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**Title:** SARC024: A blanket protocol to study oral regorafenib in patients with selected sarcoma subtypes

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# SARC Protocol: SARC024

**TITLE:** SARC024: A blanket protocol to study oral regorafenib in patients with selected sarcoma subtypes

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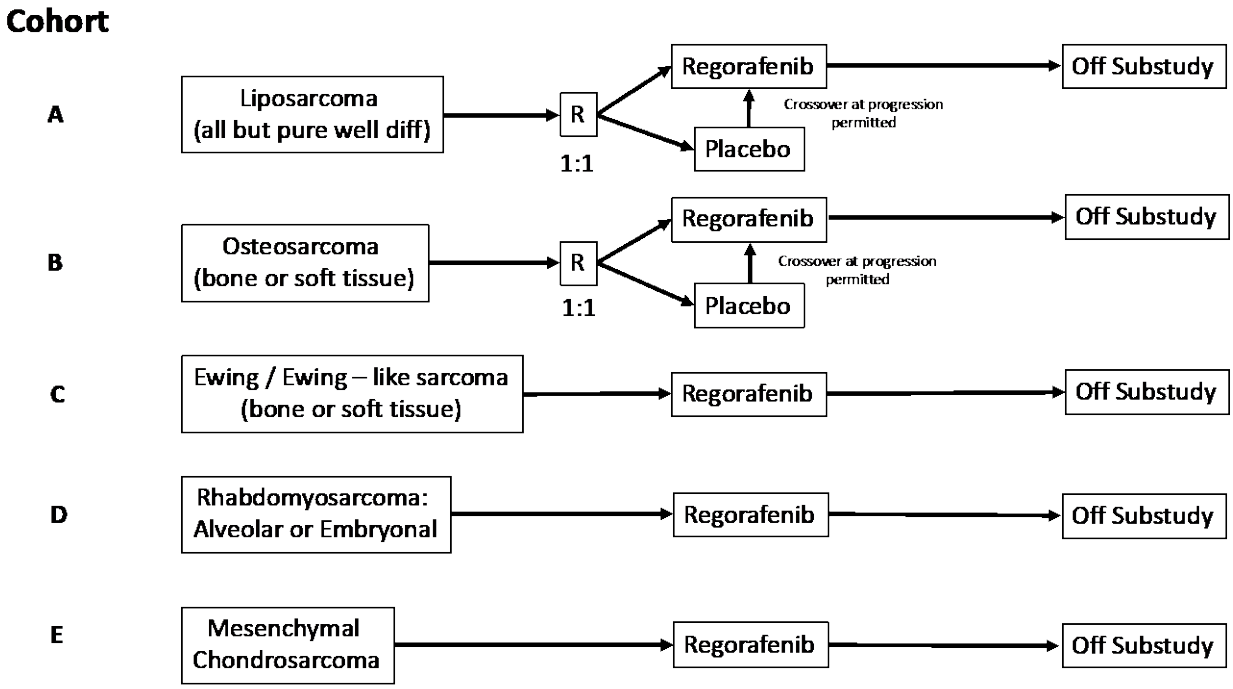
# GLOSSARY OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AJCC | American Joint Committee on Cancer |
| ALT (SGPT) | Alanine aminotransferase |
| AST (SGOT) | Aspartate aminotransferase |
| BSC | Best Supportive Care |
| CI | Confidence interval |
| CNS | Central Nervous System |
| CR | Complete Response |
| CRF | Case Report Form |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCE | Dynamic Contrast Enhanced |
| DSS | Disease-Specific Survival |
| EDC | Electronic Data Capture |
| FDA | Federal Drug Administration |
| FISH | Fluorescence in situ hybridization |
| G | Grade |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration Rate |
| GIST | Gastrointestinal Stromal Tumor |
| GMP | Good Manufacturing Practice |
| HFSR | Hand Food Skin Reaction |
| HIV | Human Immunodeficiency Virus (HIV-1 or 2, HTLV-III) |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference of Harmonisation |
| IHC | Immunohistochemistry |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| MDRD | Modified Diet in Renal Disease |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Events |
| NYHA | New York Heart Association |
| ORR | Overall response rate |

| | |
|---|---|
| OS | Overall survival |
| PI | Principal Investigator |
| PD | Progressive disease |
| PDGFR | Platelet Derived Growth Factors Receptor |
| PET | Positron Emission Tomography |
| PFS | Progression free survival |
| PTT | Partial thromboplastin time |
| PR | Partial Response |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RR | Response Rate |
| SAE | Serious Adverse Event |
| SARC | Sarcoma Alliance for Research through Collaboration |
| SD | Stable Disease |
| SMOKI | Small Molecule Oral Kinase Inhibitor |
| STBS | Soft Tissue and Bone Sarcomas |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TTP | Time to Tumor Progression |
| VEGFR | Vascular Endothelial Growth Factor |
| WHO | World Health Organization |

SCHEMA: SARC024



## Synopsis: SARC024

### Primary Objective

**Cohort A (liposarcoma):** To compare the progression-free survival (PFS) of eligible subjects treated with regorafenib or placebo according to modified RECIST version 1.1.

**Cohort B (osteogenic sarcoma):** To compare the progression-free survival (PFS) of eligible subjects treated with regorafenib or placebo according to RECIST version 1.1.

**Cohort C (Ewing/Ewing-like sarcoma)**: To estimate the RECIST 1.1 PFS rate of eligible subjects treated with regorafenib at 8 and 16 weeks.

**Cohort D (Rhabdomyosarcoma: Fusion-positive alveolar, Embryonal, Fusion-negative alveolar):** To estimate the RECIST 1.1 PFS rate of eligible subjects treated with regorafenib at 8 and 16 weeks.

**Cohort E (Mesenchymal chondrosarcoma):** To estimate the RECIST 1.1 PFS rate of eligible subjects treated with regorafenib at 24 weeks.

### Secondary Objectives

1. All cohorts: Calculate the incidence of reported CTCAE v 4.03 adverse events and abnormal laboratory test results

2. All cohorts: Estimate the overall response rate (ORR) per RECIST version 1.1, time to tumor progression (TTP), PFS at 8 and 16 weeks, overall survival (OS), disease–specific survival (DSS)

3. Cohorts A & B, after crossover: Assess PFS, RR, TTP, OS, and DSS following administration of regorafenib in the open label portion of the study.

### Exploratory endpoints

1. Assess PFS and RR in these populations by Choi criteria

2. Growth modulation index for treatment with regorafenib vs. prior line of therapy, defined as $TTP_{regorafenib}/TTP_{prior}$.

### Hypothesis and Rationale

Inhibition of angiogenesis to slow or stop cancer growth is one mechanism under scrutiny as a therapeutic option for patients with metastatic cancers of all types. Some of the agents used to examine this issue in Soft Tissue and Bone Sarcomas (STBS) are multitargeted Small Molecule

Oral Kinase Inhibitors (SMOKIs). Imatinib, sunitinib, and regorafenib have all been approved for use in gastrointestinal stromal tumors (GISTs), one of the, if not the, most common form of sarcoma.

After failure of standard cytotoxic chemotherapy, pazopanib was approved for use in patients with metastatic non-GIST metastatic soft tissue sarcomas other than liposarcoma by virtue of a phase III clinical trial in patients with metastatic soft tissue sarcoma[1]. Conversely, there are no randomized data to date regarding the activity of SMOKIs in bone sarcomas specifically, and although there are no randomized data regarding the activity of pazopanib in liposarcomas, there appears to be limited activity of SMOKIs based on the phase II study of pazopanib in soft tissue sarcomas[2].

Sorafenib, another multitargeted small molecule oral kinase inhibitor (SMOKI), demonstrated activity in a multi-arm phase II study, in which liposarcoma was also excluded. Small studies of sunitinib and anecdotes have shown at least minor activity in sarcomas[3-6]. In a phase II clinical trial of sorafenib in 35 patients with chemotherapy refractory osteogenic sarcoma, 3 patients had a partial response and 2 had a minor response, with 6 patients on treatment for more than 6 months without worsening[7]. We also note anecdotal evidence of a patient with a Ewing sarcoma with a sustained RECIST partial response (S. Attia, DO, personal communication).

Although regorafenib was approved for use in patients who had progressive GIST despite imatinib and/or sunitinib on the basis of phase II and phase III data[8,9], it has not been examined in a systematic fashion in patients with other forms of sarcoma.

Given the activity of sorafenib, sunitinib and pazopanib in soft tissue sarcomas, and evidence of activity of sorafenib in osteogenic sarcoma and possibly Ewing/Ewing-like sarcoma, there is precedent to examine SMOKIs such as regorafenib in sarcomas other than GIST. It is also recognized that SMOKIs such as regorafenib, sorafenib, pazopanib, and sunitinib have overlapping panels of kinases that are inhibited simultaneously. While not equivalent, most of these SMOKIs block vascular endothelial growth factor and platelet derived growth factors receptors (VEGFRs and PDGFRs), speaking to a common mechanism of action of several of these agents[10].

Since the protocol was developed, preclinical data from the laboratory of Raffaella Sordella at Cold Spring Harbor Laboratory indicate responsiveness to SMOKIs of mesenchymal chondrosarcoma primary tissue culture and of xenografted tumor to mice, with tumor shrinking seen of established tumors grown subcutaneously (unpublished results). As a result, this rare sarcoma subtype, typically with an *HEY1-NCOA2* fusion, may be susceptible to imatinib, sorafenib, or regorafenib; studies with the agent are underway to confirm initial data are underway as of late 2019.

We therefore propose parallel randomized phase II studies of regorafenib in patients with liposarcoma and osteogenic sarcoma to determine if there is significant activity of these agents, as has been observed with pazopanib in soft tissue sarcomas. In addition, we seek to determine the activity of regorafenib in Ewing/Ewing-like sarcoma, rhabdomyosarcoma, and mesenchymal chondrosarcoma, given anecdotal data of activity (or of promising preclinical data), planning to

examine individual cohorts of patients in a prospective phase II trial. We further note that since median time to progression with an active agent in advanced Ewing/Ewing-like sarcoma was only 1.3 months[11], it is difficult to propose a randomized study design without single cohort data.

**Trial Design**

We seek to conduct parallel clinical trials of regorafenib in five different metastatic/local-regionally recurrent STBS populations: (A) liposarcoma (pure well-differentiated liposarcoma is excluded); (B) osteogenic sarcoma; (C) Ewing/Ewing-like sarcoma; (D) fusion-positive alveolar rhabdomyosarcoma, embryonal rhabdomyosarcoma and fusion negative alveolar rhabdomyosarcoma; and (E) mesenchymal chondrosarcoma.

For cohorts A and B, we will conduct parallel randomized phase II studies. Patients will be randomized 1:1 between regorafenib and placebo, and followed for disease progression. For those patients with progression of disease on placebo, crossover to active drug will be offered to patients if they remain eligible for the clinical trial in all other respects.

Patients will be further stratified by number of prior lines of therapy (1 vs 2 or more), as well as WHO performance status (0-1 vs 2).

Since PFS with active therapy was very short in advanced Ewing/Ewing-like sarcoma using an IGF1R inhibitor, for example, a single cohort phase II clinical design will be used for cohort C to obtain initial clinical experience with this very aggressive sarcoma subtype.

For cohorts D & E, we will conduct single cohort phase II clinical designs to obtain initial clinical experience with these sarcoma subtypes in patients at least 5 years of age.

**Maximum Total Number of Subjects**

Cohort A: 48, seeking 42 events in 16 months
Cohort B: 48, seeking 42 events in 16 months
Cohort C: Single stage phase II design, n=30
Cohort D: Singe stage phase II design, n ~ 12*
Cohort E: Singe stage phase II design, n ~ 12*

*These two arms will enroll a total of 24 patients, given the study funding for 24 patients. The number of people studied in each group will vary according to the ability to accrue either diagnosis.

Number of enrolling centers: approximately 18

**Anticipated Length of Study** (patient enrollment period, overall length including follow-up)

We anticipate accrual of 4 subjects per month for Cohorts A and B and 0.5 subject per month for cohorts C, D and E.

**Study Drug(s), Dosing and Administration**

Regorafenib starting dose of 160 mg oral daily (4 tablets of 40 mg), 3 weeks on, 1 week off.

Patients under age 18 will start at 82 mg/$m^2$/dose oral daily as the initial dose (rounding to nearest 20 mg, and capped at the adult dose of 160 mg oral daily).

**Efficacy Evaluations**

Tumor reimaging and tumor measurements by CT and-or MRI every 8 weeks for 32 weeks, then every 12 weeks. Scans may be done ± 7 days of planned date.

**Specific Safety Evaluations/ Concerns**

Skin toxicity
Hypertension
Congestive heart failure
Proteinuria
Fatigue, malaise
Liver function test abnormalities
Dehydration, prerenal azotemia

**Brief Statistical Design**

Cohorts A and B: Randomized, double blinded, placebo-controlled, phase II design.

Cohorts C, D and E: Single stage, single arm, phase II design.

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## 1. OBJECTIVES

### 1.1 Primary Objective

**A. Cohort A (liposarcoma):** To compare the progression-free survival (PFS) of eligible subjects treated with regorafenib or placebo according to modified RECIST version 1.1.

**B. Cohort B (osteogenic sarcoma):** To compare the progression-free survival (PFS) of eligible subjects treated with regorafenib or placebo according to RECIST version 1.1.

**C. Cohort C (Ewing/Ewing-like sarcoma)**: To estimate the RECIST 1.1 PFS rate of eligible subjects treated with regorafenib at 8 and 16 weeks.

**D. Cohort D (Rhabdomyosarcoma: Fusion-positive alveolar, Embryonal, Fusion-negative alveolar):** To estimate the RECIST 1.1 PFS rate of eligible subjects treated with regorafenib at 8 and 16 weeks. To estimate the RECIST 1.1 response rate (PR or better) of eligible patients treated with regorafenib at 8 weeks.

**E. Cohort E (mesenchymal chondrosarcoma):** To estimate the RECIST 1.1 PFS rate of eligible subjects treated with regorafenib at 24 weeks. To estimate the RECIST 1.1 response rate (PR or better) of eligible patients treated with regorafenib at 24 weeks.

### 1.2. Secondary Objectives

A. All cohorts: Calculate the incidence of reported CTCAE v 4.03 adverse events and abnormal laboratory test results

B. All cohorts: Estimate the overall response rate (ORR) per RECIST version 1.1, time to tumor progression (TTP), PFS at 8 weeks and 16 weeks, overall survival (OS), disease–specific survival (DSS)

C. Cohorts A and B, after crossover: Assess PFS, RR, TTP, OS, and DSS following administration of regorafenib in the open label portion of the study.

### 1.3. Exploratory objectives

A. Assess PFS and RR in these populations by Choi criteria

B. Growth modulation index for treatment with regorafenib vs. prior line of therapy, defined as $TTP_{regorafenib}/TTP_{prior}$.

