[A]	X			X
Performance status	X	X[J]					X
CBC w/diff, plts[B]	X	X[J]		X			X
Serum chemistry[B]	X	X[J]		X			X
Radiologic evaluation[D]	X				X[D]		X[F]
β-HCG[C]	X						
Urinalysis for proteinuria[L]	X	X		X			
Thyroid function tests[M]	X	X		X			
Echocardiogram or Nuclear Study[N]	X[I]				X[I]		
Toxicity Assessment[G]		X				X	X[F]
Pill Count/Diary[H]		X				X	
ECG[K]	X	X[I]					
Tumor biopsy and blood sample submission for MATCH Master Protocol[E]					X	X	

A. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle). During Cycle 1, blood pressure will be monitored weekly (except for week 5).

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B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance. CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

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C. Blood pregnancy test (women of childbearing potential) required prior to beginning treatment.

Rev.2/16 [D.] Disease measurements are repeated every 2 cycles until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

[E.] Additional blood specimens and/or biopsies are to be submitted from consenting patients per Section 9.3.2 of the MATCH Master Protocol. Submit at the following time points, as applicable:

- Blood specimens are to be submitted at the end of Cycle 2 (prior to start of Cycle 3 treatment). If patient progresses or treatment is discontinued prior to Cycle 3, collect the blood at that time instead. On-treatment kits for blood sample collections will be automatically shipped to sites upon registration to the treatment step.
- Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
- At end of all MATCH study treatments, blood specimens and/or research biopsy after consent and registration to Step 8

Please refer to Section 4 of the MATCH Master Protocol to determine whether the patient proceeds to the next screening step or to follow-up (with a potential end of treatment biopsy for research purposes on Step 8). Samples are to be submitted as outlined in Section 9 of the MATCH Master Protocol. To order Step 2/4 Screening or Step 8 kits, complete the EAY131 Collection and Shipping Kit Order Form (See Appendix XII of the MATCH Master Protocol) and fax to 713-563-6506.

Rev.2/16 [F.] Every 3 months if patient is < 2 years from study entry, and every 6 months for year 3. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

[G.] Site personnel should evaluate for toxicity and discuss treatment compliance with the patient in order to ensure the medication is taken correctly; this evaluation may be conducted by telephone or in person. The Toxicity Assessment is not required prior to Cycle 1, but is required every subsequent cycle.

[H.] The pill calendar will be collected at the end of every cycle. The Pill Count/Diary is not required prior to Cycle 1, but is required every subsequent cycle.

[I.] As clinically indicated.

[J.] For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this timepoint: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications.

[K.] Within 8 weeks of treatment assignment.

[L.] If urinalysis is positive for protein excretion, obtain 24 hour urine protein.

[M.] TSH, T3, T4

Rev.2/16 Rev.10/15 [N.] Cardiac monitoring with echocardiogram or nuclear study (MUGA/First Pass) must be completed within 4 weeks prior to registration to treatment, if clinically indicated, and then repeated every 2 cycles thereafter, if clinically indicated.

[O.] For Cycles 1 and 2, an additional visit for toxicity testing will be done mid-cycle (within 3 days of Day 21) to detect any toxicities before the 2 weeks of rest.

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5. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment subprotocol prior to submitting the clinical drug request to PMB.

Drug Ordering: NCI supplied agents may be requested by the eligible participating Investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information) The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam) and the maintenance of an “active” account status, a “current” password, and an active person registration status.

NCI Supplied Agent(s) – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

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Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of agent received from the PMB using the NCI Investigational Agent Accountability Record Form for Oral Agents available on the NCI home page (http://ctep.cancer.gov). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator.

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Investigator Brochure Availability: The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov

5.1 Sunitinib malate (NSC 736511)

5.1.1 Chemical Name:

N-[2-(Diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide, compound with (S)-2-hydroxybutanedioic acid

5.1.2 Other Names:

SU011248 L-Malate, Sutent

5.1.3 Classification:

Multi-kinase inhibitor

5.1.4 Molecular Formula:

$C_{22}H_{27}FN_4O_2 \bullet C_4H_6O_5$

5.1.5 Physical Description:

Yellow to orange powder

5.1.6 CAS Registry Number:

341031-54-7

5.1.7 Solubility:

Aqueous Solubility

Solvent	**Solubility (mg/mL)**
0.1 M HCl	59.1
pH 4.5 buffer	25.4
pH 6.8 buffer	37.8
pH 7.5 buffer	0.05
In Water	1.6

Solubility in Various Solvents

Solvent	**Solubility (mg/mL)**
Acetonitrile	0.1
Dimethyl sulfoxide	92.9
Tetrahydrofuran	0.2
Methanol	1.5
Ethanol	0.3
1-Butanol	0.1
1-Butano:Water (80/20 v/v)	6.2
N,N-Dimethylacetamide	37
N,N-Dimethylformamide	18.4

5.1.8 Mode of Action:

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth,

pathologic angiogenesis, and metastatic progression of cancer. Sunitinib is an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET).

5.1.9 Storage and Stability:

Storage: Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Stability: Refer to the package label for expiration.

5.1.10 Dose Specifics:

50 mg po once a day for 4 weeks, followed by 2 weeks rest.

5.1.11 Preparation:

Sunitinib malate capsules are supplied by Pfizer, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Capsules are packaged in 28-count bottles with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients in the following strengths:

- 12.5 mg hard gelatin capsule (size 4) with orange cap and orange body, printed with white ink "Pfizer" on the cap and "STN 12.5 mg" on the body.
- 25 mg hard gelatin capsule (size 3) with caramel cap and orange body, printed with white ink "Pfizer" on the cap and "STN 25 mg" on the body.
- 50 mg hard gelatin capsule (size 2) with caramel top and caramel body, printed with white ink "Pfizer" on the cap and "STN 50 mg" on the body.

Orange gelatin capsule shells contain titanium dioxide, and red iron oxide. Caramel gelatin capsule shells contain titanium dioxide, red iron oxide, yellow iron oxide and black iron oxide. White printing ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

5.1.12 Route of Administration:

Oral administration, take with or without food.

5.1.13 Potential Drug Interactions:

Sunitinib is metabolized primarily by CYP3A4. Avoid coadministration of strong CYP3A4 inducers/inhibitors.

5.1.14 Side Effects:

See Section 3.3 for side effects.

6. Translational Studies

Please refer to the MATCH Master Protocol for information on the Translational Studies.

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Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol V: Sunitinib

Appendix I

Rev.12/16

Patient Pill Calendar

Rev.3/17

Storage: Store at Room Temperature

Pill Calendar Directions

1. Take your scheduled dose of each capsule.
2. Take the capsules with or without food once daily for 28 days, and then take no study medicine for 14 days (rest days). Each cycle is 42 days long.
3. If you forget, the missed capsules will not be taken later.
4. Please bring the empty bottle or any leftover capsules and your pill calendar to your next clinic visit.
5. Swallow capsules whole. Do not crush, chew or open capsules.

Rev.2/16

Patient Pill Calendar

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsule. **Note the times and the number of capsules that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused capsules and your completed pill calendar to your doctor's visits.

Sunitinib

DAY	Date Month	Day	Year	Time capsules taken	Number of capsules taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
Days 29-42 are rest days - Do not take any capsules						

Patient Signature: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol V: Sunitinib

Rev. Add13
Rev. Add19
Rev.Add25

Appendix II

Actionable Mutations of Interest (aMOIs)

List of Inclusion Variants:

A function has been implemented in MATCHBOX to identify any in-frame insertions and deletions in exon 9, 11, 13, and 14 of the KIT gene at Level of Evidence code 2. This function may include any in-frame insertions, deletions or known activating missense mutations in exons 9, 11, 13, and 14 of the KIT gene at Level of Evidence code 2. Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
KIT	COSM1326	Large Indel	2	p.S501_A502insAY
KIT	COSM27901	Large Indel	2	p.P551_V560delinsL
KIT	COSM1198	Large Indel	2	p.V555_V559del
KIT	COSM1230	Large Indel	2	p.W557_V560delinsF
KIT	COSM1234	Large Indel	2	p.K558_V560del
KIT	COSM1238	Large Indel	2	p.K558_N564del
KIT	COSM1235	Large Indel	2	p.K558_V559del
KIT	COSM1248	Large Indel	2	p.V559_V560del
KIT	COSM1262	Indel	2	p.E561del
KIT	COSM23560	Large Indel	2	p.N564_Y578del
KIT	COSM1281	Large Indel	2	p.V569_Q575del
KIT	COSM144983	Large Indel	2	p.T500_S501insSA
KIT	COSM219786	Large Indel	2	p.T500_S501insSA
KIT	COSM53306	Large Indel	2	p.S501_A502insAF
KIT	COSM1164	Large Indel	2	p.K550_V555delinsI
KIT	COSM1172	Large Indel	2	p.P551_E554del
KIT	COSM1169	Large Indel	2	p.Pro551_Val555del
KIT	COSM1170	Large Indel	2	p.P551_Q556del
KIT	COSM1171	Indel	2	p.P551del
KIT	COSM1174	Large Indel	2	p.P551_V555delinsL
KIT	COSM1176	Indel	2	p.P551_M552delinsL
KIT	COSM36304	Large Indel	2	p.M552_D572del
KIT	COSM1177	Large Indel	2	p.M552_W557del
KIT	COSM96881	Large Indel	2	p.M552_Y553del
KIT	COSM1182	Large Indel	2	p.M552_K558del
KIT	COSM1180	Large Indel	2	p.M552_W557del
KIT	COSM18827	Large Indel	2	p.M552_V555del
KIT	COSM1179	Large Indel	2	p.M552_Y553del
KIT	COSM1181	Large Indel	2	p.M552_E554del