## 2. BACKGROUND

### 2.1 Soft tissue and bone sarcomas (STBS)

Soft Tissue and Bone Sarcoma (STBS) are malignant tumors of mesenchymal origin. Approximately 14,000 cases are diagnosed annually in the US, accounting for less than 1% of malignancies diagnosed[12]. Surgery, with or without adjuvant radiation therapy is the mainstay of treatment for early stage soft tissue sarcoma[13]; chemotherapy is routinely used in the adjuvant setting for osteosarcomas and Ewing/Ewing-like sarcomas of bone. Despite surgical excision, between 30-60% of patients develop recurrent and/or metastatic disease. Although preoperative chemotherapy may improve resectability of advanced STBS, the use of chemotherapy after resection of metastatic STBS has not been shown to improve overall survival[13].

Complete responses to chemotherapy for recurrent or metastatic sarcomas are rare and do not seem to translate into improved survival. Most tumors develop rapid drug resistance and patients develop progressive disease within months. The median survival time from diagnosis for patients with metastatic disease is 8 to 12 months. Thus, in most patients with advanced and/or metastatic sarcoma, palliation is the main objective of treatment. Given the toxicity and lack of efficacy of chemotherapy, typically doxorubicin, ifosfamide, dacarbazine and other agents such as gemcitabine (and combinations), patients with advanced and metastatic disease are appropriate candidates for investigational therapies.

Other than cytotoxic agents, there are few options for treatment for patients with metastatic and-or local-regionally recurrent osteogenic sarcoma, liposarcoma, and Ewing/Ewing-like sarcoma. Trabectedin (ET743, Yondelis®) has been approved in Europe and the U.S. for treatment of metastatic sarcomas on the basis of a randomized phase II study[14], as well as phase III trials data.

Mifamurtide (Mepact®) has also been approved in Europe, in this case for the adjuvant treatment of osteogenic sarcoma. Eribulin, with at least some activity in a phase II study in soft tissue sarcomas, is now approved by virtue of a phase III study vs dacarbazine in advanced liposarcoma and leiomyosarcoma.

Children with relapsed and refractory childhood rhabdomyosarcoma (RMS) have a poor prognosis when treated with chemotherapy[15, 16] . Patients with embryonal histology fair better than patients with alveolar histology. Fusion-negative alveolar histology has a similar prognosis to embryonal histology[17]. Adult patients with RMS have a much poorer prognosis when compared with children[18]. A recently completed randomized phase 2 clinical trial in patients with first relapse or refractory RMS conducted by the Children's Oncology Group selected the mTOR inhibitor for further investigation in newly diagnosed patients with intermediate risk RMS[19]. A randomized clinical trial of vincristine and irinotecan with or without temozolomide has been recently completed by the European Pediatric Sarcoma Study Group and results are pending.

## 2.2 Regorafenib

Regorafenib has potent preclinical antitumor activity and long-lasting anti-angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI)[20].

Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In *in vitro* biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl at concentrations of regorafenib that have been achieved clinically. In *in vivo* models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.

## 2.3 Preclinical data regarding regorafenib

*In vivo*, regorafenib exhibited anti-angiogenic and anti-proliferative effects in human colon and breast xenografts as demonstrated by a reduction in microvessel area, reduced Ki-67 staining, and reduced pERK1/2 staining in tissue sections from tumor xenografts, and dose-dependent inhibition of tumor growth in multiple xenograft models (breast, colon, renal, NSCLC, melanoma, pancreatic, thyroid, ovarian)[20]. Immunohistochemical *ex-vivo* studies with a phospho –specific monoclonal anti-ERK 1/2 antibody demonstrated inhibition of the MAPK pathway five days after treatment with regorafenib in 2 of 3 tumor models examined (MDA-MB-231 and BxPC-3), but not in NSCLC (H460).

In addition, all tested human tumor xenografts (MDA-MB-231, H460, BxPC-3 and Colo-205) demonstrated a significant reduction in new blood vessels by histomorphometry as detected in tumor samples using a murine CD31 antibody[20]. These data suggest that regorafenib can target the tumor cell MAPK pathway (i.e., tumor cell survival) and tumor vasculature in some but not all tumors.

### 2.3.1 Preclinical pediatric oncology data

*In vitro* effects on cell proliferation were determined in 33 pediatric solid tumor cell lines of the Innovative Therapies for Children with Cancer (ITCC) panel covering five malignancies[21]. Regorafenib inhibited cell proliferation with a mean half maximal growth inhibition of 12.5 µmol/L (range 0.7 µmol/L to 28 µmol/L). *In vivo*, regorafenib was evaluated alone at 10 or 30 mg/kg/d or in combination with radiation, irinotecan or the mitogen-activated protein kinase (MEK) inhibitor refametinib against various tumor types, including patient-derived brain tumor models with an amplified platelet-derived growth factor receptor A (PDGFRA) gene.

Regorafenib moderately inhibited the proliferation of the tested pediatric tumor cell line panel and was not indicative for the selection of a certain tumor indication. *In vivo*, regorafenib demonstrated significant tumor growth delay in all models tested across the various

indications, which is consistent with the observations from a broad and diverse panel of adult tumor models. No partial or complete remissions were observed as single agent, except for the IGRM57 medulloblastoma model, which is *PDGFRA* amplified; inhibition of the PDGFR signaling pathway in tumors with amplified *PDGFRA* may be involved in its therapeutic efficacy. Mechanistically the antitumor activity of regorafenib appears to be primarily mediated by its antiangiogenic mechanism, which is accompanied by a proapoptotic activity. Similar findings of tumor growth inhibition in culture and in a xenograft model using by regorafenib, sorafenib, and imatinib have been observed in testing of materials derived from a patient with mesenchymal chondrosarcoma (R. Sordella, Cold Spring Harbor Laboratory, unpublished observations).

## 2.4 Clinical experience with regorafenib

### 2.4.1 Colorectal cancer

Two phase III global randomized studies have evaluated the efficacy of regorafenib. The CORRECT (Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy) trial is an international, multicenter, randomized, double-blind, placebo-controlled study that enrolled 760 patients with mCRC whose disease has progressed after approved standard therapies[23]. Metastatic colorectal cancer patients were randomized to regorafenib plus best supportive care (BSC) or placebo plus BSC. Treatment cycles consisted of 160 mg of regorafenib (or matching placebo) once daily for 3 weeks on, 1 week off plus BSC. The primary endpoint of this trial was overall survival. Secondary endpoints included progression-free survival, objective tumor response rate and disease control rate. The safety and tolerability of the 2 treatment groups were also compared.

At a preplanned second interim analysis, there was a statistically significant survival benefit for regorafenib. The estimated hazard ratio for overall survival was 0.773 (95% confidence interval [CI], 0.635 to 0.941; 1-sided p = .0051). Patients treated with regorafenib had a median overall survival of 6.4 months, compared with 5.0 months for placebo — a 29% increase in survival. In addition to improved overall survival, progression-free survival was superior; median progression-free survival was 1.9 months (95% CI, 1.88 to 2.17) for regorafenib and 1.7 months (95% CI, 1.68 to 1.74) for placebo. The estimated hazard ratio for progression-free survival was 0.493 (95% CI, 0.42 to 0.58; 1-sided p<0.0001). There was a substantial difference in disease control rate in the regorafenib and placebo groups (44% vs. 15%; p<0.0001). Regorafenib demonstrated comparable efficacy benefits across patient subgroups analyzed including age, number of metastases, number of lines of prior therapy, and *KRAS* status.

The most frequent grade 3+ adverse events in the regorafenib group were hand–foot skin reaction (17%), fatigue (15%), diarrhea (8%), hyperbilirubinemia (8%), and hypertension (7%). The efficacy and safety from the CORRECT study supported FDA approval in September 2012.

### 2.4.2 GIST (gastrointestinal stromal tumor)

The efficacy and safety of regorafenib were examined in the Phase III GRID trial in patients with gastrointestinal stromal tumors (GISTs) who had exhausted all other treatment options. The study involved 199 patients with metastatic and/or unresectable GIST that had become resistant to imatinib and sunitinib[9]. Patients were randomized 2:1 to regorafenib (160 mg orally once daily on a 3 weeks on, 1 week off cycle) or placebo, plus best supportive care.

The results showed that treatment with regorafenib led to a statistically significant 3.9 month improvement in progression-free survival (PFS), compared with placebo (4.8 months vs. 0.9 months; hazard ratio [HR] = 0.27; p <0.0001). Overall survival was statistically similar between groups as expected due to a trial design that allowed crossover to regorafenib for disease progression (85% for placebo and 31% for regorafenib randomized patients). The median survival period without tumor growth among patients on regorafenib was 4.8 months while for the control group on placebo it was less than a month. The overall disease control rate combining partial responses with durable stable disease for at least 12 weeks was 53% with regorafenib compared with 9% in the control group. The most common grade ≥ 3 adverse events associated with regorafenib were hand-foot skin reaction (56.1%), hypertension (48.5%), and diarrhea (40.9%). The efficacy and safety of the GRID study data supported FDA approval February 2013.

### 2.4.3 Pediatric tumors: phase I clinical trial and RP2D determination

Regorafenib was evaluated as a single agent in a multicenter, open-label, non-randomized, phase I dose-escalating study designed to define the safety profile, MTD, RP2D, PK, pharmacodynamics, preliminary tumor response, and acceptability/palatability of the formulations (tablets and granulates) in pediatric subjects with solid malignant tumors which are recurrent or refractory to standard therapy. Data from this trial is described below (all information were taken from the study interim report, dated 19 August 2016).

A total of 55 pediatric subjects with advanced, histologically or cytological confirmed solid malignant tumors were enrolled at 4 different regorafenib dose levels. Forty-one subjects who received at least 1 dose of regorafenib were valid for the safety and PK analyses, 23 subjects were valid and included in the analysis of MTD, and 39 subjects were valid for the efficacy analysis. The median age of subjects was 13.0 years (range: 3 to 17 years of age).

Safety: Regorafenib was tolerable at doses up to 82 mg/m2 in pediatric patients, and safety was consistent with the known safety profile of regorafenib in the adult population. All 41 treated subjects had at least 1 TEAE.

The most frequent TEAEs (≥ 10% of 41 treated subjects) were: vomiting (51.2%), pyrexia (48.8%), headache (43.9%), AST increased, fatigue and nausea (41.5% each), ALT increased (39.0%), palmar-plantar erythrodysaesthesia syndrome (HFSR) and blood bilirubin increased (31.7% each). (MedDRA preferred terms). The most common TEAEs of Grade 3 or above (Grades 3/4/5), irrespective of relationship to study drug, occurring in more than 5% of all 41 treated subjects were death (12.2%), headache (9.8%), lymphopenia, neutropenia, thrombocytopenia, vomiting, ALT increased, hydrocephalus, dyspnoea, and rash maculo-papular (7.3% each).

In total, 40 of all 41 treated subjects (97.6%) reported at least 1 regorafenib related TEAE and the majority were Grade 2 (22 subjects, 53.7%). Drug-related TEAEs occurring in ≥ 20% subjects in the safety analysis set were AST increased (34.1%), nausea, fatigue, ALT increased, blood bilirubin increased, and palmar-plantar erythrodysaesthesia syndrome (HFSR) (31.7% each), pyrexia (29.3%), decreased appetite (26.8%), neutropenia, and thrombocytopenia (24.4% each).

Fifteen subjects (36.6%) experienced drug-related TEAEs of worst CTCAE severity Grade ≥ 3, with 11 subjects (26.8% of 41) and 4 subjects (9.8%) having drug-related TEAEs of worst Grades 3 and 4, respectively. Drug-related TEAEs of CTCAE Grade 5 did not occur. Common drug-related TEAEs of CTCAE Grade 3 or above (Grades 3/4), occurring in ≥ 5% of all 41 treated subjects (by MedDRA preferred term) were thrombocytopenia and rash maculo-papular (7.3% each).

Dose-limiting toxicities were thrombocytopenia at 60 mg/m2, rash maculopapular at 72 mg/m2, fever at 82 mg/m2, and hypertension and erythroderma at 93 mg/m2. An increased incidence of Grades 3/4 hematological events was observed across dose levels; it appeared that subjects with a history of myelosuppressive therapies such as high dose chemotherapy with stem cell rescue or craniospinal irradiation were at a higher risk for such events.

Overall, 27 out of 41 subjects (65.9%) had at least one dose modification, and the majority of dose modifications were due to AEs; 14 dose reductions (34.1%) were reported for the 41 subjects treated. No subject had more than one dose reduction. Three out of 6 subjects (50.0%), 10 out of 14 subjects (71.4%), 7 out of 14 subjects (50.0%), and 6 out of 7 subjects (85.7%) had AEs leading to dose interruptions in Dose Levels 1, 2, 3 and 4, respectively. The most commonly reported TEAEs (any grade) leading to interruption of study drug in at least 5% subjects of any dose level were pyrexia, platelet count decreased, and rash maculo-papular (7.3% of each). The median duration of regorafenib treatment interruptions or delays (excluding the protocol defined 7 days rest period) was 4 days (range: 1-17 days).

Pharmacokinetics: Regorafenib exposure at all dose levels (60, 72, 82 and 93 mg/m2) was comparable to that observed in adults; including high inter-subject variability. The observed geometric mean exposure for the 82 mg/m2 dose group of 50.1 and 47.8 (mg*h/L), based on nominal and actual dosing, is in the same range as that observed (48.4 mg*h/L) in adults at the dose level of 160 mg q.d.

Tumor response: No clear relationship between dose level and best tumor response could be observed. None of the treated subjects achieved a CR and only 1 subject (alveolar rhabdomyosarcoma) had a transient PR. Fifteen subjects had stable disease and 1 subject with "CNS anaplastic ependymoma" completed 30 cycles of regorafenib treatment.

Based on the overall safety profile and drug exposure across dose levels observed in this phase 1 study, 82 mg/m2 q.d. in a 3-weeks-on/1-week-off schedule is the selected RP2D to be studied in subsequent clinical trials of regorafenib when used as monotherapy in children and adolescents with solid tumors. The hematologic toxicity will continue to be followed closely

in the proposed expansion cohort phase of this study. For subsequent studies in combination with other anticancer agents, a dose finding and/or dose confirmation phase 1b study to determine the optimal dose of regorafenib when combined with chemotherapy is warranted.

**2.5 Rationale**

Inhibition of angiogenesis to slow or stop cancer growth is one mechanism under scrutiny as a therapeutic option for patients with metastatic cancers of all types. Some of the agents used to examine this issue in STBS are multitargeted Small Molecule Oral Kinase Inhibitors (SMOKIs). Imatinib, sunitinib, and regorafenib have all been approved for use in gastrointestinal stromal tumors (GISTs), which is perhaps the most common form of sarcoma.

After failure of standard cytotoxic chemotherapy, pazopanib was approved for use in patients with metastatic soft tissue sarcomas other than liposarcoma by virtue of a phase III clinical trial in patients with metastatic soft tissue sarcoma[1]. Conversely, there are no randomized data to date regarding the activity of SMOKIs in bone sarcomas specifically, and although there are no randomized data regarding the activity of pazopanib in liposarcomas, there appears to be activity of SMOKIs based on the phase II study of pazopanib in soft tissue sarcomas[2].

Sorafenib, another multitargeted small molecule oral kinase inhibitor (SMOKI), demonstrated activity in a multi-arm phase II study, in which liposarcoma was also excluded. In a phase II clinical trial of sorafenib in 35 patients with chemotherapy refractory osteogenic sarcoma, 3 patients had a partial response and 2 had a minor response, with 6 patients on treatment for more than 6 months without worsening[7]. Sunitinib shows minor activity in at least a subset of sarcomas in small phase II studies or as anecdotes[3,4]. We also note evidence of an anecdote of a patient with a Ewing sarcoma with a sustained RECIST partial response (S. Attia, MD, personal communication).

Although regorafenib was approved for use in patients who had progressive GIST despite imatinib and/or sunitinib, it has not been examined in a systematic fashion in patients with other forms of sarcoma.

Given the activity of sorafenib and pazopanib in soft tissue sarcomas, and evidence of activity of sorafenib in osteogenic sarcoma and possibly Ewing/Ewing-like sarcoma, there is precedent to examine SMOKIs such as regorafenib in sarcomas other than GIST. It is also recognized that SMOKIs such as regorafenib, sorafenib, pazopanib, and sunitinib have overlapping panels of kinases that are inhibited simultaneously. While not equivalent, most of these SMOKIs block vascular endothelial growth factor and platelet derived growth factors receptors (VEGFRs and PDGFRs), speaking to a common mechanism of action of several of these agents[10].

We propose parallel randomized phase II studies of regorafenib in patients with liposarcoma (excluding purely well differentiated liposarcoma) and osteogenic sarcoma to determine if there is significant activity of these agents, as has been observed with pazopanib in soft tissue sarcomas. In addition, we seek to determine the activity of regorafenib in Ewing/Ewing-like

sarcoma, given anecdotal data of activity, planning to examine a single cohort of patients in a prospective phase II fashion.

As of amendment 5, the Ewing sarcoma cohort (C) completed accrual. As of amendment 6, only the rhabdomyosarcoma cohort is open to accrual; the slow accrual to this arm of the study has led to opening another arm of the trial to obtain initial data with regorafenib in mesenchymal chondrosarcoma as a new cohort (E).

In addition, given the completion of a pediatric phase I study of regorafenib, it is now possible to safely dose patients under age 18 with regorafenib. This allows both for including younger patients on study and investigating diagnoses that are far more common in children than adults. Osteogenic sarcoma, rhabdomyosarcoma, and Ewing sarcoma and its relatives all occur in the pediatric population, and a substantial majority of embryonal and alveolar rhabdomyosarcoma patients fall into the pediatric age group. The limiting factor for treatment with regorafenib is weight, given available tablet sizes. A minimum weight and body surface area is specified in the entry criteria to help ensure patient safety.

Rhabdomyosarcoma has an incidence much greater in younger children, below the age of 10, compared to older children or adults. Patients with recurrence/metastatic rhabdomyosarcoma have a dismal prognosis and will die of disease, nearly universally within 24 months of diagnosis. Accordingly, one goal of this study is to ensure that the appropriate populations of patients can be treated with a novel therapeutic that may extend their survival. Since rhabdomyosarcoma is more common between the ages of 0-10 than in older children, it is reasonable to treat patients who can tolerate the therapy proposed in the protocol amendment, namely children ages 5 and older (as well as adults), to ensure that an appropriate population of patients with metastatic rhabdomyosarcoma are being treated. lastly, given the pediatric phase I data noted in the protocol, a dose and schedule of regorafenib have already been determined in pediatric patients, making the use of regorafenib more tenable for patients and families with this nearly uniformly fatal diagnosis.

### 2.6 Study Design

We seek to conduct parallel clinical trials of regorafenib in five different metastatic/local-regionally recurrent STBS populations: (A) liposarcoma (excluding purely well-differentiated liposarcoma); (B) osteogenic sarcoma; (C) Ewing/Ewing-like sarcoma; (D) rhabdomyosarcoma (only embryonal or alveolar subtypes); (E) mesenchymal chondrosarcoma.

For cohorts A and B, we will conduct parallel randomized phase II studies. Patients will be randomized 1:1 between regorafenib and placebo, and follow for disease progression. For those patients with progression of disease on placebo, crossover to active drug will be offered to patients if they remain eligible for the clinical trial in all other respects. If patients are deemed to have disease that is too rapidly progressive to be considered for a randomized clinical trial, they should be excluded from consideration.

Since there are even fewer data regarding the small round blue cell tumor family characterized rhabdomyosarcoma, the Ewing sarcoma family of tumors, and mesenchymal chondrosarcoma, which are often more aggressive than either liposarcoma subtypes or osteogenic sarcoma, single stage phase II clinical designs will be used to obtain initial clinical experience with these very aggressive sarcoma subtypes. Patients will be further stratified by number of prior lines of therapy (1 vs 2 or more), as well as WHO performance status (0-1 vs 2).

## 3. PATIENT SELECTION

### 3.1 Inclusion Criteria

3.1.1 Age ≥ 10 year for Liposarcoma, Osteosarcoma, Ewing sarcoma, and Mesenchymal chondrosarcoma
Age ≥ 5 years for Rhabdomyosarcoma cohorts

3.1.2 Weight ≥ 15 kg (33 lb)

3.1.3 Minimum BSA 0.65 $m^2$

3.1.4 Patients must have histologically or cytologically confirmed advanced/metastatic liposarcoma, osteogenic sarcoma, Ewing/Ewing-like sarcoma of soft tissue or bone, fusion-positive alveolar rhabdomyosarcoma, embryonal rhabdomyosarcoma/fusion-negative alveolar rhabdomyosarcoma, or mesenchymal chondrosarcoma. This study will accept the diagnosis made at the investigator's center.

Patients will be categorized into the following groups as follows:

**Cohort A: Liposarcoma (enrollment complete as of amendment 5)**

Specify one of the mutually exclusive categories:

(1) Dedifferentiated liposarcoma. Patients with solely well-differentiated liposarcoma (including atypical lipoma) are specifically excluded (see below)
(2) Myxoid and/or round cell
(3) Pleomorphic
(4) Liposarcoma of unknown subtype/cannot determine.

**Cohort B: Osteogenic sarcoma (enrollment complete as of amendment 5)**

Specify tissue of origin & subtype:

1. Bone
    a. Specify bone and laterality
    b. Specify location of primary sarcoma within bone

i. Central
ii. Surface
iii. Gnathic (maxilla, mandible)
iv. Multifocal
v. Unable to determine

c. Specify predominant histology of primary
i. Osteoblastic
ii. Chondroblastic
iii. Fibroblastic
iv. Telangiectatic
v. Small cell
vi. Other histology or not indicated

d. Specify other defining characteristics
i. e.g. giant cell rich, surface dedifferentiated, change in histology over time, etc.

2. Soft tissue (extraosseous osteosarcoma)
a. Specify defining characteristics per AJCC staging criteria– primary site, primary size, superficial or deep location, metastatic sites.

**Cohort C. Ewing/Ewing-like sarcoma (enrollment complete as of Amendment 5)**

1. Specify soft tissue or bone primary site
2. Specify type:
a. Ewing/Ewing-like sarcoma family of tumors (includes Ewing sarcoma, Primitive neuroectodermal tumor (PNET), Askin tumor of chest wall) with evidence of translocation (e.g. by FISH, PCR)
b. Ewing-like sarcoma with proof of novel translocation involving *CIC-DUX4* or *BCOR-CCNB3* or related genes
c. Histological diagnosis of Ewing sarcoma family of tumors, but no proof of translocation.

**Cohort D. Rhabdomyosarcoma**

1. Specify one of the mutually exclusive categories:
- Fusion-positive alveolar rhabdomyosarcoma
a. Indicate translocation, (e.g. *PAX3-FOXO1, PAX7-FOXO1*)
- Embryonal rhabdomyosarcoma
- Fusion-negative alveolar rhabdomyosarcoma

(Note: pleomorphic rhabdomyosarcoma and rhabdomyosarcoma, not otherwise specified (NOS) do not fall into these categories and are excluded)

2. Specify anatomic primary site

**Cohort E. Mesenchymal chondrosarcoma**

1. Specify anatomic primary site

3.1.5 WHO Performance Status 0, 1 or 2. To assess performance status for pediatric patients, Lansky (> 16 years) and Karnofsky (≥ 16 years)should be converted to WHO_ECOG in order to determine eligibility for patients under 18 years of age.

3.1.6 At least one prior line of systemic therapy for the sarcoma diagnosis (neoadjuvant, adjuvant or metastatic disease).

3.1.7 All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v 4.03 Grade 1 or less (except alopecia, grade 0-2 permitted, and anemia, grade 0-2 permitted) at the time of signing the Informed Consent Form (ICF).

3.1.8 Subject must be able to swallow and retain oral medication.

3.1.9 At least one site of measurable disease on x-ray/CT/MRI scan as defined by RECIST 1.1. Baseline imaging must be performed within 28 days of first study drug administration.

3.1.10 Adequate organ function within 14 days of registration, defined as:

| | |
|---|---|
| Absolute neutrophil count (ANC) | ≥ 1,500/μL (microliter)<br>≥1,000/μL (for patients < 18 yrs. old) |
| Platelets | ≥ 100,000/μL<br>≥75,000/μL (for patients < 18 yrs. old) |
| Total bilirubin | ≤ 1.5 mg/dL |
| INR* | ≤ 1.5 |
| AST(SGOT)/ALT(SGPT) | all ≤ 2.5 × ULN (up to 5 × ULN for patients with liver involvement by tumor) |
| Creatinine | ≤ 1.5 × ULN or GFR† > 30 ml/min |
| Serum albumin | ≥ 3 g/dL |
| Amylase | ≤1.5 x the ULN |
| Serum lipase | ≤ 1.5 × ULN |

*International normalized ratio (INR): Subjects who are prophylactically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists, according to the written documentation of the treating physician. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care.

†Glomerular filtration rate (GFR): according to the Modified Diet in Renal

Disease (MDRD) abbreviated formula[23], GFR (mL/min/1.73 $m^2$) = 175 × ($S_{Cr}$)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American).

Adequate hematological function assessed by the following laboratory requirements conducted within 7 days before starting study treatment:

| | |
|---|---|
| Peripheral ANC | ≥ 1.0 x $10^9$/L |
| Platelet count | ≥ 100 x $10^9$/L (≥75 x $10^9$/L for patients < 18 years of age at enrollment (transfusion independent) |
| Hemoglobin | ≥ 8.0 g/ dL |
| Lipase | ≤ 1.5 x ULN |
| AST/ALT | ≤ 3.0 x ULN |
| Bilirubin (sum of conjugated + unconjugated) | ≤ 1.5 ULN |

Adequate renal function defined as creatinine clearance based on Schwartz Estimate ≥ 70 ml/min/1.73 $m^2$

International normalized ratio (INR) ≤ 1.5 x upper limit of normal (ULN) and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN

Alkaline phosphatase limit ≤ 2.5 x ULN for age (≤ 5 x ULN for subjects with bone tumors or metastases to bone)

3.1.11 Written, voluntary informed consent.

3.1.12 Fertile men and women of childbearing potential must agree to use an effective method of birth control from Day 1 of study and for 3 months after last study drug administration in both sexes, as assessed by the investigator. Women of childbearing potential include pre-menopausal women and women within the first 2 years of the onset of menopause. Women of childbearing potential must have a negative pregnancy test ≤ seven days prior to Day 1 of study. The definition of adequate contraception will be based on the judgment of the investigator.

3.1.13 Evidence of progression of disease as defined by RECIST 1.1 (i.e. new disease sites or 20% growth of target lesions) within 6 months of registration.

3.1.14 Patients with central nervous system disease are eligible for enrollment if they have received prior radiotherapy or surgery to sites of CNS metastatic disease and are without evidence of clinical progression for at least 12 weeks after therapy.

**3.2 Exclusion Criteria**

3.2.1 Patients with documentation of well differentiated liposarcoma only (of the well

differentiated/dedifferentiated liposarcoma family) are specifically excluded, owing to its characteristically slow growth. If high grade areas are suspected (dedifferentiation), but not proved by pathology analysis (e.g. after primary resection of a well-differentiated liposarcoma), a biopsy must be performed to demonstrate the high-grade dedifferentiated disease. If there is a question regarding the diagnosis, the Cohort PI should be consulted.

3.2.2 Prior systemic therapy with a small molecule oral kinase inhibitor, including but not limited to: pazopanib, sunitinib, sorafenib, everolimus, sirolimus, vemurafenib, dasatinib and trametinib.

3.2.3 Previous assignment to treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study. Patients who progress on placebo are specifically allowed to enroll on the treatment arm of the study if they meet all other entry criteria.

3.2.4 Concurrent, clinically significant, active malignancies within 12 months of study enrollment.

3.2.5 Patients with severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol.

3.2.6 Major surgery within 28 days prior to study registration or those patients who have not recovered adequately from prior surgery.

3.2.7 Patients who have received wide field radiotherapy ≤ 28 days (defined as > 50% of volume of pelvis bones or equivalent) or limited field radiation for palliation < 14 days prior to study registration or those patients who have not recovered adequately from side effects of such therapy.

3.2.8 Patients who have received prior systemic therapy < 14 days prior to study registration or have not recovered adequately from toxicities to CTCAE v. 4.03 grade 1 or less (except alopecia); prior investigational therapy may not have been given < 5 half-lives of last dose of treatment, or < 14 days, whichever is greater.

3.2.9 Patients who have had prior autologous, or allogeneic bone marrow transplant.

3.2.10 Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v 4.03] on repeated measurement) despite optimal medical management. Uncontrolled hypertension for this study will be defined as greater than 95$^{th}$ percentile for age on two anti-hypertensives.

3.2.11 Active or clinically significant cardiac disease including:

1) Congestive heart failure–New York Heart Association (NYHA) > class II.
2) Active coronary artery disease.
3) Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
4) Unstable angina (anginal symptoms at rest), new onset angina within 3 months before randomization, or myocardial infarction within 6 months before randomization.

3.2.12 Evidence or history of bleeding diathesis. Patients on warfarin, heparinoids, or factor X inhibitors are permitted on study.

3.2.13 Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to study registration.

3.2.14 Subjects with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 6 months of start of study treatment.

3.2.15 Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.

3.2.16 Ongoing infection > Grade 2 NCI-CTCAE v 4.03.

3.2.17 Presence of a non-healing wound, non-healing ulcer, or benign bone fracture (patients with stress insufficiency fractures e.g. from osteoporosis or pathological fracture from tumor are eligible for study).

3.2.18 Patients with seizure disorder requiring medication.

3.2.19 Proteinuria > 100 mg/dl on urine analysis.

3.2.20 Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.

3.2.21 Pleural effusion or ascites that causes respiratory compromise (≥ NCI-CTCAE version 4.03 Grade 2 dyspnea).

3.2.22 History of organ allograft (including corneal transplant).

3.2.23 Known or suspected allergy or hypersensitivity to regorafenib, or excipients of the formulations given during the course of this trial.

3.2.24 Any malabsorption condition.

3.2.25 Women who are pregnant or breast-feeding.

3.2.26 Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.

3.2.27 Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.

3.2.28 Inability to comply with protocol required procedures, including swallowing tablets.

3.2.29 Use of any herbal remedy (e.g. St. John's wort [*Hypericum perforatum*]).

### 3.3 Inclusion of Women and Minorities

Men, women, children (at least age 5 years) and members of all ethnic and racial groups may be eligible for this trial.