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
KIT	COSM1327	Large Indel	2	p.M552_Q556del
KIT	COSM96880	Large Indel	2	p.M552_E561delinsK
KIT	COSM36311	Large Indel	2	p.M552_E554delinsK
KIT	COSM96868	Large Indel	2	p.M552_Q556delinsK
KIT	COSM96863	Indel	2	p.M552_Y553delinsN
KIT	COSM133636	Large Indel	2	p.M552_W557delinsR
KIT	COSM1185	Large Indel	2	p.M552_V555delinsI
KIT	COSM1190	Large Indel	2	p.M552_W557del
KIT	COSM1187	Large Indel	2	p.M552_W557delinsK
KIT	COSM1189	Large Indel	2	p.M552_Q556delinsK
KIT	COSM1191	Large Indel	2	p.Y553_V559del
KIT	COSM22275	Large Indel	2	p.Y553_T574delinsS
KIT	COSM96947	Large Indel	2	p.E554_N564del
KIT	COSM36294	Large Indel	2	p.E554_D572del
KIT	COSM36310	Large Indel	2	p.E554_E562del
KIT	COSM36291	Large Indel	2	p.E554_I571del
KIT	COSM1194	Large Indel	2	p.E554_E561del
KIT	COSM1192	Large Indel	2	p.E554_K558del
KIT	COSM1203	Large Indel	2	p.V555_P573del
KIT	COSM37027	Large Indel	2	p.E554_N564del
KIT	COSM1196	Large Indel	2	p.V555_I563del
KIT	COSM1200	Large Indel	2	p.V555_I571del
KIT	COSM1197	Large Indel	2	p.V555_Y570del
KIT	COSM1202	Large Indel	2	p.V555_V560del
KIT	COSM1199	Large Indel	2	p.V555_K558del
KIT	COSM1201	Large Indel	2	p.V555_Q556del
KIT	COSM96870	Large Indel	2	p.V555_N566delinsD
KIT	COSM1209	Large Indel	2	p.Q556_T574del
KIT	COSM36308	Large Indel	2	p.Q556_P573del
KIT	COSM1205	Large Indel	2	p.Q556_L576del
KIT	COSM36309	Large Indel	2	p.Q556_W557del
KIT	COSM1206	Large Indel	2	p.Q556_E561del
KIT	COSM1204	Large Indel	2	p.Q556_V560del
KIT	COSM36315	Large Indel	2	p.Q556_V559del
KIT	COSM23418	Large Indel	2	p.Q556_K558del
KIT	COSM1212	Large Indel	2	p.Q556_D572delinsH
KIT	COSM36312	Large Indel	2	p.W557_E562del
KIT	COSM1330	Large Indel	2	p.W557_E561del
KIT	COSM1210	Large Indel	2	p.W557_K558del
KIT	COSM133642	Indel	2	p.Q556_W557delinsR
KIT	COSM1365	Large Indel	2	p.W557_I571del