## 4. REGISTRATION PROCEDURES

### 4.1 General Guidelines

Subjects enrolling on this clinical trial must meet all inclusion and exclusion criteria. Exceptions will not be granted.

Data will be entered via a web portal into a SARC study specific database. While all study evaluations must be performed by the Investigator as described in Section 9, Study Evaluations and Study Calendar, only data related to the primary and secondary endpoints, as well as safety data, will be captured in the eCRFs.

### 4.2 Registration Process

Prior to beginning patient registration, the site clinical research associate should review all the eligibility criteria with the site Principal Investigator as well as the follow-up requirements for the study to ensure that the patient to be enrolled meets all the eligibility requirements. A patient failing to meet all the eligibility requirements **should not** be registered for the study and should not be enrolled in the study database. Once the data has been entered into the study database for enrollment of the patient, a unique patient identification number will be assigned by the computer and will be used for the patient throughout trial participation.

SARC024 uses a web based electronic data capture system (EDC) for data submission. All sites must complete training prior to using the web based EDC system. Data managers and other authorized users will be provided with a unique user identification number and password to access the EDC system.

All eligible subjects must be registered prior to the start of treatment. All subject registrations and case report forms will be submitted electronically via the EDC system.

Any problems accessing the EDC system or questions regarding the registration process should be directed to the SARC Operations Office via phone (734-930-7600) or via email, at sarc024@sarctrials.org.

### 4.3 Treatment assignment

Eligible patients will be registered by the site personnel and randomized at time of registration by the SARC operations office. For patients on substudies requiring randomization, subjects will be randomly assigned to receive either regorafenib 160 mg once daily or placebo (1:1), 3 weeks on, 1 week off.

Patients, investigators who give the treatment, those assessing outcomes, and those who will perform outcome analyses are blinded as to the allocation. Treatment allocation will remain masked until the time of disease progression, at which time assignment will be unblinded, so that patients on placebo may be crossed over to active treatment.

### 4.4 Screen Failures and Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" and withdrawn from study participation. Situations in which a subject is defined as a "dropout" include: if the subject has already been registered, randomized, assigned to treatment/run-in/wash-out or administered at least one dose of study drug.

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see above) is regarded a "screening failure".

### 4.5 Replacement

No withdrawn subjects (i.e. dropouts) will be replaced.

## 5. TREATMENT PLAN

### 5.1 Agent Administration

**Cohorts A and B**: patients with liposarcoma or osteosarcoma will be randomized 1:1 to receive regorafenib or placebo. Crossover of the placebo group is permitted if patients still meet all entry criteria to continue on treatment. (Accrual completed as of amendment 5)

**Cohort C:** patients with Ewing sarcomas will all receive regorafenib from the start of the study. (Accrual completed as of amendment 5)

**Cohort D:** patients with rhabdomyosarcoma (fusion-positive alveolar, embryonal, and fusion-negative alveolar) will all receive regorafenib from the start of the study

**Cohort E:** patients with mesenchymal chondrosarcoma will all receive regorafenib from the start of the study

In all cases the length of one cycle of therapy is 28 days (3 weeks on, 1 week off). If a patient experiences toxicity and is not due to resume therapy until the 1 week of the cycle off treatment, the subsequent cycle of therapy may start after a minimum of 1 week off regorafenib.

Example 1: A patient experiences toxicity at the day 8 visit of a cycle and treatment is held until day 15. After resuming treatment from day 15 until day 22, the patient is off treatment from days 22-28, and starts again on day 29, which is day 1 of the new cycle of therapy.

Example 2: A patient experiences toxicity at day 17 and treatment is held through day 24, which is after the expected end of treatment that cycle on day 22. The patient may resume therapy with a new cycle of therapy as early as day 25, or may stay off therapy through day 28, resuming treatment cycle day 29/day 1 of the new cycle.

Conversely, imaging studies will be performed as outlined in the protocol and no changes in the scheduled scans are permitted. However, patients with clinical deterioration may have imaging studies earlier than scheduled, which may take the patient off study earlier than expected.

## 5.2 Regorafenib and placebo

For the randomized cohorts of the study, regorafenib and placebo tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 30 tablets and a 3 gram desiccant. The bottles will have a label affixed containing study identification, product identification, and quantity of tablets. Once the drug has been received it must be kept in a secure, dry location. Study drugs must be stored in their original bottles at a temperature of 20-25 °C (68-77 °F); provisional temperature limits permitted to 15-30 °C (59-86 °F).

The study drugs must be exclusively used for the investigation specified in this protocol and they will only be accessible to authorized staff.

## 5.3 Blinding and unblinding

### 5.3.1 Blinding

In compliance with applicable regulations, in the event of a SUSAR, the patient's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators if the SUSAR was related to the blinded treatment.

### 5.3.2 Emergency unblinding by the investigator, and unblinding at progression

Unblinding may occur in the randomized portion of the study for emergency purposes only. Patients who have disease worsening on study who were on placebo will be offered crossover to active treatment if they otherwise meet all entry criteria for the study.

The local pharmacist will be the data source regarding blinding of a specific patient. If unblinding is necessary for the treatment of a subject for a serious adverse event, every attempt should be made to contact the Cohort PI prior to unblinding. If this is not feasible, then the overall Principal Investigator must be contacted within 24 hours of unblinding.

If SARC does not receive a response from the Cohort PI or designee within 3 hours, SARC will notify the person that initiated the unblinding request and state that the treatment assignment will not be unblinded at that time and treatment of the patient should proceed as if the blinded drug is regorafenib.

## 5.4 Study drug administration

Regorafenib (or placebo) is administered as monotherapy during the study. For adults on the study, the starting dose is 160 mg daily for 3 weeks on, 1 week off, taken in the morning with a low-fat meal each day.

The medication should be taken within 8 hours of the same time each day, otherwise should be marked as a missed dose. One cycle is 28 days.

For adults, four 40 mg regorafenib or placebo tablets should be taken in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast. Some examples of low-fat breakfasts are:

- Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat).

- One cup of cereal, 8 ounces (240 mL) of skim milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories).

The medication will be taken in a similar fashion in pediatric patients (< 18 years). … Pediatric patients on trial will receive tablets according to the dosing table below (Table 5.4). The starting dose is 82 mg/m$^2$ daily with the same 3 week on, 1week off schedule as for adult patients. The regorafenib dose will be rounded to the nearest 20 mg and capped at 160 mg as with adult patients. The lowest permissible dose is 20 mg. The minimum body surface area to participate is 0.65m$^2$ and minimum weight is 15 Kg. (33 lbs.)

Table 5.4 – Pediatric Doses

| | BSA > 0.65$m^2$ |
|---|---|
| Dose level 0 (standard starting dose) | 82 mg/$m^2$ oral daily |

For dose modifications, for adult and pediatric patients, refer to tables in Section 6 of the protocol.

Patients, or their guardians, should be instructed to record daily regorafenib or placebo dose on the Study Drug diary which will be provided to them (Appendix C).

### 5.5 General Concomitant Medication and Supportive Care Guidelines

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. All medications taken within 2 weeks prior to the start of the study and during the study must be recorded in the subject's source documentation, including start/stop dates, dose frequency, route of administration, and indication. Specific caution should be taken when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6 and CYP2C9. Such concomitant medications should be avoided, if possible.

Co-administration of a strong CYP3A4 inducer (rifampin) with a single 160 mg dose of regorafenib decreased the mean exposure of regorafenib, increased the mean exposure of the active metabolite M-5, and resulted in no change in the mean exposure of the active metabolite M-2. Avoid concomitant use of regorafenib with strong CYP3A4. A listing of strong CYP3A4 inducers is provided in **Appendix D**.

Co-administration of a strong CYP3A4 inhibitor (ketoconazole) with a single 160 mg dose of regorafenib increased the mean exposure of regorafenib and decreased the mean exposure of the active metabolites M-2 and M-5. Avoid concomitant use of regorafenib with strong inhibitors of CYP3A4 activity. A listing of strong CYP3A4 inhibitors is provided in **Appendix D**.

Permitted concomitant therapy includes:

- Standard therapies for concurrent medical conditions
- Supportive care for any underlying illness
- Hematopoietic growth factors: subjects are permitted to take chronic erythropoietin. If a patient develops neutropenia, patients should have doses reduced, and not use growth factors such as filgrastim to artificially elevate the neutrophil count. Use of pegfilgrastim or related growth factors for an episode of febrile neutropenia is permitted
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the investigator
- Bisphosphonates

- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are stable, as determined by the investigator.

The following are **not** permitted while the patient is on study:

- Other investigational treatment during or within 14 days (or 5 half-lives, whichever is longer) before starting study treatment
- Radiation therapy: any need for radiation therapy will be defined as clinical (if not radiographic) worsening of disease, and represent a progression event
- Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, immunotherapy, and hormonal therapy
- Bone marrow transplant or stem cell rescue
- Subjects taking **narrow therapeutic index medications** should be monitored proactively (e.g. **warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin**). Warfarin is metabolized by the cytochrome enzyme CYP2C9 and warfarin levels may be especially affected by regorafenib
- Use of any herbal remedy (e.g. St. John's Wort [*Hypericum perforatum*]).

### 5.6 Duration of Therapy

Treatment may continue until one of the following criteria applies:

- Disease progression as defined by RECIST 1.1
- Greater than 28 days have elapsed since the last dose of study drug
- Patient decides to withdraw from the study during the treatment phase of the study
- Patient decides to withdraw from the study during the follow up phase after completion of treatment on the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

### 5.7 Duration of Follow Up

Subjects will be contacted by phone once between 30 and 45 days after termination of study treatment or until death, whichever occurs first. Patients removed from study for adverse event(s) will be followed until resolution or stabilization of the adverse event.

### 5.8 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.6 applies. The reason for study removal and the date the patient was removed must be documented in the eCRF including death or lost to follow up.

Subjects **must be withdrawn from the trial** (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result
- Pregnancy. Pregnancy will be reported as an SAE. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being
- Subject is lost to follow-up
- Death.

Subjects **may be** withdrawn from the study for the following reasons:

- The subject is non-compliant with study drug (regorafenib or placebo), trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol
- Severe allergic reaction to regorafenib (such as exfoliative erythroderma or Grade 3 or 4 hypersensitivity reaction)
- Development of a second cancer
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints
- Deterioration of WHO performance status to 4
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable. In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's medical records.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

### 6.1 Dose Reduction Levels

**In adults, the starting dose of regorafenib is 160 mg once daily for Cohorts C, D and E. The starting dose for Cohorts A and B is 4 tablets of regorafenib or placebo daily.**

**For pediatric patients (< 18 years of age), the starting dose is 82 mg/m$^2$ (rounding to nearest 20 mg), with a maximum daily dose capped at 160 mg. Please refer to dosing table in Section 5.2.**

Study medication will be administered on a 3-weeks on, 1-week off schedule (3 weeks out of every 4).

Doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to protocol therapy according to the guidelines shown in the Dose Delays/Dose Modifications table that follows. In general, this will mean clinically meaningful G 3 or worse toxicity, although clinically significant G 2 toxicity may qualify, according to the treating physician. Dose modifications will follow predefined dose levels. Dose adjustments for hematologic toxicity are based on the blood counts obtained in preparation for the day of treatment.

**Table 6.1.1 Dose reduction levels – adult patients**

| The modifications of regorafenib or placebo dosing will follow the following predefined dose levels: | | |
|---|---|---|
| Dose level **0** (standard starting dose) | **160 mg oral daily** | Four 40 mg tablets of regorafenib or placebo |
| Dose level **-1** | **120 mg oral daily** | Three 40 mg tablets of regorafenib or placebo |
| Dose level **-2** | **80 mg oral daily** | Two 40 mg tablets of regorafenib or placebo |

**Table 6.1.2 Dose reduction levels – pediatric patients**

| The modifications of regorafenib or placebo dosing will follow the following predefined dose levels: | |
|---|---|
| Dose level **0** (standard starting dose) | **82 mg/m$^2$ oral daily, rounding to nearest 20 mg** |
| Dose level **-1** | **72 mg/m$^2$ oral daily, rounding to nearest 20 mg** |
| Dose level **-2** | **60 mg/m$^2$ oral daily, rounding to nearest 20 mg** |

If a subject experiences more than 1 toxicity, dose reduction should be according to the toxicity with the highest grade.

In the case of 2 or more toxicities of the same grade, the investigator may dose reduce according to that deemed most causally related to study treatment.

### 6.2 Management of toxicity (other than hand-foot skin reaction, hypertension and LFT abnormalities)

The table below outlines dose adjustments for **most hematologic and non-hematologic toxicities related to regorafenib** except hand-foot skin reaction (HFSR) and hypertension and LFT abnormalities.

In addition to these recommended dose modifications, subjects who develop diarrhea (see

Section 6.6), mucositis, anorexia or other events predisposing to fluid loss or inadequate fluid intake should be carefully monitored and rehydrated as clinically necessary. This is in order to minimize the risk of postural hypotension and renal failure.

**Table 6.2 Recommended dose modification for most toxicities, except hand-foot skin reaction, hypertension and ALT/AST/bilirubin**

| NCI-CTCAE v 4.03[a] | Dose Interruption | Dose Modification [b] | Dose for Subsequent Cycles |
|---|---|---|---|
| **Grade (G) 0-2** | Treat on time | No change | No change |
| **G 3** | Delay until ≤ G 2[c] | Reduce by 1 dose level | If toxicity remains < G2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ G3) recurs, institute permanent dose reduction. |
| **G 4** | Delay until ≤ G 2[c] | At a minimum, reduce by 1 dose level.<br><br>**Strongly consider** permanent discontinuation for G4 events such as: gastrointestinal perforation/fistula, severe or life-threatening hemorrhage, reversible posterior leukencephalopathy syndrome, or wound dehiscence. | |

a. G: Grade; NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.03
b. Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and nonclinical and asymptomatic laboratory abnormalities.
c. If no recovery after a 4 week delay, treatment should be permanently discontinued unless subject is deriving clinical benefit and is discussed with the SARC Medical Officer.

### 6.3 Management of hand-foot skin reaction

**At first occurrence of HFSR, independent of grade, prompt institution of supportive measures such as topical emollients, low potency steroids, or urea-containing creams should be administered.**

Grading and dose alterations are noted in Tables 6.3 and 6.4 below.

Recommended prevention/management strategies for skin toxicities consistent with HFSR are summarized below:

**Control of calluses**

Before initiating treatment with regorafenib:

- Check condition of hands and feet
- Suggest a manicure/pedicure, when indicated
- Recommend pumice stone use for callus or 'rough spot' removal.

During regorafenib treatment:

- Avoid pressure points
- Avoid items that rub, pinch or create friction.

**Use of creams**

Non-urea based creams may be applied liberally

- Keratolytic creams (e.g. 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 (e.g. lidocaine 2%) are to be considered for pain control
- Topical corticosteroids like clobetasol 0.05% should be considered for subjects with G 2 or 3 HFSR. Avoid systemic steroids.

**Tender areas should be protected as follows:**

- Use socks/gloves to cover moisturizing creams
- Wear well-padded footwear
- Use insole cushions or inserts (e.g. silicon, gel)
- Foot soaks with tepid water and Epson salts.

**Table 6.3.1 Grading for Hand-Foot Skin Reaction**

| | **G 1** | **G 2** | **G 3** |
|---|---|---|---|
| NCI-CTCAE v 4.03 Palmar-plantar erythrodysesthesia syndrome(a) | Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain | Skin changes (e.g., peeling, blisters bleeding, edema, or hyperkeratosis) with pain | Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain |
| Further description / examples of skin | Numbness, dysesthesia / paresthesia tingling, | Painful erythema and swelling of the hands | Moist desquamation, ulceration, blistering, |

| | | | |
|---|---|---|---|
| changes | painless swelling, or erythema of the hands and/or feet | and/or feet | or severe pain of the hands and/or feet |
| Effect on activities | Does not disrupt normal activities | Limiting instrumental activities of daily life (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money) | Limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications) and not bedridden |
| (a) Palmar-plantar erythrodysesthesia syndrome is a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of hands or the soles of the feet.<br>G: grade | | | |

**Table 6.3.2 Recommended dose modification for hand-foot-skin reaction[a]**

| Grade of event (NCI-CTCAE v 4.03) | Occurrence | Suggested Dose Modification |
|---|---|---|
| Grade (G) 1 | Any | Maintain dose level and immediately institute supportive measures for symptomatic relief |
| G 2 | 1st occurrence | Consider decreasing dose by one dose level and immediately institute supportive measures. If no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to G 0-1 [b, c] |
| | No improvement within 7 days or 2nd occurrence | Interrupt therapy until toxicity resolves to G 0-1.[c] When resuming treatment, decrease dose by one dose level [b] |
| | 3rd occurrence | Interrupt therapy until toxicity resolves to G 0-1. [c] When resuming treatment, decrease dose by one dose level. [b, d] |
| | 4th occurrence | Discontinue therapy |
| G 3 | 1st occurrence | Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to G 0-1. [c] When resuming treatment, decrease dose by one dose level. [b, d] |
| | 2nd occurrence | Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to G 0-1. [c] When resuming treatment, decrease dose by one additional dose level [b, d] |
| | 3rd occurrence | Discontinue treatment permanently. |

a. More conservative management is allowed if judged medically appropriate by the investigator.
b. If toxicity returns to G 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the investigator if subject has completed one cycle at reduced dose without recurrence of event.
c. If there is no recovery after a 4 week delay, treatment with regorafenib or placebo will be discontinued permanently.
d. Subjects requiring > 2 dose reductions should go off protocol therapy.
e. The maximum daily dose is 160 mg

### 6.4 Hypertension

Hypertension is a recognized AE associated with regorafenib treatment. Subject will have their blood pressure measured at least weekly at the study site on weeks 1, 2, 3, 5, and 7. If additional blood pressure measurements are done outside the study site, and the blood pressure is > 140 mm Hg systolic or > 90 mm Hg diastolic (NCI CTCAE v 4.03), then the subject must contact study personnel. The management of hypertension, including the choice of antihypertensive medication, will be performed according to local standards and to the usual practice of the investigator. Every effort should be made to control blood pressure by medical means other than study drug dose modification. If necessary, **Table 6.5** below outlines suggested dose reductions.

**Table 6.4.1 Management of Treatment-Emergent Hypertension**

| Grade (CTCAE v 4.03) | Antihypertensive Therapy | Regorafenib or placebo Dosing |
|---|---|---|
| **G 1**<br>Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg) | None | • Continue regorafenib or placebo<br>• Consider increasing blood pressure (BP) monitoring |
| **G 2**<br>Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR<br>Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits | • Treat with the aim to achieve diastolic BP ≤ 90 mm Hg:<br>• If BP previously within normal limits, start anti-hypertensive monotherapy<br>• If patient already on anti-hypertensive medication, titrate up the dose. | • Continue regorafenib or placebo<br>• If symptomatic, hold regorafenib or placebo until symptoms resolve AND diastolic BP ≤ 90 mm Hg[a]. When regorafenib or placebo is restarted, continue at the same dose level. |
| **G 3**<br>Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg<br>OR<br>More than one drug or more intensive therapy than previously used indicated | Treat with the aim to achieve diastolic BP ≤ 90 mm Hg:<br>Start anti-hypertensive medication<br>**AND/OR**<br>Increase current anti-hypertensive medication<br>**AND/OR**<br>Add additional anti-hypertensive medications. | • Hold regorafenib or placebo until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve[a].<br>• When regorafenib or placebo is restarted, continue at the same dose level.<br>• If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level[b].<br>• If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level[c]. |
| **G 4**<br>Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis) | Per institutional guidelines | Discontinue therapy |

a. Patients requiring a delay of > 4 weeks should will discontinue regorafenib or placebo and stop participation in the study.
b. If BP remains controlled for at least one cycle, dose re-escalation is permitted per investigator's discretion.
c. Patients requiring > 2 dose reductions should go off protocol therapy.
G: Grade

**Table 6.4.2 Management of Treatment Emergent Hypertension for pediatric patients**

**Please refer to appendix:**

| Grade (CTCAE v 4.03) | Antihypertensive Therapy | Regorafenib or placebo Dosing |
|---|---|---|
| Grade 1 If age ≤ 17 years: Asymptomatic, transient (< 24 hrs) BP increase > ULN; intervention not indicated. If age > 17 | Consider increased BP monitoring; start anti-hypertensive medication if appropriate | No modification |

| | | |
|---|---|---|
| years: (SBP 120-139 mmHg or DBP 80-89 mmHg) | | |
| Grade 2 asymptomatic If age ≤ 17 years: Recurrent or persistent (≥ 24 hrs) BP > ULN; If age > 17 years: (SBP 140-159 mmHg or DBP 90-99 mmHg) | -If age ≤ 17 years: monotherapy indicated, -If age > 17 years: As in Table 6.5 | Continue Study drug |
| Grade 2 symptomatic OR Grade 3: (> 17 years: SBP > 160 mmHg or DBP > 100 mmHg) requiring more than one drug or more intensive therapy than previously (all ages) | • Start or adjust anti-hypertensive medication as in table 6.5 | • Hold study drug until symptoms resolve AND BP < 95th percentile ULN for age, height, and gender, if age ≤ 17 years; or BP < 160/90 mmHg if age > 17 years. Resume study at 100% (full) dose. If similar toxicity recurs, discontinue study drug. |
| Grade 4 (all ages) life threatening (eg, hypertensive crisis or malignant hypertension) | Per institutional guidelines | Discontinue study drug |

90th and 95th PERCENTILE BLOOD PRESSURE BY PERCENTILE HEIGHT IN GIRLS AGE 1-17 YEARS

| Age (Year) | BP Percentile | Systolic BP (mmHg) Percentile of Height | | | | | | | Diastolic BP (mmHg) Percentile of Height | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ↓ | | **5th** | **10th** | **25th** | **50th** | **75th** | **90th** | **95th** | **5th** | **10th** | **25th** | **50th** | **75th** | **90th** | **95th** |
| 1 | 90th | 97 | 97 | 98 | 100 | 101 | 102 | 103 | 52 | 53 | 53 | 54 | 55 | 55 | 56 |
| | 95th | 100 | 101 | 102 | 104 | 105 | 106 | 107 | 56 | 57 | 57 | 58 | 59 | 59 | 60 |
| 2 | 90th | 98 | 99 | 100 | 101 | 103 | 104 | 105 | 57 | 58 | 58 | 59 | 60 | 61 | 61 |
| | 95th | 102 | 103 | 104 | 105 | 107 | 108 | 109 | 61 | 62 | 62 | 63 | 64 | 65 | 65 |
| 3 | 90th | 100 | 100 | 102 | 103 | 104 | 106 | 106 | 61 | 62 | 62 | 63 | 64 | 64 | 65 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 95th | 104 | 104 | 105 | 107 | 108 | 109 | 110 | 65 | 66 | 66 | 67 | 68 | 68 | 69 |
| 4 | 90th | 101 | 102 | 103 | 104 | 106 | 107 | 108 | 64 | 64 | 65 | 66 | 67 | 67 | 68 |
| | 95th | 105 | 106 | 107 | 108 | 110 | 111 | 112 | 68 | 68 | 69 | 70 | 71 | 71 | 72 |
| 5 | 90th | 103 | 103 | 105 | 106 | 107 | 109 | 109 | 66 | 67 | 67 | 68 | 69 | 69 | 70 |
| | 95th | 107 | 107 | 108 | 110 | 111 | 112 | 113 | 70 | 71 | 71 | 72 | 73 | 73 | 74 |
| 6 | 90th | 104 | 105 | 106 | 108 | 109 | 110 | 111 | 68 | 68 | 69 | 70 | 70 | 71 | 72 |
| | 95th | 108 | 109 | 110 | 111 | 113 | 114 | 115 | 72 | 72 | 73 | 74 | 74 | 75 | 76 |
| 7 | 90th | 106 | 107 | 108 | 109 | 111 | 112 | 113 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| | 95th | 110 | 111 | 112 | 113 | 115 | 116 | 116 | 73 | 74 | 74 | 75 | 76 | 76 | 77 |
| 8 | 90th | 108 | 109 | 110 | 111 | 113 | 114 | 114 | 71 | 71 | 71 | 72 | 73 | 74 | 74 |
| | 95th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| 9 | 90th | 110 | 110 | 112 | 113 | 114 | 116 | 116 | 72 | 72 | 72 | 73 | 74 | 75 | 75 |
| | 95th | 114 | 114 | 115 | 117 | 118 | 119 | 120 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| 10 | 90th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 73 | 73 | 73 | 74 | 75 | 76 | 76 |
| | 95th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| 11 | 90th | 114 | 114 | 116 | 117 | 118 | 119 | 120 | 74 | 74 | 74 | 75 | 76 | 77 | 77 |
| | 95th | 118 | 118 | 119 | 121 | 122 | 123 | 124 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| 12 | 90th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 119 | 120 | 121 | 123 | 124 | 125 | 126 | 79 | 79 | 79 | 80 | 81 | 82 | 82 |
| 13 | 90th | 117 | 118 | 119 | 121 | 122 | 123 | 124 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 80 | 80 | 80 | 81 | 82 | 83 | 83 |
| 14 | 90th | 119 | 120 | 121 | 122 | 124 | 125 | 125 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| | 95th | 123 | 123 | 125 | 126 | 127 | 129 | 129 | 81 | 81 | 81 | 82 | 83 | 84 | 84 |
| 15 | 90th | 120 | 121 | 122 | 123 | 125 | 126 | 127 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| | 95th | 124 | 125 | 126 | 127 | 129 | 130 | 131 | 82 | 82 | 82 | 83 | 84 | 85 | 85 |
| 16 | 90th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 78 | 78 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 128 | 130 | 131 | 132 | 82 | 82 | 83 | 84 | 85 | 85 | 86 |
| 17 | 90th | 122 | 122 | 123 | 125 | 126 | 127 | 128 | 78 | 79 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 129 | 130 | 131 | 132 | 82 | 83 | 83 | 84 | 85 | 85 | 86 |

Source: Adapted from: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents; NIH Publication No. 05-5267.

## 90th and 95th PERCENTILE BLOOD PRESSURE BY PERCENTILE HEIGHT IN BOYS AGE 1-17 YEARS

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) Percentile of Height | | | | | | | Diastolic BP (mmHg) Percentile of Height | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 90th | 94 | 95 | 97 | 99 | 100 | 102 | 103 | 49 | 50 | 51 | 52 | 53 | 53 | 54 |
| | 95th | 98 | 99 | 101 | 103 | 104 | 106 | 106 | 54 | 54 | 55 | 56 | 57 | 58 | 58 |
| 2 | 90th | 97 | 99 | 100 | 102 | 104 | 105 | 106 | 54 | 55 | 56 | 57 | 58 | 58 | 59 |
| | 95th | 101 | 102 | 104 | 106 | 108 | 109 | 110 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| 3 | 90th | 100 | 101 | 103 | 105 | 107 | 108 | 109 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 95th | 104 | 105 | 107 | 109 | 110 | 112 | 113 | 63 | 63 | 64 | 65 | 66 | 67 | 67 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 90th | 102 | 103 | 105 | 107 | 109 | 110 | 111 | 62 | 63 | 64 | 65 | 66 | 66 | 67 |
| | 95th | 106 | 107 | 109 | 111 | 112 | 114 | 115 | 66 | 67 | 68 | 69 | 70 | 71 | 71 |
| 5 | 90th | 104 | 105 | 106 | 108 | 110 | 111 | 112 | 65 | 66 | 67 | 68 | 69 | 69 | 70 |
| | 95th | 108 | 109 | 110 | 112 | 114 | 115 | 116 | 69 | 70 | 71 | 72 | 73 | 74 | 74 |
| 6 | 90th | 105 | 106 | 108 | 110 | 111 | 113 | 113 | 68 | 68 | 69 | 70 | 71 | 72 | 72 |
| | 95th | 109 | 110 | 112 | 114 | 115 | 117 | 117 | 72 | 72 | 73 | 74 | 75 | 76 | 76 |
| 7 | 90th | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 70 | 70 | 71 | 72 | 73 | 74 | 74 |
| | 95th | 110 | 111 | 113 | 115 | 117 | 118 | 119 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| 8 | 90th | 107 | 109 | 110 | 112 | 114 | 115 | 116 | 71 | 72 | 72 | 73 | 74 | 75 | 76 |
| | 95th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| 9 | 90th | 109 | 110 | 112 | 114 | 115 | 117 | 118 | 72 | 73 | 74 | 75 | 76 | 76 | 77 |
| | 95th | 113 | 114 | 116 | 118 | 119 | 121 | 121 | 76 | 77 | 78 | 79 | 80 | 81 | 81 |
| 10 | 90th | 111 | 112 | 114 | 115 | 117 | 119 | 119 | 73 | 73 | 74 | 75 | 76 | 77 | 78 |
| | 95th | 115 | 116 | 117 | 119 | 121 | 122 | 123 | 77 | 78 | 79 | 80 | 81 | 81 | 82 |
| 11 | 90th | 113 | 114 | 115 | 117 | 119 | 120 | 121 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 117 | 118 | 119 | 121 | 123 | 124 | 125 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| 12 | 90th | 115 | 116 | 118 | 120 | 121 | 123 | 123 | 74 | 75 | 75 | 76 | 77 | 78 | 79 |
| | 95th | 119 | 120 | 122 | 123 | 125 | 127 | 127 | 78 | 79 | 80 | 81 | 82 | 82 | 83 |
| 13 | 90th | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 75 | 75 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 124 | 126 | 128 | 129 | 130 | 79 | 79 | 80 | 81 | 82 | 83 | 83 |
| 14 | 90th | 120 | 121 | 123 | 125 | 126 | 128 | 128 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| | 95th | 124 | 125 | 127 | 128 | 130 | 132 | 132 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| 15 | 90th | 122 | 124 | 125 | 127 | 129 | 130 | 131 | 76 | 77 | 78 | 79 | 80 | 80 | 81 |
| | 95th | 126 | 127 | 129 | 131 | 133 | 134 | 135 | 81 | 81 | 82 | 83 | 84 | 85 | 85 |
| 16 | 90th | 125 | 126 | 128 | 130 | 131 | 133 | 134 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 95th | 129 | 130 | 132 | 134 | 135 | 137 | 137 | 82 | 83 | 83 | 84 | 85 | 86 | 87 |
| 17 | 90th | 127 | 128 | 130 | 132 | 134 | 135 | 136 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| | 95th | 131 | 132 | 134 | 136 | 138 | 139 | 140 | 84 | 85 | 86 | 87 | 87 | 88 | 89 |

Source: Adapted from: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents; NIH Publication No. 05-5267.