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
KIT	COSM1221	SNV	2	p.W557G
KIT	COSM1220	Indel	2	p.W557del
KIT	COSM1213	Large Indel	2	p.Q556_V560delinsH
KIT	COSM133641	Large Indel	2	p.Q556_V559delinsH
KIT	COSM1214	Large Indel	2	p.Q556_V559delinsHT
KIT	COSM133639	Large Indel	2	p.W557_Q575del
KIT	COSM1223	Large Indel	2	p.W557_V560del
KIT	COSM1218	Large Indel	2	p.W557_V559del
KIT	COSM24748	Indel	2	p.W557_K558delinsE
KIT	COSM1229	Large Indel	2	p.W557_P573delinsS
KIT	COSM1226	Large Indel	2	p.W557_V559delinsF
KIT	COSM1239	Large Indel	2	p.K558_E562del
KIT	COSM1232	Large Indel	2	p.W557_V560delinsC
KIT	COSM1233	Large Indel	2	p.W557_V559delinsC
KIT	COSM36303	Large Indel	2	p.K558_Q575del
KIT	COSM1236	Large Indel	2	p.K558_G565del
KIT	COSM1237	Large Indel	2	p.K558_D572del
KIT	COSM28991	Large Indel	2	p.K558_Y570delinsN
KIT	COSM1250	Large Indel	2	p.V559_E561del
KIT	COSM1240	Large Indel	2	p.K558_G565delinsR
KIT	COSM1241	Large Indel	2	p.K558_V560delinsI
KIT	COSM27069	Large Indel	2	p.K558_V560delinsN
KIT	COSM21976	Indel	2	p.K558delinsNP
KIT	COSM1244	Indel	2	p.K558_V559delinsN
KIT	COSM1245	Indel	2	p.K558delinsNP
KIT	COSM36300	Large Indel	2	p.V559_L576del
KIT	COSM1249	Large Indel	2	p.V559_G565del
KIT	COSM36301	Large Indel	2	p.V559_I571del
KIT	COSM1247	Indel	2	p.V559del
KIT	COSM1252	SNV	2	p.V559D
KIT	COSM36293	Large Indel	2	p.V560_L576del
KIT	COSM1257	SNV	2	p.V560D
KIT	COSM1260	SNV	2	p.V560G
KIT	COSM30545	Large Indel	2	p.V559_P573delinsA
KIT	COSM18897	Large Indel	2	p.V559_E562del
KIT	COSM133640	Large Indel	2	p.V560_I571del
KIT	COSM29442	Large Indel	2	p.I563_L576del
KIT	COSM1268	Large Indel	2	p.I563_D572del
KIT	COSM24839	Large Indel	2	p.N564_T574del
KIT	COSM1270	Large Indel	2	p.N564_L576del
KIT	COSM1269	Large Indel	2	p.N564_P577del

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
KIT	COSM36299	Large Indel	2	p.N564_P573delinsT
KIT	COSM133635	Large Indel	2	p.V569_L576del
KIT	COSM1282	Large Indel	2	p.V569_D572del
KIT	COSM1285	Large Indel	2	p.Y570_L576del
KIT	COSM29016	Large Indel	2	p.I571_N587del
KIT	COSM29857	Large Indel	2	p.Y570_I571insIDPTQLPYDHKWEFPSD
KIT	COSM41198	Large Indel	2	p.Y570_I571insIDPTQLPYDH
KIT	COSM133754	Large Indel	2	p.I571_L576del
KIT	COSM23417	Large Indel	2	p.Y570_I571insIDPTQLPYD
KIT	COSM308544	Large Indel	2	p.I571_D572insDPTQLPYD
KIT	COSM18751	Large Indel	2	p.I571_D572insDPTQLPYDHKWEF
KIT	COSM30595	Large Indel	2	p.I571_D572insDPTQLPYDHKWEFP
KIT	COSM34126	Large Indel	2	p.D572_P573insPTQLPYDH
KIT	COSM36322	Large Indel	2	p.D572_P573insPTQLPYDHKWEFP
KIT	COSM18668	Large Indel	2	p.D572_P573insPTQLPYD
KIT	COSM33906	Large Indel	2	p.D572_P573insPTQLPYDHKWEF
KIT	COSM1289	Indel	2	p.L576del
KIT	COSM1300	Large Indel	2	p.Q575_L576insLPYDHKWEFP
KIT	COSM1298	Large Indel	2	p.Q575_L576insLPYDHKWEF
KIT	COSM41632	Large Indel	2	p.L576_P577insPYDHKWEF
KIT	COSM1290	SNV	2	p.L576P
KIT	COSM98379	Large Indel	2	p.P577_D579del
KIT	COSM1296	Large Indel	2	p.L576_P577insPYDH
KIT	COSM1291	Large Indel	2	p.P577_Y578del
KIT	COSM1684822	Indel	2	p.P577de
KIT	COSM18666	Large Indel	2	p.L576_P577insPYDH
KIT	COSM96866	Large Indel	2	p.D579_H580insSYD
KIT	COSM28995	Large Indel	2	p.P577_Y578insYDH
KIT	COSM1294	Indel	2	p.D579del
KIT	COSM1295	Indel	2	p.H580del
KIT	COSM36323	Large Indel	2	p.F584_P585insIDPTQLPYDHKWEFR
KIT	COSM1304	SNV	2	p.K642E
KIT	COSM12706	SNV	2	p.V654A
KIT	COSM1253	SNV	2	p.V559G
KIT	COSM12708	SNV	2	p.T670I
KIT	COSM4383740	SNV	3	p.S476N
KIT	COSM219784	SNV	3	p.S476I
KIT	COSM327599	SNV	3	p.E490K
KIT	COSM6957947	SNV	3	p.D496N
KIT	COSM133685	SNV	3	p.T500I
KIT	COSM96885	SNV	3	p.K509I