### 6.5 Liver Function Abnormalities

For patients with observed worsening of serum liver tests considered related to regorafenib (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring advice in Table 6.6 should be followed.

Regorafenib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert syndrome. Note in Table 6.6 that hyperbilirubinemia itself is not a reason for dose reduction. Patients with Gilbert syndrome who develop elevated transaminases should be managed as per the recommendations outlined for ALT/AST elevations.

**Table 6.5.1 Recommended measures and dose modification in case of drug-related liver function test abnormalities**

| Observed elevations of ALT and/or AST | Occurrence | Recommended measures and dose modification |
|---|---|---|
| ≤ 5 times upper limit of normal ULN **(maximum Grade 2)** | Any occurrence | Continue regorafenib or placebo treatment.<br><br>Monitor liver function weekly until transaminases return to < 3 times ULN (Grade 1) or baseline. |
| >5 times ULN to ≤ 20 times ULN **(Grade 3)** | 1st occurrence | Interrupt regorafenib or placebo treatment.<br><br>Monitor transaminases weekly until return to < 3 times ULN or baseline.<br><br>Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-initiate regorafenib or placebo treatment, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks. |
| | Re-occurrence | Discontinue treatment with regorafenib or placebo permanently. |
| > 20 times ULN **(Grade 4)** | Any occurrence | Discontinue treatment with regorafenib or placebo permanently. |
| > 3 times ULN **(Grade 2 or higher)** with concurrent **hyperbilirubinemia > 2 times ULN** | | Discontinue treatment with regorafenib or placebo permanently.<br><br>Monitor liver function weekly until resolution to < 3 times ULN or return to baseline.<br><br>Exception: patients with Gilbert syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective elevation of ALT and/or AST. |

### 6.6 Prevention/management strategies for diarrhea

Diarrhea can be a common side effect of regorafenib. The preventive/management strategies for diarrhea should be consistent with local standards (e.g., anti-diarrheals and optimized hydration status).

Anti-diarrheal medications may be introduced if symptoms occur. Previous trials have shown that the diarrhea could be managed with **loperamide**. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours.

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting. For routine reporting it is expected that all adverse events grade 3 or greater are recorded.

## 7.1 Adverse Event and Laboratory Abnormalities

### 7.1.1 Clinical AEs

#### 7.1.1.1 Definition of Adverse Events

Per the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during a study are to be reported as AEs.

#### 7.1.1.2 CTCAE term (AE description)

The descriptions found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

#### 7.1.1.3 Intensity

**Intensity** of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events v 4.03 (CTCAE) on a five-point scale (grades 1 to 5) and all grade 3 and above will be reported in detail on the eCRF. Adverse events not listed on the CTCAE should be graded as follows:

**Table 7.1 CTC AE version 4.03 adverse event grading**

| CTC Grade | Equivalent To: | Definition |
|---|---|---|
| Grade 1 | Mild | Discomfort noticed but no disruption of normal daily activity |
| Grade 2 | Moderate | Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient |
| Grade 3 | Severe | Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk. |
| Grade 4 | Life threatening/ disabling | An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival. |
| Grade 5 | Death | AE resulting in death |

#### 7.1.1.4 Drug-Adverse Event relationship

The causality relationship of study drug to the adverse event will be assessed by the investigator as either:
**Yes or No**

If there is a reasonable suspected causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**. In other studies, the terms that qualify for a "Yes" assignation include "Definite", "Probable", or "Possible".

The following criteria should be considered in order to assess the relationship as **Yes:**

- Reasonable temporal association with drug administration
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- Reappears on rechallenge.

The following criteria should be considered in order to assess the relationship as **No;** in other studies, the terms that qualify for a "No" assignation include "Unlikely", or "Unrelated":

- It does not follow a reasonable temporal sequence from administration of the drug
- It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject
- It does not follow a known pattern of response to the suspected drug
- It does not reappear or worsen when the drug is re-administered.

#### 7.1.1.5 Definition of Serious Adverse Events

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any Adverse Event that at any dose fulfils at least one of the following criteria:

- Is fatal; (results in death; NOTE: death is an outcome, not an event)
- Is Life-Threatening (NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

#### 7.1.1.6 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST 1.1. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on

symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

### 7.1.2 Treatment and Follow-up AEs

After the discontinuation of therapy with regorafenib continue to follow up AEs as follows:

**Related AEs:** Follow until one of the following occurs:
- Resolved or improved to baseline
- Relationship is reassessed as unrelated
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure
- Death.

**Unrelated severe or life threatening AEs:** Follow until one of the following occurs:
- Resolved or improved to baseline
- Severity improved to grade 2
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure
- Death.

The final outcome of each adverse event must be recorded on the CRF.

**Unrelated Grade 1 or Grade 2 AEs:** Follow as clinically indicated

### 7.1.3 Laboratory Test Abnormalities

Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such.

Any treatment-emergent abnormal laboratory result that is clinically significant, i.e., meeting one or more of the following conditions, should be recorded on the adverse event eCRF:
- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication,

therapy or treatment).

### 7.1.4 Follow-up of Abnormal Laboratory Test

In the event of medically significant unexplained abnormal laboratory test values, the test should be repeated and followed until it has returned to the normal range, baseline value and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded in the eCRF.

## 7.2 Handling of Safety Parameters

### 7.2.1 Reporting of Adverse Events

**All adverse events (related and unrelated) Grade 3 or worse** occurring during the study and up to 30 days after the last dose of study medication must be reported. Reporting the specific time of onset of a given AE is only necessary when it occurs in relation to study drug administration.

### 7.2.2 Reporting of Serious Adverse Events (immediately reportable)

Any clinical adverse event or abnormal laboratory test value that is *serious* and which occurs during the course of the study (as defined in section 7.1 above), regardless of the treatment arm, must be reported to SARC **within *24 hours*** of the Principal Investigator becoming aware of the event (expedited reporting). SARC will then forward MedWatch data form(s) to the overall study PI and Cohort Principal Investigators and the supporter upon receipt. If only limited information is initially available, follow-up reports are required. The original SAE Form must be kept on file at the study site.

SAEs must be reported on the MedWatch Form 3500A along with the completed Fax Coversheet and faxed or sent electronically to SARC as listed. (See **Appendix B**).

Related Serious Adverse Events ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated Serious Adverse Events must be collected and reported during the study and for up to 30 days after the last dose of study medication.

### 7.2.3 Pregnancy

Females must be instructed to stop taking the study medication and immediately inform the investigator if pregnancy occurs during the study. Pregnancies occurring up to 3 months after the completion of the study medication must also

be reported to the investigator. The investigator should report all pregnancies within 24 hours to the sponsor.

The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Pregnancy occurring in the partner of a male patient participating in the study should also be reported to the investigator and the sponsor. The partner should be counseled and followed as described above.

## 8. PHARMACEUTICAL INFORMATION

### 8.1 Regorafenib: description of mechanism of action

Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment.

### 8.2 Administration of Study Drugs

Regorafenib or placebo will be administered as monotherapy during the study. The starting dose of regorafenib on study is 160 mg daily for 3 weeks on, 1 week off. The pediatric starting dose is 82 mg/m$^2$, rounding to the nearest 20 mg, and capping at 160 mg as with adult patients. One cycle is 28 days. Dose reduction levels are noted elsewhere in this protocol document (see Section 6.1.2).

Four 40 mg regorafenib or four placebo tablets should be taken in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast. Some examples of low fat breakfasts are:

- Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat)

- One cup of cereal, 8 ounces (240 mL) of skim milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories).

### 8.3 Formulation, Packaging and Labelling of Study Drugs

Tablets:

Regorafenib 40 mg tablets contains regorafenib and the inactive excipients microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, colloidal anhydrous silica, polyvinyl alcohol-part hydrolyzed, talk, titanium dioxide E171 (color index 77891), Macrogol/PEG 33350, lecithin (soy), iron oxide yellow – E172 (color index 77491), iron

oxide red – E172.

Where applicable, placebo control tablets without regorafenib will be provided by Bayer.

Regorafenib or placebo tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 30 tablets and a 3 gram desiccant. The bottles will have a label affixed containing study identification, product identification, and quantity of tablets. Once the drug has been received it must be kept in a secure, dry location. Study drugs must be stored in their original bottles at a temperature of 20-25 °C (68-77 °F); provisional temperature limits permitted to 15-30 °C (59-86 °F). The study drugs must be exclusively used for the investigation specified in this protocol and they will only be accessible to authorized staff.

### 8.4 Agent Ordering

Regorafenib and placebo tablets for this trial will be provided by Bayer, and distributed by a third party pharmaceutical distribution firm to the individual sites. Details will be provided in the Operations Manual.

### 8.5 Agent Accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and the instructions given by the clinical supplies department of the Institution and will be inaccessible to unauthorized personnel.

Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records.

Accurate records must be kept for each study drug provided by the sponsor. The drug dispensing log must be kept current and contain the following information:

- Documentation of drug shipments received from the sponsor (date received and quantity)
- Disposition of unused study drug not dispensed to patient
- The identification of the patient to whom the study medication was dispensed
- The date(s) and quantity of the study medication dispensed to the patient.

All supplies, including partially used or empty containers must be returned to the treating institution at the end of the study, and destroyed as required by local or institutional regulations (Section 8.7). Copies of the dispensing & inventory logs must be sent to SARC (use the address in Section 8.7).

Patients will also keep a Study Drug diary to indicate their compliance with therapy and adverse events they experience. These diaries will be reviewed and collected at each patient visit.

### 8.6 Destruction of study drugs

All unused and expired supplies of regorafenib and placebo should be destroyed according to institutional policies. A completed "Unused Study Drug Disposition Form Destruction Confirmation" should be sent to SARC by email to:

eantalis@sarctrials.org or SARC024@sarctrials.org

OR **faxed** to: **734-930-7557**.

## 9. STUDY EVALUATIONS AND STUDY CALENDAR

### 9.1 Screening Studies

The patient must sign the informed consent form before proceeding with screening.

The following procedures will be performed during the screening period (within 14 days of protocol registration):

- History/demographics
- Physical exam
- Vital signs, to include height, weight, WHO performance status
- Concomitant medications, including herbal and other homeopathic remedies
- Hematology: complete blood count, platelet count, differential, PT (INR), PTT
- Serum Chemistry: electrolytes, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, serum albumin, total protein, calcium, magnesium, phosphorus, lipase, amylase
- Urinalysis
- Serum or urine pregnancy test (for women of childbearing potential)
- Baseline radiologic imaging
- The same modalities should be used throughout the study as this baseline, unless allergies or other adverse events intervene)
- Images must be obtained within 28 days of the 1$^{st}$ day of therapy on study
- Baseline tumor measurements from physical exam
- ECG.

The screening period will be up to 14 days prior to study registration. Laboratory baseline evaluations are to be conducted within 14 days prior to study registration. Radiologic imaging must be done within 28 days of the first day of study treatment. For patients for whom there are 14 days or fewer between registration and the start of treatment, the day 1 laboratory data may be omitted.

Study treatment (day 1) should begin no later than 21 days (and within 28 days of baseline images) after patient enrollment into the study.

### 9.2 On Study Evaluation

The following procedures will be performed during the treatment period. Please note that visits may occur ± 2 days of the scheduled date, ± 3 days for weeks of bank holidays. Tumor measurements and reimaging may be done ± 7 days of the anticipated date. Tumor imaging may be performed at other times as clinically indicated. These will be considered non-protocol standard of care scans.

**Cycle 1, Week 1 day 1**

- Demographics, interval history
- Concurrent medications
- Physical Exam
- Vitals signs
- Weight
- WHO performance status
- Hematology: complete blood count, platelet count, differential
- Serum Chemistry: electrolytes, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, serum albumin, total protein, calcium, magnesium, phosphorus, lipase, amylase
- For patients for whom there are 14 days or fewer between registration and the start of treatment, the day 1 blood chemistries and hematology may be omitted
- Adverse event evaluation
- Dispense study drug
- Distribute study drug diary, if not already done.

**Cycle 1 Week 1, between days 4-6**

A phone call will be made to the patient during this period to review adverse events.

**Cycle 1 Week 2, day 1**

- Demographics, interval history
- Concurrent medications
- Physical Exam
- Vitals signs
- Weight
- WHO performance status
- Hematology: complete blood count, platelet count, differential
- Serum Chemistry: electrolytes, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, serum albumin, total protein, calcium, magnesium, phosphorus, lipase, amylase
- Adverse event evaluation.

**Cycle 1 Week 3, day 1**

- Demographics, interval history
- Concurrent medications
- Physical Exam
- Vitals signs
- Weight
- WHO performance status
- Hematology: complete blood count, platelet count, differential
- Serum Chemistry: electrolytes, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, serum albumin, total protein, calcium, magnesium, phosphorus, lipase, amylase
- Adverse event evaluation.

**Cycle 1 Week 4**

Off week from treatment.

- The same modalities should be used throughout the study as baseline, unless allergies or other adverse events intervene.

**Cycle 2 Week 1, day 1 (Week 5 overall)**

- Demographics, interval history
- Concurrent medications
- Physical Exam
- Vitals signs
- Weight
- WHO performance status
- Hematology: complete blood count, platelet count, differential
- Serum Chemistry: electrolytes, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, serum albumin, total protein, calcium, magnesium, phosphorus, lipase, amylase
- Adverse event evaluation
- Dispense study drug
- Distribute study drug diary
- Collect study drug diary for previous cycle.

**Cycle 2 Week 3, day 1 (Week 7 overall)**

- Demographics, interval history
- Concurrent medications
- Physical Exam
- Vitals signs
- Weight

- WHO performance status
- Hematology: complete blood count, platelet count, differential
- Serum Chemistry: electrolytes, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, serum albumin, total protein, calcium, magnesium, phosphorus, lipase, amylase
- Adverse event evaluation.

**Week 8**

Off week from treatment.
Imaging studies for comparison to baseline to be conducted this week.

- The same modalities should be used throughout the study as baseline, unless allergies or other adverse events intervene).

**Cycle 3 Week 1, day 1 (Week 9 overall) and later**

Treatment continues 3 weeks on, 1 week off.
Visits every 2 weeks until end of cycle 4, then every 4 weeks.

- Tumor measurements and imaging every 8 weeks for 32 weeks, then every 12 weeks. Scans may be done ± 7 days of expected date.

**At each visit:**

- Demographics, interval history
- Concurrent medications
- Physical Exam
- Vitals signs
- Weight
- WHO performance status
- Hematology: complete blood count, platelet count, differential
- Serum Chemistry: electrolytes, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, serum albumin, total protein, calcium, magnesium, phosphorus, lipase, amylase
- Adverse event evaluation
- Dispense study drug
- Distribute study drug diary
- Collect study drug diary for previous cycle.

## 9.3 Off Study Evaluations

**Off study**

- Demographics, interval history

- Concurrent medications
- Physical Exam
- Vitals signs
- Weight
- WHO performance status
- Hematology: complete blood count, platelet count, differential, if not done as part of end of cycle evaluation
- Serum Chemistry: electrolytes, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, serum albumin, total protein, calcium, magnesium, phosphorus, lipase, amylase, if not done as part of end of cycle evaluation
- Serum or urine chemistry pregnancy test (for women of childbearing potential)
- Tumor measurements and imaging, if not done as part of end of cycle evaluation
- Adverse event evaluation
- Collect study drug diary.

**Follow up phone call 30-45 days after off study visit date**

- Interval history
- Concurrent medications.

NOTE: Patients removed from study for adverse event(s) will be followed until resolution or stabilization of the adverse event.

To reiterate: Visits may occur ± 2 days of the scheduled date, ± 3 days for weeks of bank holidays. Tumor measurements and reimaging may be done ± 7 days of the anticipated date.

## 9.4 STUDY CALENDAR

| | Pre study | Wk 1, d1 | Wk 1, d 4-6 | Wk 2, d1 | Wk 3, d1 | Wk 4 | Wk 1, d1 | Wk 2, | Wk 3, d1 | Wk 4 | Wk 1 d1 | Off study | 30-45d F/U |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **CYCLE** | **--** | **Cycle 1 (2)** | | | | | **Cycles 2-4 (3)** | | | | **5+ (4)** | **--** | **--** |
| **Regorafenib or placebo (1)** | | X | X | X | X | | X | X | X | | X | | |
| Informed Consent | X | | | | | | | | | | | | |
| Demographics, interval history, concurrent medications, adverse event evaluation | X | X | | X | X | | X | | X | | X | X | X |
| Phone contact | | | X | | | | | | | | | | X |
| Physical exam | X | X | | X | X | | X | | X | | X | X | |
| Vital signs, weight, WHO performance status | X | X | | X | X | | X | | X | | X | X | |
| Height | X | | | | | | | | | | | | |
| CBC with diff, plts; Comprehensive serum chemistry (includes LFTs) (6); lipase, amylase | X | X | | X | X | | X | | X | | X | X | |
| Urinalysis | X | | | | | | | | | | | | |
| PT(INR), PTT | X | | | | | | | | | | | | |
| ECG | X | | | | | | | | | | | | |
| Collect Study drug diary | | | | | | | X | | | | X | X | |
| Radiological evaluation and tumor measurements | X | | | | | | | | | X(5) | X(5) | X(5) | |
| Beta HCG (7) | X | | | | | | | | | | | X | |

(1) Therapy schedule consists of 3 weeks on and 1 week off for all cycles, until off study.
(2) For cycle 1 only, visits are weekly for the first 3 weeks, and may occur ± 2 days of the scheduled date, ± 3 days for weeks of bank holidays.
(3) For cycles 2-4, visits are every 2 weeks, and may occur ± 2 days of the scheduled date, ± 3 days for weeks of bank holidays.
(4) For cycle 5 and beyond, visits are every 4 weeks and may occur ± 2 days of the scheduled date and ± 3 days for weeks of bank holidays.

(5) Tumor measurements and reimaging occurs every 8 weeks for the first 32 weeks, then every 12 weeks. Scans may be performed ± 7 days of the anticipated date. Tumor imaging may be performed at other times as clinically indicated; however, these will be considered non-protocol standard of care scans. The cycle length may not be the same as the time between imaging studies depending on toxicity on treatment.
(6) See above in Section 9 for details of blood collection requirements
(7) For women of childbearing potential within 7 days of day 1 of study treatment.

## 10. MEASUREMENT OF EFFECT

### 10.1 Antitumor Effect – Solid Tumors, with modifications for well differentiated-dedifferentiated liposarcoma

For the purposes of this study, patients should be re-evaluated for response every 8 weeks for the first 32 weeks, then every 12 weeks thereafter. At the discretion of the treating physician, additional imaging should be obtained if the patient has symptoms consistent with potential progression of disease. If progression is confirmed, the treatment will be unblinded as outlined in section 5.3. Scans may be done up to ± 7 days of the scheduled dates.

Response and progression will be evaluated in this study using the international criteria of the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J CA* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST. We will modify choice of target lesions on this study to focus on the most aggressive component of well-differentiated-dedifferentiated liposarcoma, i.e. the dedifferentiated components, since the well differentiated component often cannot be distinguished from normal fat.

#### 10.1.1 Definitions

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

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

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

10.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or as ≥ 10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

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

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

reference to further characterize any objective tumor regression in the measurable dimension of the disease.

For patients with well-differentiated dedifferentiated liposarcoma (WD-DDLS), the well differentiated component often does not change in size over a period of months to years, or if it does, it does not change in size quickly. For this reason, we will examine specifically in WD-DDLS patients the dedifferentiated components of the tumor. These can be identified as having a CT density of > 0 Hounsfield units, or have increased signal on T2-weighted images and/or less intense in T1-weighted series than the fatty T1-intense well-differentiated components of well-differentiated liposarcoma. By the same token, any lesions that are deemed to be sarcoma but not the dedifferentiated component will be considered non-target lesions, and their evaluation will be as with other non-target lesions as describe immediately below. Significant worsening of the well differentiated component in a WD-DDLS patient will be considered non-target lesion progression.

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

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

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

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT

scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

Ultrasound: Ultrasound is not an accepted standard for the assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both

CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000]. This criterion is generally not germane for sarcoma patients, since there are no sarcoma-specific tumor markers in common use.

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

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

FDG-PET: FDG-PET will not be used for tumor evaluation on this study. If an FDG-PET scan is done as part of routine monitoring of the patient, then scans of metastatic sites should be done with **diagnostic quality images** of those sites.

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

| | |
|---|---|
| Complete Response (CR): | Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. |
| Partial Response (PR): | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. |
| Progressive Disease (PD): | At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). |

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

10.1.4.2 Evaluation of Non-Target Lesions

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

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

**Table 10.1 Tumor Time Point Response**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR* | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not Evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |

| | | | |
|---|---|---|---|
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

*CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease, NE = inevaluable. See text for more details.

10.1.4.3 Evaluation of Best Overall Response

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

**Table 10.2 Best Overall Tumor Response when confirmation of CR and PR required**

| **Overall response First time point** | **Overall Response Subsequent time point** | **Best Overall Response** |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| NE | NE | NE |

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, and NE = inevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

10.1.5 Duration of Response

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

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

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

10.1.6 Progression-Free Survival (PFS), Time to progression (TTP)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. TTP is defined as the duration of time from start of treatment to time of progression, omitting death.

10.1.7 Response Review

A post hoc central radiology review will be conducted and data regarding PFS and TTP will be recalculated based on these measurements as an additional endpoint. However, the interpretation of the images from the individual site will be used for the primary endpoint of PFS. De-identified images will be stored in a SARC designated centrally located bank.

**10.2 Antitumor Effect – Solid Tumors: Choi criteria**

As an exploratory endpoint we will examine alternate criteria and their relationship to RECIST overall response rate, progression free survival and overall survival[24].

Parameters to characterize a radiological outcome are indicated in **Table 10.3** below. The central radiology review will calculate Choi criteria response and relationship to RECIST.

**Table 10.3 Evaluation of radiological response by Choi criteria**

| Parameter | RECIST | Choi |
|---|---|---|
| PD | ↑20% SLD (min 5 mm ↑) OR new lesion OR non target lesion progression | ↑10% SLD (↓<15% MLD) OR new Lesion OR new or ↑ tumor within tumor |
| SD | ↓< 30% SLD to ↑< 20% SLD; no new lesions; no obvious progression of non-target lesions | ↓10% SLD to ↑10% SLD (↓<15% MLD); no symptomatic deterioration attributed to tumor progression |
| PR | ↓at least 30% SLD; no new lesions; no obvious progression of non-target lesions | ↓10% SLD (+ ↓at least 15% MLD); no new lesions; no obvious progression of non-measurable disease |
| CR | Disappearance of all lesions; no new lesions | Disappearance of all lesions; no new lesions |

SLD: Sum of longest diameters
MLD: median lesion density

## 11. DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

### 11.1 Data Reporting

#### 11.1.1 Method

Electronic case report forms (eCRFs) will be created by SARC, the overall Principal Investigator and reviewed by the statistician. The database will be built within the MEDIDATA RAVE system for data collection for this study.

The definition of serious adverse events (SAEs) is given in Section 7.1. Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. For purposes of this study, a laboratory abnormality that is assigned grade 3 or 4, according to CTCAE version 4.03 is reportable as an SAE. CTCAE v 4.03 grade 3 or 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion / exclusion criteria.

When required, and according to local law and regulations, serious adverse events must be reported to the IRB and Regulatory Authorities.

All serious adverse events should be reported to SARC within 24 hours. In the event of such an event, the investigator should refer to the Adverse Reporting section of the Operations Manual for reporting procedures.

**The Investigator will report serious adverse events (SAEs) using the MedWatch 3500A form, which is attached in Appendix B.**

All reports shall be sent electronically to SARC:

**SARC:** **sarc@sarctrials.org**

**SARC will send the SAE reports and coversheets to Bayer within 1 working day.**

**Bayer Electronic Mailbox:** DrugSafety.GPV.US@bayer.com

**Facsimile:** (973) 709-2185

**Address:**
**Mail only:**
Global Pharmacovigilance - USA
Bayer HealthCare Pharmaceuticals Inc.
P.O. Box 1000
Montville, NJ 07045-1000

**Address:**
**FDX or UPS only**
340 Changebridge Road
Pine Brook, NJ 07058

**Reports for all Bayer products can also be phoned in via our Clinical Communications Dept.:**

**Phone:** 1-888-765-3203

### 11.1.2 Expected serious adverse events

For this study, the applicable reference document is the most current version of the investigator's brochure (IB)/summary of product characteristics.

The expectedness of SAEs will be determined by the SARC overall Principal Investigator.

### 11.1.3 Adverse events of special safety interest

As with any new chemical entity, there is always potential for unexpected adverse events, including hypersensitivity reactions.

Based on data from prior studies with regorafenib and from current knowledge of the pharmacological properties of other small molecule tyrosine kinase inhibitors in this drug

class, as soon as there is reasonable suspicion of any of the following AEs, the investigator should immediately notify the sponsor as outlined in Section 11.1.1.

These events include:

- Acute renal failure (NCI-CTCAE version 4.03 ≥ G3) or severe proteinuria (NCI-CTCAE version 4.03 ≥ G3)
- Interstitial lung disease
- Acute cardiac failure
- Clinically significant bleeding (NCI-CTCAE version 4.03 ≥ G3)
- Stevens-Johnson syndrome and erythema multiforme
- Hepatic failure

### 11.1.4 Pregnancies

The investigator must report to SARC any pregnancy occurring in a study subject, or in his partner, during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

### 11.1.5 Further safety documentation

Progressive disease

If progressive disease leads to signs and symptoms that meet the criteria for an SAE (i.e., hospitalization, disability, death, or important medical event), the signs and symptoms should be reported as an SAE and not the underlying progressive disease.

Death

If any subject dies during the trial or within 30 days of the end-of-treatment visit, the investigator will inform SARC and record the cause of death in detail (using the SAE Form) within 24 hours.

### 11.1.6 Data Safety Monitoring

#### 11.1.6.1 Data Safety Monitoring

An Independent Data Monitoring Committee will be formed to monitor safety and efficacy. The IDMC will be comprised of two oncologists and a statistician experienced

in clinical trials.

#### 11.1.6.2 Additional Data Safety Monitoring

The SARC Clinical Trials Review Committee convenes monthly and will provide safety oversight for this trial. The purpose of the Clinical Trials Review Committee is to review the status of the ongoing SARC studies, which includes but is not limited to:

- Review of all safety data (Serious Adverse Events reported)
- Review of any protocol violations
- Review of study progress/accrual
- Discussion of statistical aspects of protocol as appropriate.

The committee is chaired by the SARC Medical Officer, who is responsible for leading the meeting and providing medical oversight. Attendance includes all Principal Investigators on active SARC studies, SARC Research Project Managers, SARC President and a biostatistician.

Safety oversight for this trial is also supported by the SARC Clinical Research Committee, which is made of senior sarcoma investigators. This committee reviews the findings of the Clinical Research Committee on a monthly basis. This committee provides an additional level of medical oversight for this trial.

### 11.1.7 Patient Accrual and Participating Centers

There will be approximately 18 SARC centers collaborating to accrue patients to this study. We anticipate accrual will take approximately 18-24 months.

This trial will be posted at the www.clinicaltrials.gov website.

## 11.2 Multi-Institutional Guidelines

The trial coordinating center (Operations Center) will be SARC. Patients will be registered electronically via the study website and adverse events (as defined in section 7.0) will be reported to the SARC Operations Center.

*IRB approvals*:

The protocol must be approved by the treating institution prior to enrolling patients. Documentation of individual IRB approval for the current protocol must be provided to the SARC Operations Center prior to enrolling patients on the trial. In addition, documentation of approval of all protocol amendments and of yearly continuing review must be provide to the Research Project Manager either electronically or via mail to the following address:

SARC
24 Frank Lloyd Wright Drive, PO Box 406
Ann Arbor, MI 48105
Fax: 734-930-7557
Email: sarc@sarctrials.org

*Patient Registration*

Patient registration will be centrally managed electronically via the study website (see section 4.2).

*Data Collection and Toxicity Reporting*

Registration reports will be generated by the Operations Center to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies by the SARC. Any potential problems will be brought to the attention of the study Principal Investigator(s) for discussion and action.

Access to the password protected study website will be limited to individuals involved in the clinical trial including: SARC staff, overall Study and Cohort PIs, participating site PIs, research nurse and data managers responsible for this trial.

Shipment and receipt of specimens and imaging studies sent for correlative studies will be entered and tracked on the study website. Details regarding handling and shipping will be outlined in the study operations manual.

### 11.3 Data and Participating Institution Monitoring

Data monitoring for this trial will be managed remotely. A data monitoring and site monitoring plan will be developed for this trial. Should areas of concern be identified through the remote monitoring process, an on-site monitoring visit may be warranted. Findings will be discussed with the overall study PI and Cohort PIs, participating site PIs, Clinical Trials Review Committee and the SARC medical officer.

### 11.4 Human Subjects Protection

#### 11.4.1 Rationale for Subject Selection

Subjects of both genders and from all racial and ethnic groups are eligible for this trial if they meet the eligibility criteria as outlined in section 3.1. No groups will be excluded from participation in the trial.

#### 11.4.2 Evaluation of the Benefits and Risks/Discomforts

The primary risk to patients participating in this research study is from toxicity associated with regorafenib, which has been approved by the FDA for the treatment of metastatic

renal cancer and gastrointestinal stromal tumors. The primary objectives of this phase 2 study are for Cohorts A & B to compare PFS of subjects treated with regorafenib or placebo and for Cohort C to estimate PFS at 8 and 16 weeks. A crossover option will be available for patients who progress on placebo as outlined in Section 5.