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
KIT	COSM133699	SNV	3	p.G510D
KIT	COSM5686734	SNV	3	p.P551A
KIT	COSM1183	SNV	3	p.M552L
KIT	COSM734168	SNV	3	p.M552L
KIT	COSM133763	SNV	3	p.Y553N
KIT	COSM1216	SNV	3	p.W557R
KIT	COSM1219	SNV	3	p.W557R
KIT	COSM133700	SNV	3	p.W557C
KIT	COSM19108	SNV	3	p.W557C
KIT	COSM30551	SNV	3	p.K558E
KIT	COSM1246	SNV	3	p.K558N
KIT	COSM1255	SNV	3	p.V559A
KIT	COSM1253	SNV	3	p.V559G
KIT	COSM36302	SNV	3	p.V560A
KIT	COSM1264	SNV	3	p.E561K
KIT	COSM133701	SNV	3	p.R586K
KIT	COSM5702513	SNV	3	p.S628N
KIT	COSM1600403	SNV	3	p.R634W
KIT	COSM96871	SNV	3	p.K642Q
KIT	COSM133675	SNV	3	p.G663E
KIT	COSM36053	SNV	3	p.H697Y
KIT	MVAR183	SNV	3	p.H802T
KIT	COSM18681	SNV	3	p.Y823D
KIT	COSM24637	SNV	3	p.F469L
KIT	COSM24639	SNV	3	p.N486D
KIT	COSM24638	SNV	3	p.V489A
KIT	COSM29015	SNV	3	p.K558R
KIT	COSM1246	SNV	3	p.K558N
PDGFRA	MVAR189	Indel	3	p.W559_R560del
PDGFRA	COSM739	SNV	3	p.V561D
PDGFRA	COSM742	Indel	3	p.S566_E571>R
PDGFRA	COSM12418	Indel	3	p.S566_E571>R
PDGFRA	COSM30546	Indel	3	p.S566_E571>R
PDGFRA	COSM22414	SNV	3	p.N659K
PDGFRA	COSM22415	SNV	3	p.N659K
PDGFRA	COSM743	SNV	3	P.T674I
PDGFRA	COSM12397	SNV	3	p.D842Y
PDGFRA	COSM737	Indel	3	p.I843_D846delIMHD
PDGFRA	COSM12396	SNV	3	p.D842Y
PDGFRA	COSM96892	Indel	3	p.I843_D846delIMHD
PDGFRA	COSM12400	Indel	3	p.I843_D846delIMHD

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
PDGFRA	COSM12407	Indel	3	p.I843_S847>T
PDGFRA	COSM4969655	Indel	3	p.I843delI
PDGFRA	COSM738	Indel	3	p.H845_N848>P
PDGFRA	COSM12399	SNV	3	p.D846Y
PDGFRA	COSM94952	SNV	3	p.Y849C
PDGFRB	VCV000375557	InDel	3	p.I538_L539insR
PDGFRB	VCV000055848	SNV	3	p.R561C
PDGFRB	VCV000375682	SNV	3	p.W566R
PDGFRB	VCV000375555	Indel	3	p.W566_V568delinsL
PDGFRB	COSM6916840	SNV	3	p.N666K
PDGFRB	COSM6927334	SNV	3	p.D850V
PDGFRA	BCR-PDGFRA.B12ins12P12	Fusion	3	BCR-PDGFRA.B12ins12P12
PDGFRA	BCR-PDGFRA.B1P13	Fusion	3	BCR-PDGFRA.B1P13
PDGFRA	BCR-PDGFRA.B7ins24P12	Fusion	3	BCR-PDGFRA.B7ins24P12
PDGFRA	CDK5RAP2-PDGFRA.C13ins40P12	Fusion	3	CDK5RAP2-PDGFRA.C13ins40P12
PDGFRA	DIP2C-PDGFRA.D1P10	Fusion	3	DIP2C-PDGFRA.D1P10
PDGFRA	DIP2C-PDGFRA.D1P11	Fusion	3	DIP2C-PDGFRA.D1P11
PDGFRA	ETV6-PDGFRA.E6P12	Fusion	3	ETV6-PDGFRA.E6P12
PDGFRA	FIP1L1-PDGFRA.F10P12del47	Fusion	3	FIP1L1-PDGFRA.F10P12del47
PDGFRA	FIP1L1-PDGFRA.F10int10P12del106	Fusion	3	FIP1L1-PDGFRA.F10int10P12del106
PDGFRA	FIP1L1-PDGFRA.F10int10P12del22	Fusion	3	FIP1L1-PDGFRA.F10int10P12del22
PDGFRA	FIP1L1-PDGFRA.F10int10P12del67	Fusion	3	FIP1L1-PDGFRA.F10int10P12del67