### 11.4.3 Management of Patient Data

All patient data will be captured and maintained in a study specific database with password-protected access. Data is entered using an assigned study subject identification number.

The data provided to those reviewing the results, for example the study statistician will include the subject identification numbers but will not include patient identifiable data.

The research samples obtained on this study will only be sent using the study subject identification number, which can only be linked to the patient at a given institution by the treating physician.

All documentation that contains personal health information that may include patient identifiable information will be maintained at the site to preserve patient confidentiality.

## 11.5 Premature termination of study

This study may be closed prematurely for any of the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example:
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in **Section 5.8**.

# 12. STATISTICAL CONSIDERATIONS

## 12.1 Efficacy and safety variables

### 12.1.1 Efficacy variables

Efficacy variables to analyze include:

- Progression free survival (PFS, as assessed by RECIST 1.1), defined as time from randomization (or 1st day of treatment, cohort C, D and E) to site determined radiographic tumor progression or death from any cause (whichever occurs first). For patients alive without progression, censoring occurs at the date of last tumor assessment. In PFS analyses, if the exact progression date is unknown, the date of progression is taken to be the date the first time at which progression can be declared
- Proportions of patients who are progression-free (and alive)
- Proportions of patients without progression or death at landmark times (in particular at 8 and 16 weeks)
- Overall survival is defined as the time from randomization (or 1st day of treatment, cohorts C, D and E) until death from any cause. Censoring occurs at the date of last contact.
- Disease-specific survival is defined as the time from randomization (or 1st day of treatment cohorts C, D and E) until death from sarcoma
- Time to progression (as assessed by RECIST 1.1), defined as time from randomization (or 1st day of treatment, cohort C) to centrally-determined radiographic tumor progression, censoring for death without progression. Progression is defined, according to RECIST 1.1, as a 20% increase from nadir and a minimum of 5 mm increase over the lowest sum, the appearance of one or more new target or non-target lesions, or unequivocal progression of existing non-target lesions determined by radiographic assessment. In TTP analyses, the exact progression date is unknown. Date of progression is taken to be the date the first time at which progression can be declared
- Change in target lesion size. Target lesion size will be measured by imaging methods. Tumor size will be measured as a unidimensional tumor measurement per RECIST 1.1.
- Overall response rate (ORR as assessed by RECIST 1.1) defined as the portion of patients evaluable for response who achieved partial response or better and stable disease or better

### 12.1.2 Safety variables

A treatment-associated adverse event (TAAE) is defined as an AE that was not present at baseline, or an exacerbation of a pre-existing AE. For laboratory data, a treatment-associated abnormal laboratory value (TAAV) represents an abnormal value that was normal at baseline.

Safety variables of analysis include the following:

- Proportions of patients with any TAAEs
- Proportions of patients with serious TAAEs
- Proportions of patients with Grade 3 or greater TAAEs
- Proportions of patients with severe TAAE
- Proportions of patients with TAAEs leading to study drug discontinuation
- Proportions of patients with TAAEs leading to dose modifications
- Proportions of patients with drug-related TAAEs
- Proportions of patients with TAAVs
- Mean and median changes from baseline in vital signs
- Mean and median changes from baseline in clinical laboratory measures
- Mean and median changes from baseline in measures from electrocardiography.

It is noted that patients who cross over from placebo to receive open-label regorafenib will have treatment-related derivations from first dose of placebo during the double-blind period and treatment-related derivations from first dose of regorafenib during the open-label portion of the study.

**12.2 Study Design/Endpoints**

**Cohorts A and B (liposarcoma and osteosarcoma)**

Each of cohorts A and B will be studied using a randomized placebo controlled phase II design with a progression free survival endpoint. Outcomes will be determined on an intention to treat analysis.

Each cohort substudy will be powered to detect a difference of at least 3 months in median PFS, which has been discussed among expert sarcoma oncologists as a clinically meaningful difference in outcome. This corresponds to a median control group PFS of 2 months, median treatment group PFS of 5 months, and hazard ratio of 0.4 for treatment/control groups.

42 events are needed to detect a targeted difference with 90% power and 5% one-sided significance level. The final analysis of the primary PFS endpoint will be conducted when at least 42 patients had disease worsening. 48 eligible patients are expected to be randomized, to achieve the 42 expected events with an enrollment rate of 4 eligible patients per month per substudy. With the predicted accrual rate and PFS parameters, the 42 events are expected to occur in 16 months.

We will limit to a maximum of 16 patients per substudy A & B with WHO performance status of 2. There is no such limitation for substudy C.

Survival will be estimated by the Kaplan-Meier method. The treatment groups will be compared with a one-sided stratified log rank test. All analyses will be done in the intention-to-treat population.

We will conduct a prognostic factor analysis for PFS using a univariate Cox model; significant factors subsequently will be included in a multivariable Cox regression model (cutoff $p<0{\cdot}05$). For a predictive analysis of PFS, Cox models will be generated with the investigated factor, treatment, and their interaction, with a significance value of $p<0{\cdot}05$. P-values will not be adjusted for multiple comparisons.

**Cohort C (Ewing/Ewing-like sarcoma):**

Since progression free survival is so short in Ewing/Ewing-like sarcoma, even with an active agent such as an IGF1R inhibitor (1.3 months in one study), a single-stage design examining PFS at 8 and 16 weeks will be employed for this cohort.

We will take median PFS of 0.5 at 8 weeks as evidence of activity for this cohort, in comparison to an uninteresting median PFS (8 weeks) of 0.25. For this 30 patient cohort with these parameters, this yields a false positive rate of 0.05 (alpha) and power (1-beta) of 0.91.

The response rate will be estimated and a confidence interval will be constructed. A sample size of 30 patients and 50% PFS rate at 8 weeks yields a 95% binomial confidence interval of (31%, 69%).

**Cohort D (Rhabdomyosarcoma: Fusion-positive alveolar, Embryonal, Fusion-negative alveolar):**

Since published estimates of progression free survival in rhabdomyosarcoma patients after more than one relapse are scarce, we will estimate the RECIST 1.1 Response rate (PR or better) at 8 weeks. Cohort D will accrue separately to approximately 12 patients with either of (1) fusion-positive alveolar rhabdomyosarcoma and (2) embryonal rhabdomyosarcoma/fusion negative alveolar rhabdomyosarcoma, and will be analyzed as a combined cohort. We will consider a disease control rate (CR+PR+stable disease at 8 weeks) of 30% to be evidence of activity, in comparison to a disease control rate of 10% as not useful to pursue further.

A total of ~ 12 patients will be accrued to Cohort D and ~ 12 to Cohort E, below. Since funding is available for 24 patients in Cohorts D and E, the below are estimates of accruals, and the actual accrual will be used to define success vs failure for each cohort based on final accrual, maintaining similar disease control rates at 8 weeks (30% [active] vs 10% [not active]) for Cohort D, regardless of final accrual total.

For a 12-patient cohort with a type I error of 0.10 and a power of 0.90, if 2 or fewer patients have disease control, then regorafenib will be determined to be unworthy of further study in this setting. If 3 or more patients have disease controlled at 8 weeks, regorafenib will be considered worthy of further investigation in Cohort D. A sample size of 12 patients will permit determination of disease control rate of 30% with 95% binomial confidence interval of (10%, 57%).

**Cohort E (Mesenchymal chondrosarcoma):**

Published estimates of progression free survival on chemotherapy for patients with metastatic mesenchymal chondrosarcoma patients are also unavailable. However, existing data indicate the overall survival of patients with metastatic mesenchymal chondrosarcoma is similar to those with unselected soft tissue sarcomas, in the 18 month range (Amer et al. J Orthop Res 2019, https://doi.org/10.1002/jor.24463), so we will estimate the RECIST 1.1 response rate (PR or better) at 24 weeks. Cohort E will accrue to ~ 12 patients with metastatic mesenchymal chondrosarcoma. We will consider a disease control rate (CR+PR+stable disease) at 24 weeks of 50% to be evidence of activity, as is the case with 1st line doxorubicin or gemcitabine in unselected STS (GEDDiS study) in comparison to a disease control rate of 25%, as not useful to pursue further.

A total of ~ 12 patients will be accrued to Cohort E,. Since funding is available for 24 patients in Cohorts D and E, the estimates of accruals, and the actual accrual will be used to define success vs failure for each cohort based on final accrual, maintaining similar disease control rates at 24 weeks (50% [active] vs 25% [not active]) for Cohort E, regardless of final accrual total.

The design is based on a Simon's two-stage using only the first stage. A 12-patient cohort with a type I error of 0.10 and a power of 0.80, yields a decision rule that if 3 or fewer patients have disease control at 24 weeks, then regorafenib will be determined to be unworthy of further study in this setting. If 4 or more patients have disease controlled at 24 weeks, regorafenib will be considered a worthy of further investigation in Cohort E. A sample size of 12 patients will permit determination of 24-week disease control rate of 50% with 95% binomial confidence interval of (21%, 79%).

**12.3 Sample Size/Accrual Rate**

Enrollment in cohorts A & B is expected to be 4 patients per month per cohort, with a total of 48 patients per cohort enrolled 1:1 between regorafenib: placebo. Enrollment is expected to be completed in 12 months with a minimum follow-up period of 6 months.

For cohort C, enrollment is expected to be 3 per month for a total enrollment of 30 patients over 10 months. (Enrollment for this cohort is complete.)

For cohort D, enrollment is expected to be 0.5 per month (1 each fusion positive, fusion negative types) for a total enrollment of 12 patients over 24 months.

For cohort E, enrollment is expected to be 0.5 per month (1 each fusion positive, fusion negative types) for a total enrollment of 12 patients over 24 months.

### 12.4 Stratification Factors

Patients will be stratified by WHO performance status ([0 or 1] vs 2) and by number of prior lines of therapy (1 vs 2 or more). No more than 1/3 of patients will be permitted on cohorts A and B with WHO performance status 2.

### 12.5 Analysis of Secondary Endpoints

Descriptive statistics will be generated for secondary endpoint variables.
Methodologies for variables that are proportions will include construction of confidence intervals for each group and for the difference between groups. For example, a Fisher exact test will be used for single-population analyses, while a Mantel-Haenszel test will be used for analyses combining data across strata.

Methodologies for time-to-event variables will include construction of 95% confidence intervals for each group separately and for the difference between groups. For analysis, a log-rank test will be used. Logistic regression and analysis of covariance methods on measured variables with baseline measures as covariables. Kaplan Meier curves will be displayed for time-to-event data.

## 13. ETHICAL AND LEGAL CONDUCT OF THE STUDY

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IRBs will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IRB approval must be obtained and also forwarded to SARC.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by SARC and the sponsor, Bayer. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/SARC/Bayer approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator.

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and properly documented.

Subjects will not be paid to participate in this study.

**13.1 Subject information and consent**

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement will be uploaded into the database and will remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

1. If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of Bayer and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

2. For minors or adults under legal protection, consent shall be given by the legal guardian(s). The consent of a minor or adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

3. In emergency situations, when prior consent of the patient is not possible, the consent of the patient's legal representative(s) or proxy consenter, if present, should be requested. The patient should be informed about the study as soon as possible and his/her consent to continue

the study should be requested.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

### 13.2 Publication policy

Timely publication is central to SARC's mission. A manuscript should be prepared and submitted for publication within one year of availability of the study results. Authorship will align with the SARC publication policy.

### 13.3 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

## 14. REFERENCES


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**APPENDIX A: Performance Status Criteria**

| WHO Performance Status Scale | |
|---|---|
| **Grade** | Descriptions |
| 0 | **Asymptomatic** (Fully active, able to carry on all pre-disease activities without restriction) |
| 1 | **Symptomatic but completely ambulatory** (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work) |
| 2 | **Symptomatic, <50% in bed during the day** (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours) |
| 3 | **Symptomatic, >50% in bed, but not bedbound** (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours) |
| 4 | **Bedbound** (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair) |
| 5 | **Deceased** |

**APPENDIX B. SARC024 Fax/Email Coversheet and MedWatch form**

SARC
collaborating to cure sarcoma

24 Frank Lloyd Wright Dr.
Ann Arbor, MI 48105
Tel. 734-930-7600
Fax. 734-930-7557
sarc024@sarctrials.org

**Fax or email to the following within *24 hours* of PI becoming aware of event:**

sarc024@sarctrials.org; Fax: (734) 930-7557

| | |
|---|---|
| **Study Title** | **SARC024: A blanket protocol to study oral regorafenib in patients with selected sarcoma subtypes** |
| **Site PI Name** | |
| **Patient Unique Study #** | |
| **Adverse Event (CTCAE v4.03)** | |
| **Adverse Event Grade** | |
| **Adverse Event Causality Relationship** | ❒ **Yes**<br>❒ **No** |
| **Type of Report (Check one)** | ❒ **Initial** ❒ **Follow-up** |
| All serious adverse events will be reported and documented on Form FDA 3500 A (MedWatch Form) Please fax completed MedWatch Form along with this Fax Coversheet. | |

**Completed by:** _____
**Date:** _____

## APPENDIX C. Study Drug Diary Template

(See subsequent page)

## SARC024 Study Drug Diary

| **To be completed by the site**: Patient ID: _____ Cycle number: _____ Cycle Start Date _____ | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Date** | | | | | | | | | | | | | | | | | | | | |
| Study drug<br>Number of tablets taken* | | | | | | | | | | | | | | | | | | | | |
| Reason for missed dose | | | | | | | | | | | | | | | | | | | | |
| **Watching for Side Effects** | | | | | | | | | | | | | | | | | | | | |
| Blood pressure** | | | | | | | | | | | | | | | | | | | | |
| **Nausea*****<br>(see scale below) | | | | | | | | | | | | | | | | | | | | |
| **Vomiting**<br>(number of times) | | | | | | | | | | | | | | | | | | | | |
| **Diarrhea**<br>(number of times) | | | | | | | | | | | | | | | | | | | | |
| **Watching for Other Side Effects** | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| **Other Medications** | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |

***ONLY TAKE STUDY DRUG FOR 3 WEEKS (21 DAYS). DO NOT TAKE ANY STUDY DRUG DURING WEEK 4 OF EACH CYCLE.***

* If you are 8 hours or more late from your scheduled dose, do not take the dose, and please write "**M**" in the box.

** Check blood pressure every week.

*** Rate nausea "**1**" if you are able to eat and drink a reasonable amount, "**2**" if you can eat and drink but the amount is decreased significantly, or "**3**" if you can't eat and drink.

Note: Try to take the study drug daily at the same time, if possible, and consistently with or without food. Do not retake if vomiting occurs.

**Grapefruit/grapefruit juice must be avoided while on study**

Your initials/Parent or guardian initials: _____

## APPENDIX D. Strong CYP3A4 inducers and inhibitors

**Listing of strong CYP3A4 inducers to avoid while on study**

Carbamazepine
Phenobarbital
Phenytoin
Rifampin
St. John's wort

**Listing of strong CYP3A4 inhibitors to avoid while on study**

Clarithromycin
Grapefruit juice
Itraconazole
Ketoconazole
Posaconazole
Telithromycin
Troleandomycin
Voriconazole

Source: U.S. Food and Drug Administration: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm
Accessed - 04/04/2017