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
PDGFRA	FIP1L1-PDGFRA.F11P12del24	Fusion	3	FIP1L1-PDGFRA.F11P12del24
PDGFRA	FIP1L1-PDGFRA.F11P12del26	Fusion	3	FIP1L1-PDGFRA.F11P12del26
PDGFRA	FIP1L1-PDGFRA.F11P12del45	Fusion	3	FIP1L1-PDGFRA.F11P12del45
PDGFRA	FIP1L1-PDGFRA.F11P12del77	Fusion	3	FIP1L1-PDGFRA.F11P12del77
PDGFRA	FIP1L1-PDGFRA.F11P12del77.1	Fusion	3	FIP1L1-PDGFRA.F11P12del77.1
PDGFRA	FIP1L1-PDGFRA.F12P12del107	Fusion	3	FIP1L1-PDGFRA.F12P12del107
PDGFRA	FIP1L1-PDGFRA.F12P12del84	Fusion	3	FIP1L1-PDGFRA.F12P12del84
PDGFRA	FIP1L1-PDGFRA.F13P12del71	Fusion	3	FIP1L1-PDGFRA.F13P12del71
PDGFRA	FIP1L1-PDGFRA.F13P12del75	Fusion	3	FIP1L1-PDGFRA.F13P12del75
PDGFRA	FIP1L1-PDGFRA.F13ins11P12del99	Fusion	3	FIP1L1-PDGFRA.F13ins11P12del99
PDGFRA	FIP1L1-PDGFRA.F13insP12del91	Fusion	3	FIP1L1-PDGFRA.F13insP12del91
PDGFRA	FIP1L1-PDGFRA.F16ins16P12del71	Fusion	3	FIP1L1-PDGFRA.F16ins16P12del71
PDGFRA	FIP1L1-PDGFRA.F9P12del38	Fusion	3	FIP1L1-PDGFRA.F9P12del38
PDGFRA	FOXP1-PDGFRA.F16P12	Fusion	3	FOXP1-PDGFRA.F16P12
PDGFRA	KDR-PDGFRA.K13ins35P10	Fusion	3	KDR-PDGFRA.K13ins35P10
PDGFRA	KIF5B-PDGFRA.K23P12	Fusion	3	KIF5B-PDGFRA.K23P12
PDGFRA	SCAF11-PDGFRA.S1P2	Fusion	3	SCAF11-PDGFRA.S1P2

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
PDGFRA	STRN-PDGFRA.S6P12	Fusion	3	STRN-PDGFRA.S6P12
PDGFRA	STRN-PDGFRA.S6P12.1	Fusion	3	STRN-PDGFRA.S6P12.1
PDGFRA	TNKS2-PDGFRA.T25P12	Fusion	3	TNKS2-PDGFRA.T25P12
PDGRB	ATF7IP-PDGFRB.A13P11	Fusion	3	ATF7IP-PDGFRB.A13P11
PDGRB	BIN2-PDGFRB.B9P12	Fusion	3	BIN2-PDGFRB.B9P12
PDGRB	CAPRIN1-PDGFRB.C7P11	Fusion	3	CAPRIN1-PDGFRB.C7P11
PDGRB	CCDC6-PDGFRB.C7P11	Fusion	3	CCDC6-PDGFRB.C7P11
PDGRB	CCDC88C-PDGFRB.C10P12	Fusion	3	CCDC88C-PDGFRB.C10P12
PDGRB	CCDC88C-PDGFRB.C12P11	Fusion	3	CCDC88C-PDGFRB.C12P11
PDGRB	CCDC88C-PDGFRB.C25P11	Fusion	3	CCDC88C-PDGFRB.C25P11
PDGRB	CEP85L-PDGFRB.C11P12	Fusion	3	CEP85L-PDGFRB.C11P12
PDGRB	CPSF6-PDGFRB.C5P11	Fusion	3	CPSF6-PDGFRB.C5P11
PDGRB	DTD1-PDGFRB.D4P12	Fusion	3	DTD1-PDGFRB.D4P12
PDGRB	EBF1-PDGFRB.E11P11	Fusion	3	EBF1-PDGFRB.E11P11
PDGRB	EBF1-PDGFRB.E14P11	Fusion	3	EBF1-PDGFRB.E14P11
PDGRB	EBF1-PDGFRB.E15P11	Fusion	3	EBF1-PDGFRB.E15P11
PDGRB	ERC1-PDGFRB.E15P10	Fusion	3	ERC1-PDGFRB.E15P10

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
PDGRB	ERC1-PDGFRB.E15P11	Fusion	3	ERC1-PDGFRB.E15P11
PDGRB	ETV6-PDGFRB.E4P11	Fusion	3	ETV6-PDGFRB.E4P11
PDGRB	ETV6-PDGFRB.E4P9	Fusion	3	ETV6-PDGFRB.E4P9
PDGRB	ETV6-PDGFRB.E7P10	Fusion	3	ETV6-PDGFRB.E7P10
PDGRB	ETV6-PDGFRB.E7ins34P12	Fusion	3	ETV6-PDGFRB.E7ins34P12
PDGRB	GIT2-PDGFRB.G12P11	Fusion	3	GIT2-PDGFRB.G12P11
PDGRB	GOLGA4-PDGFRB.G10P11	Fusion	3	GOLGA4-PDGFRB.G10P11
PDGRB	GOLGB1-PDGFRB.G10P12	Fusion	3	GOLGB1-PDGFRB.G10P12
PDGRB	HIP1-PDGFRB.H30P11	Fusion	3	HIP1-PDGFRB.H30P11
PDGRB	KANK1-PDGFRB.K2P9	Fusion	3	KANK1-PDGFRB.K2P9
PDGRB	MPRIP-PDGFRB.M20P12	Fusion	3	MPRIP-PDGFRB.M20P12
PDGRB	MYO18A-PDGFRB.M41P10	Fusion	3	MYO18A-PDGFRB.M41P10
PDGRB	NDE1-PDGFRB.N6P11	Fusion	3	NDE1-PDGFRB.N6P11
PDGRB	NIN-PDGFRB.N30P12	Fusion	3	NIN-PDGFRB.N30P12
PDGRB	PDE4DIP-PDGFRB.P16P11	Fusion	3	PDE4DIP-PDGFRB.P16P11
PDGRB	PRKG2-PDGFRB.P3P12	Fusion	3	PRKG2-PDGFRB.P3P12
PDGRB	PRKG2-PDGFRB.P6P12	Fusion	3	PRKG2-PDGFRB.P6P12

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
PDGRB	RABEP1-PDGFRB.R14P11	Fusion	3	RABEP1-PDGFRB.R14P11
PDGRB	SART3-PDGFRB.S15P11	Fusion	3	SART3-PDGFRB.S15P11
PDGRB	SPECC1-PDGFRB.S3P11	Fusion	3	SPECC1-PDGFRB.S3P11
PDGRB	TNIP1-PDGFRB.T14P11	Fusion	3	TNIP1-PDGFRB.T14P11
PDGRB	TP53BP1-PDGFRB.T23P11	Fusion	3	TP53BP1-PDGFRB.T23P11
PDGRB	TPM3-PDGFRB.T7P11	Fusion	3	TPM3-PDGFRB.T7P11
PDGRB	TRIP11-PDGFRB.T16P11	Fusion	3	TRIP11-PDGFRB.T16P11
PDGRB	WDR48-PDGFRB.W9P12	Fusion	3	WDR48-PDGFRB.W9P12
PDGRB	ZEB2-PDGFRB.Z9P9	Fusion	3	ZEB2-PDGFRB.Z9P9

List of Exclusion Variants:

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
KIT	COSM1311	SNV	2	p.D816H
KIT	COSM1310	SNV	2	p.D816Y
KIT	COSM24675	SNV	2	p.D816A
KIT	COSM12711	SNV	3	p.D816G
KIT	COSM1314	SNV	2	p.D816V
KIT	COSM19285	SNV	3	p.D816E
KIT	COSM12710	SNV	2	p.D820Y
KIT	COSM133670	SNV	2	p.D820A
KIT	COSM1316	SNV	2	p.D820G
KIT	COSM12709	SNV	2	p.D820E
KIT	COSM19280	SNV	2	p.D820E
KIT	COSM1318	SNV	2	p.N822H
KIT	COSM1321	SNV	2	p.N822K
KIT	COSM1322	SNV	2	p.N822K
KIT	COSM18681	SNV	2	p.Y823D
KIT	COSM13172	SNV	2	p.A829P

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Appendix III

Medications That May Cause QTc Prolongation

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes	Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amitriptyline /Elavil®
Amiodarone /Pacerone®	Amantadine /Symmetrel®	Ciprofloxacin /Cipro®
Arsenic trioxide /Trisenox®	Atazanavir /Reyataz®	Citalopram /Celexa®
Astemizole /Hismanal®	Azithromycin /Zithromax®	Clomipramine /Anafranil®
Bepridil /Vascor®	Chloral hydrate /Noctec®	Desipramine /Pertofrane®
Chloroquine /Aralen®	Clozapine /Clozaril®	Diphenhydramine /Benadryl®
Chlorpromazine /Thorazine®	Dolasetron /Anzemet®	Diphenhydramine /Nytol®
Cisapride /Propulsid®	Dronedarone /Multaq®	Doxepin /Sinequan®
Clarithromycin /Biaxin®	Felbamate /Felbatrol®	Fluconazole /Diflucan®
Disopyramide /Norpace®	Flecainide /Tambocor®	Fluoxetine /Sarafem®
Dofetilide /Tikosyn®	Foscarnet /Foscavir®	Fluoxetine /Prozac®
Domperidone /Motilium®	Fosphenytoin /Cerebyx®	Galantamine /Reminyl®
Droperidol /Inapsine®	Gatifloxacin /Tequin®	Imipramine /Norfranil®
Erythromycin /Erythrocin®	Gemifloxacin /Factive®	Itraconazole /Sporanox®
Erythromycin /E.E.S.®	Granisetron /Kytril®	Ketoconazole /Nizoral®
Halofantrine /Halfan®	Indapamide /Lozol®	Mexiletine /Mexitil®
Haloperidol /Haldol®	Isradipine /Dynacirc®	Nortriptyline /Pamelor®
Ibutilide /Corvert®	Lapatinib /Tykerb®	Paroxetine /Paxil®
Levomethadyl /Orlaam®	Lapatinib /Tyverb®	Protriptyline /Vivactil®
Mesoridazine /Serentil®	Levofloxacin /Levaquin®	Sertraline /Zoloft®
Methadone /Dolophine®	Lithium /Lithobid®	Solifenacin /VESIcare®
Methadone /Methadose®	Lithium /Eskalith®	Trimethoprim-Sulfa /Sulfa®
Pentamidine /Pentam®	Moexipril/HCTZ /Uniretic®	Trimethoprim-Sulfa /Bactrim®
Pentamidine /NebuPent®	Moxifloxacin /Avelox®	Trimipramine /Surmontil®
Pimozide /Orap®	Nicardipine /Cardene®	
Probucol /Lorelco®	Nilotinib /Tasigna®	
Procainamide /Pronestyl®	Octreotide /Sandostatin®	
Procainamide /Procan®	Ofloxacin /Floxin®	

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes	Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Quinidine /Cardioquin®	Ondansetron /Zofran®	
Quinidine /Quinaglute®	Oxytocin /Pitocin®	
Sotalol /Betapace®	Paliperidone /Invega®	
Sparfloxacin /Zagam®	Perflutren lipid microspheres /Definity®	
Terfenadine /Seldane®	Quetiapine /Seroquel®	
Thioridazine /Mellaril®	Ranolazine /Ranexa®	
	Risperidone /Risperdal®	
	Roxithromycin* /Rulide®	
	Sertindole /Serlect®	
	Sertindole /Serdolect®	
	Sunitinib /Sutent®	
	Tacrolimus /Prograf®	
	Tamoxifen /Nolvadex®	
	Telithromycin /Ketek®	
	Tizanidine /Zanaflex®	
	Vardenafil /Levitra®	
	Venlafaxine /Effexor®	
	Voriconazole /VFend®	
	Ziprasidone /Geodon®	

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Appendix IV

NCI/DCTD Collaborative Agreements Language

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company(ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of

human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

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Appendix V

Patient Clinical Trial Wallet Card

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov