A Randomized, Double-Blinded, Placebo-Controlled, Multi-Institutional, Cross-Over,
Phase II.5 Study of Saracatinib (AZD0530), a Selective Src Kinase Inhibitor,
In Patients with Recurrent Osteosarcoma Localized to the Lung

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Distributor	AstraZeneca		
Study Sponsor	SARC		
IND Holder	SARC		
IND Number	103,268		
Version/Date	Version 5/ 9-4-2015		

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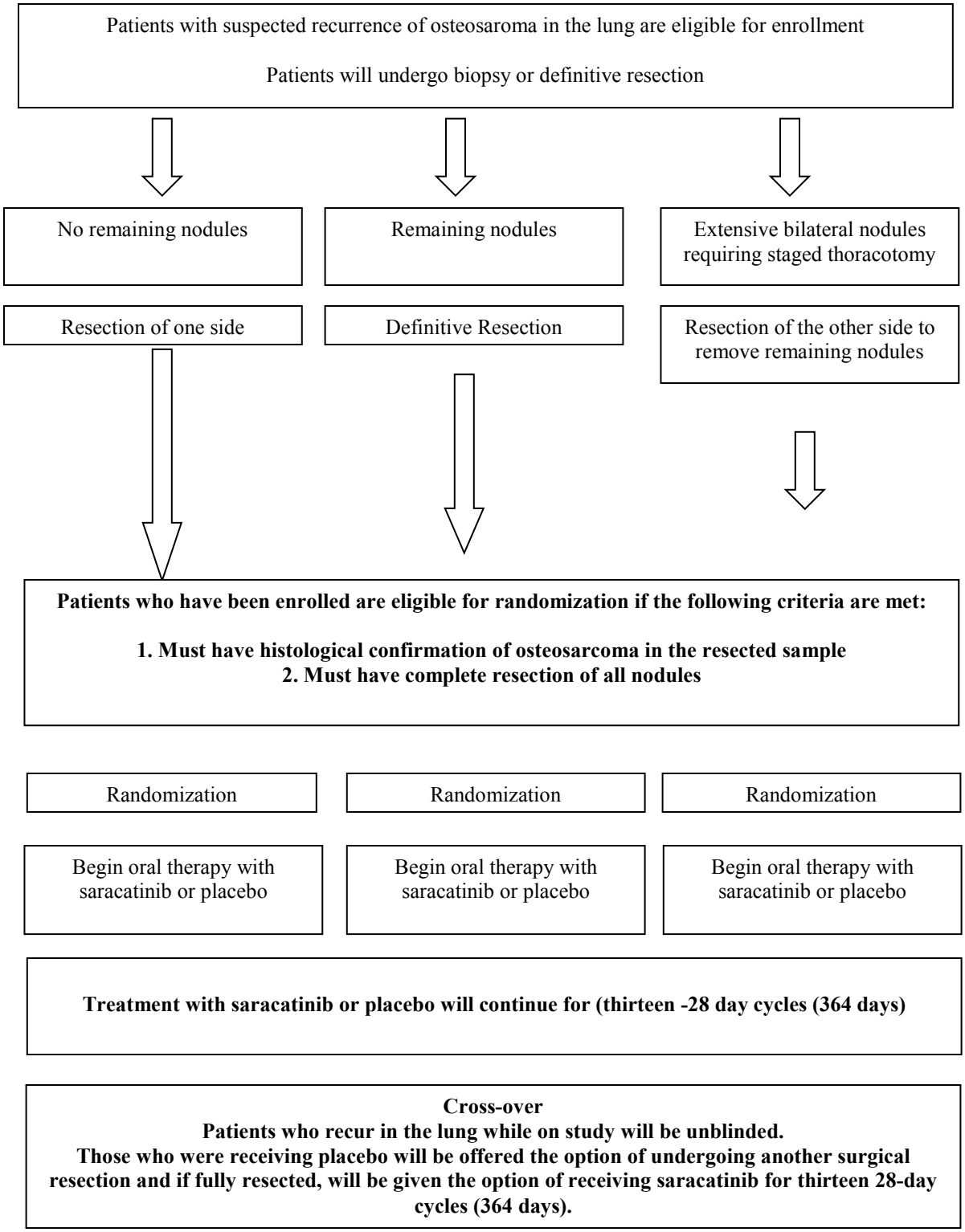
Treatment Schema



Precis

Background

- Saracatinib is a potent and selective Src kinase inhibitor.
- In vitro studies demonstrate that 95% of patients with osteosarcoma have activation of Src, or one of its substrates.
- A Phase I study of saracatinib, given daily, in adult patients with advanced solid malignancies, has identified 175 mg as the maximum tolerated dose.

Primary Objective

- To determine if the addition of saracatinib to pulmonary metastasectomy, versus placebo and pulmonary metastasectomy, results in an increase in progression free survival.

Secondary Objectives

- To determine if the addition of saracatinib to pulmonary metastasectomy, versus placebo and pulmonary metastasectomy, results in an increase in overall survival.
- To determine if the addition of saracatinib to pulmonary metastasectomy, versus placebo and pulmonary metastasectomy, results in an increase in the time to treatment failure, defined as a composite endpoint measuring time from randomization to discontinuation of treatment for any reason, including disease progression, treatment toxicity, or death.
- To perform microarray analysis of tumor samples to identify a gene signature that predicts for recurrence of osteosarcoma.
- To evaluate tumor samples for biomarkers related to activation of Src and Src substrates.
- To establish cell lines and murine xenografts from recurrent tumor samples.
- To perform sequencing analysis of DNA and RNA in tumor samples compared to normal blood to detect mutations that may be causative for recurrent osteosarcoma.

Eligibility

- Patients $\geq$15 and <75 years of age, with suspected recurrence of osteosarcoma, localized to the lung, are eligible for enrollment
- Patients with histological confirmation of recurrent osteosarcoma, localized to the lung, who have had complete surgical removal of all lung nodules, will be eligible for randomization.

Design

- Only after complete resection of all lung nodules, patients will be randomized to treatment with saracatinib or placebo. Eighty-eight patients will be randomized, 44 patients in each arm of the study. This will be a multi-institutional study.

- Saracatinib, or placebo, will be administered as a once daily, oral dose of 175 mg, for a 28-day cycle, with no breaks between cycles. The duration of treatment with saracatinib or placebo will be 13 cycles (364 days total).
- Patients will begin cycle 1 after complete surgical resection.

Cross-Over Component

- Patients who recur in the lung while on-study and who are thought to be amenable to complete surgical resection will be un-blinded. Those patients who were receiving placebo may then have the option of undergoing surgical resection. If fully resected (staged thoracotomy is acceptable), they will be given the option of receiving oral therapy with saracatinib. Saracatinib will be administered as a once daily, oral dose of 175 mg, for a 28-day cycle, with no breaks between cycles. The duration of treatment with saracatinib will be **thirteen 28-day cycles** (364 days total).

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INVESTIGATOR SIGNATURE SHEET

I have read the attached protocol and agree that it contains all the necessary details for conducting *SARC012: A Randomized, Double-Blinded, Placebo-Controlled, Multi-Institutional, Phase II.5 Study of* Saracatinib *(AZD0530), a Selective Src Kinase Inhibitor, In Patients with Recurrent Osteosarcoma Localized to the Lung*

I will provide copies of the protocol and any pre-clinical information on the study drug, which were furnished to me by SARC, to all members of the study team for whom I am responsible and who participate in the study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

Once the protocol has been approved by the IRB, I will not modify this protocol without obtaining the prior approval of SARC and of the IRB.

I understand the protocol and agree to follow the principles of Good Clinical Practice (current ICH guidelines), and the Declaration of Helsinki (1964) including all amendments up to and including the Tokyo Clarification (2004).

Print Name	Investigator's Signature	Date

1 Introduction

1.1 Study Objectives

1.1.1 Primary Objective

To determine if the addition of saracatinib to pulmonary metastasectomy, versus placebo and pulmonary metastasectomy, results in an increase in progression free survival.

1.1.2 Secondary Objectives

To determine if the addition of saracatinib to pulmonary metastasectomy, versus placebo and pulmonary metastasectomy, results in an increase in overall survival.

To determine if the addition of saracatinib to pulmonary metastasectomy, versus placebo and pulmonary metastasectomy, results in an increase in the time to treatment failure.

To perform microarray analysis of tumor samples to identify a gene signature that predicts for recurrence of osteosarcoma.

To evaluate tumor samples for biomarkers related to activation of Src and Src substrates.

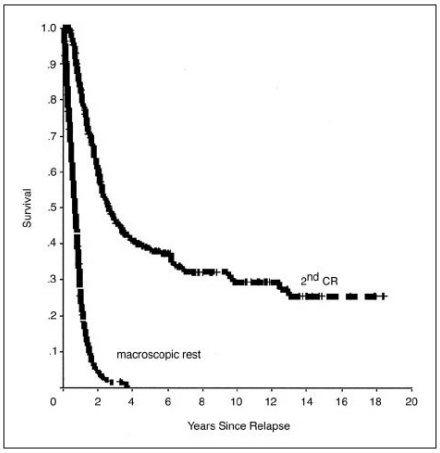
To establish cell lines and murine xenografts from recurrent tumor samples.

1.2 Background and Rationale

1.2.1 Recurrent Osteosarcoma

Osteosarcoma is the most common malignant bone tumor in the United States and Europe. Historically, this was once a fatal diagnosis. However, with the increasing use of chemotherapy in the late 1970s, patients who underwent both surgery and chemotherapy had a marked improvement in survival. Currently the overall cure rate is 65%, representing a dramatic improvement over previous decades (1,2). Unfortunately, patients who recur with disease have only a 25% five-year survival rate (3,4). Approximately 33% of patients who have completed therapy for osteosarcoma will recur. In large retrospective analyses performed by the Cooperative Osteosarcoma Study Group (3) and the Rizzoli Institute (4), the only patients who survived long-term were those who achieved complete surgical removal of recurrent tumor, illustrated in the survival curve

on the right (3). Specifically, 291 patients did not achieve surgical remission, and none of these patients survived long-term. In contrast, 512 patients achieved surgical remission and five-year overall survival rates were 38% and 30% in the two studies. These patients received either multi-agent, single agent or no chemotherapy, but they shared the common feature that everyone had achieved a second surgical remission. It did not appear that the addition of adjuvant treatment increased survival (40% survival with chemotherapy versus 35% survival without chemotherapy, p=0.35) (3). However, this trend may eventually prove to be statistically significant in larger cohorts. Conversely, for those treated with chemotherapy or radiation therapy only without surgery, there were no survivors (4).



One of the significant prognostic factors that predicts for long-term survival is the number of nodules at the time of recurrence. In the Cooperative Osteosarcoma Study Group study, patients who had one nodule had a 38% 5-year overall survival rate, compared to 15% for patients with two or more nodules ($p<0.01$) (3). Comparably, in the Rizzoli Institute study, patients who had one or two nodules had a 44% 5-year event free survival rate, compared to 22% for patients with three or more nodules ($p<0.01$) (4).

Another factor that impacts outcome is the number of recurrences. The only study that has examined these subsets of patients is the retrospective analysis performed at the Rizzoli Institute (4). The following shows the number of long-term survivors as a percentage of those who were able to obtain surgical remission. First relapse – 30.6% (53 of 173 patients). Second relapse – 25.9% (14 of 54 patients). Third relapse – 16.7% (2 of 12 patients). Ten patients had a fourth relapse and six of these patients achieved surgical remission. However, all six patients progressed to have a fifth relapse. Not surprisingly, patients have decreased survival probability when they have multiple recurrences.

The role of chemotherapy in the treatment of recurrent osteosarcoma is unclear. To date, there have not been any randomized studies that have evaluated the benefit of chemotherapy in this setting. However, multiple Phase II studies have failed to show improvement in outcome. Several of these include the use of cyclophosphamide and topotecan (5), docetaxel (6), ecteinascidin 743 (7), as well as imatinib mesylate (8). The latter is a potent inhibitor of the abl receptor tyrosine kinase family, including platelet-derived growth factor receptor and KIT kinase, but is a poor inhibitor of Src. The use of high-dose chemotherapy followed by stem cell rescue showed that induction of complete remission was feasible, but that treatment outcomes were not improved (9,10).

A report from the Children's Cancer Group showed a small increase in overall response following treatment with ifosphamide, carboplatin and etoposide, however, the result was not statistically significant (11). A retrospective report from the Memorial Sloan-Kettering Cancer Center suggested a benefit from the addition of high-dose ifosphamide following surgery, but the result did not reach statistical significance (12). The use of

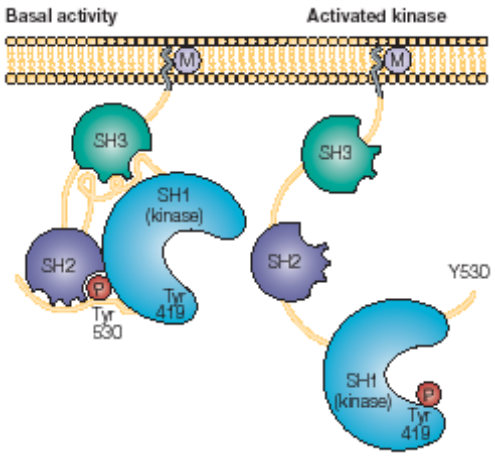
high-dose ifosphamide for recurrent osteosarcoma at the M.D. Anderson Cancer Center resulted in 30% (5/16 patients) disease-free survival (13). However, three of these patients had not previously received ifosphamide. In addition, four patients developed renal toxicity, two of which, progressed to acute renal failure. To date, there has not been a study of sufficient size to justify the use of high-dose ifosphamide in this setting.

Unfortunately, these results show that there is no effective salvage regimen for patients with recurrent osteosarcoma. Therefore, the current standard of care is to resect the recurrent tumor if possible, followed by observation. If any chemotherapeutic agent with activity against osteosarcoma (adriamycin, cisplatin, ifosphamide, methotrexate) was not used during treatment of the primary tumor, then that agent may be administered as adjuvant therapy following surgical resection. Unfortunately, even those patients who achieve complete surgical remission have only a 35% long-term survival rate. All of these factors point to the importance of identifying new biological agents for the treatment of recurrent osteosarcoma.

1.2.2 Src and Cancer

In 1911, Peyton Rous described his work on hens that had large tumors that could be transplanted into other chickens (14). Surprisingly, cell-free filtrates of these tumors were also able to produce tumors when injected into healthy birds. Forty years later, Harry Rubin showed that the tumor cells released infectious virus, subsequently called Rous sarcoma virus. In addition to the three proteins that are needed for the virus to replicate and package its genome, Rous sarcoma virus also contained a fourth gene named v-src, for viral sarcoma. It was the v-src gene that was responsible for the tumor potential of the virus and v-src was the first oncogene to be identified.

The relevance of v-src to human cancers came with the demonstration that many oncogenes had normal counterparts in humans (14). The gene c-src, the human homolog of v-src, is a member of the tyrosine kinase family. Src contains four SH (Src Homology) domains, as illustrated in the diagram on the right (15). SH1 is the catalytic kinase domain. The SH2 domain binds peptides that contain phosphorylated tyrosine residues. The SH3 domain binds proline rich sequences and the SH4 domain contains the myristoylation site that allows for membrane localization. There is a tyrosine residue (Tyr 530) at the carboxy terminal of c-src. When this residue is phosphorylated, it binds the SH2 domain of Src, resulting in a closed inactivate molecular conformation. Conversely, Src activation occurs following removal of the carboxy phosphotyrosine, resulting in the loss of intramolecular interactions and an open conformation. Complete activation of Src involves additional phosphorylation of the Tyr 419 residue.



Src is a non-receptor tyrosine kinase (14,15). Activation of Src frees the SH2 and SH3 domains to participate in interactions that target Src to its substrates. Src can directly phosphorylate its substrates or act as a docking site for the binding of other signaling proteins that contain SH2 domains. This dual mechanism involves Src, both directly and indirectly, in many signaling pathways. Some of these include the PI3K/AKT/mTOR, Ras/Raf/MEK/MAPK and STAT3 pathways, all of which affect proliferation and survival of the cell. Src also targets another set of substrates at focal adhesions including focal adhesion kinase (FAK) and paxillin. The latter is a scaffolding molecule that regulates the organization of the actin cytoskeleton and plays an important role in cell motility (16). Upon integrin signaling, recruitment of FAK to sites of cell-extracellular matrix contact, leads to phosphorylation of paxillin and multiple downstream signaling events, eventually resulting in cell migration (17).

Increased Src activity was first described in sarcomas. Examination of tumor samples from nine patients with sarcomas showed that 33% had enzyme activity levels that were 4-10 fold higher than that seen in normal tissue (18). Similar findings were also found in mammary carcinomas (18). Subsequently, increased activity or expression of Src has been seen in many common solid tumors, including the lung and several gastrointestinal tumors involving the esophagus, stomach, liver, pancreas and colon (15). In some cancers, Src activity correlated with poor prognosis. Most importantly, Irby et al, showed that a small number of metastatic colon cancer cases had a single base pair mutation in Src, resulting in truncation of the protein at codon 531 (19). Although the tyrosine residue at codon 530 was still phosphorylated, it was unlikely to be capable of functioning in a negative regulatory role due to lack of C-terminal residues. Transfection of this truncated form of Src into 3Y1 rat fibroblasts, followed by injection into nude mice, resulted in formation of lung metastases and 100% mortality. In contrast, cells transfected with wildtype c-src were not metastatic, demonstrating that the truncation mutant was highly activating. These findings are concordant with the fact that v-src also contains various base pair substitutions, one of which results in truncation of the carboxy terminal prior to the phosphorylation site, leading to constitutive activation of Src (14). The sum of these results confirms the important role of Src activation in human tumor progression.

1.2.3 Src and Osteosarcoma

Recent data from microarray analysis of 61 primary and metastatic osteosarcoma patient samples revealed that Src is expressed in all of the samples (20). In addition, a tissue array containing 23 osteosarcoma patient samples was tested for activation of Src, and its substrates, FAK and paxillin, by immunohistochemistry (21). 15 of 17 (88%) samples showed activated Src. 18 of 19 (94%) samples were positive for phosphorylated FAK. 10 of 20 (50%) samples were positive of phosphorylated paxillin. In total, 19 of 20 (95%) samples had activation of at least one of the above three genes. These findings demonstrate that the Src pathway is activated in 95% of patients with osteosarcoma. This included two patients with recurrent osteosarcoma and both of these samples had very high levels of Src activation.

A large body of in vitro data also reveals the importance of Src activation in the progression of osteosarcoma. CD99 is a transmembrane glycoprotein that shows very little expression in human osteosarcoma samples. Forced expression of CD99 into a metastatic osteosarcoma cell line drastically reduced the number of lung metastases (22). CD99 over-expressing cells were found to have decreased phosphorylation of the Src Tyr 419 residue (resulting in decreased Src activity). In addition, CD99 was found to co-localize with Src and the scaffold protein caveolin-1, possibly resulting in allosteric inhibition of Src activity. Treatment of cells with PP1 and PP2 (Src kinase inhibitors) resulted in suppression of motility of parental cells, again suggesting the importance of Src activation for the migratory behavior of wild-type cells.

Further underscoring the importance of the above are the more recent findings that caveolin-1 (Cav-1) expression reduces osteosarcoma metastases by inhibiting Src activity and Met signaling (23). Specifically, the mean number of metastatic nodules was >250 in mice receiving Cav-1 deficient osteosarcoma cells, and 0 in mice inoculated with Cav-1 over-expressing cells. There were high levels of both expression and activity of Src in Cav-1 deficient cells, whereas Cav-1 over-expressing cells had a significant decrease in Src kinase activity. Over-expression of Cav-1 also resulted in inhibition of anchorage independent growth, migration and invasion in vitro.

Similar results were obtained in osteosarcoma cells treated with dasatinib, a small molecule inhibitor of Src kinase activity (24). Inhibition of Src signaling was accompanied by blockade of cell migration (wound healing assay), invasion (matrigel invasion chamber) and apoptosis in two osteosarcoma cell lines. In addition, inhibition of Src protein expression by small interfering RNA also induced apoptosis, indicating that these osteosarcoma cell lines were dependent on Src activity for survival (24).

Src interacts with Focal Adhesion Kinase (FAK), leading to the subsequent phosphorylation of paxillin and p130 Crk-associated substrate. Neither molecule has intrinsic enzymatic activity. However, they have multiple domains that interact with cytoskeletal and signaling molecules, allowing them to function as scaffold proteins. One murine osteosarcoma model suggests the importance of paxillin expression in metastatic disease (25). Highly metastatic variants of the human osteosarcoma cell line HuO9 showed high phospho-paxillin expression, while poorly metastatic variants of the cell line showed low phospho-paxillin expression. Treatment of highly metastatic cells with PP2 (Src kinase inhibitor) resulted in suppression of motility. These results demonstrate the importance of activated Src kinase in the metastatic process.

Src activation is also required for anoikis resistance of human osteosarcoma cells (26). Anoikis is a form of apoptosis that is triggered when survival signals generated from interactions with the extracellular membrane are severed. Physiological anoikis is important in the maintenance of homeostasis and tissue architecture. Transformed cells that are resistant to anoikis have increased survival times in the absence of matrix attachments, thus facilitating their migration and colonization at secondary sites. Src was found to be upregulated in anoikis resistant SAOS human osteosarcoma cells and pharmacological inhibition of Src activity resulted in restoration of anoikis sensitivity. In total, these results identify biochemical mechanisms that link the activation of Src kinase to the metastatic process.

1.2.4 Saracatinib

Saracatinib is a highly selective, orally bio-available, dual-specific Src/Abl kinase inhibitor that has high potency against all Src family members tested (27). This includes c-yes and c-fyn, the members that are most closely related to c-src. IC_{50} c-src = 2.7 nM. IC_{50} c-yes = 4 nM. IC_{50} c-fyn = 10 nM.

1.2.5 Effects of saracatinib on Osteoclast Activity

Bone remodeling is the key metabolic process that regulates bone structure, and osteoclasts are the predominant mediators of this function (28). Most adult skeletal diseases, such as osteoporosis and cancers that metastasize to bone, are due to excessive osteoclastic activity and increased bone resorption. The important role of c-src in osteoclasts was identified when Src knockout mice were generated (29). These mice developed osteopetrosis (excessive bone density), secondary to a severe deficiency in osteoclast function. Although they had increased numbers of osteoclasts, they remained in an inactive form due to the failure to form ruffled borders. Src is activated in osteoclasts in response to integrin binding and allows signaling to proceed through RANK (receptor activator of nuclear factor κB). This results in intracellular cytoskeletal reorganization, the formation of a ruffled border, and activation of the osteoclast.

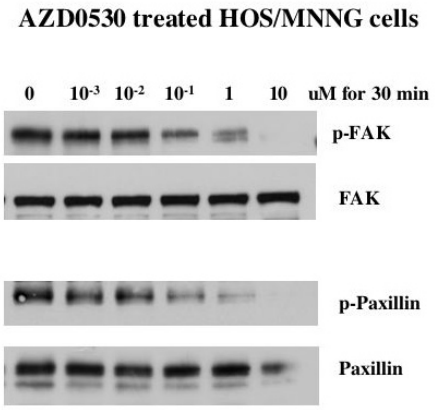
The effect of saracatinib on osteoclast activity was tested in a series of in vitro experiments. Treatment with saracatinib reduced the resorption area and the number of resorption pits when isolated rabbit osteoclasts were applied to bone slices (30). In addition, saracatinib inhibited calcium release from pre-labeled neonatal mouse calvariae in a dose-dependent manner (30). Both of these results strongly suggested that saracatinib is a potent inhibitor of osteoclast-mediated bone resorption.

In healthy adult volunteers, once daily treatment with saracatinib for 10-14 days resulted in a significant, dose-dependent reduction in serum beta-CTx (C-terminal telopeptide), serum TRAP 5b (tartrate-resistant acid phosphatase) and urinary NTx/creatinine (N-telopeptide/creatinine) (31). Beta-CTx and NTx are specific resorption markers for degradation of type I bone collagen by osteoclasts. The TRAP 5b isoform is specific to osteoclasts and is required in activated osteoclasts. The effect was evident as early as one day after the start of dosing and up to 24 days after the cessation of dosing. Similar results, with a trend towards dose-dependence, were seen in patients with advanced cancer who had received saracatinib (32). Taken together, these data demonstrate that saracatinib inhibits osteoclast activity in a dose-dependent manner, thereby proving mechanism of action.

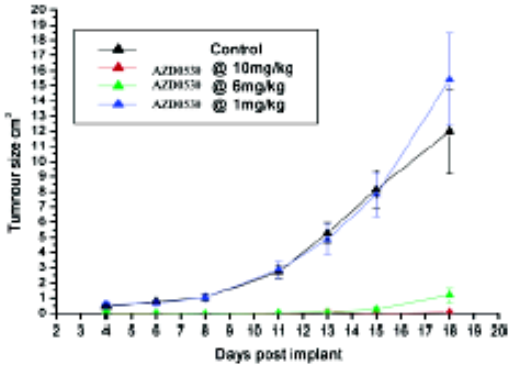
1.2.6 Activity of Saracatinib in Pre-Clinical Studies

Preliminary studies by Dr. Chand Khanna have utilized two metastatic osteosarcoma cell lines (20). K7M2 is a murine cell line and MNNG/HOS is a chemically transformed variant of the human osteosarcoma cell line HOS. Treatment of either of these osteosarcoma cell lines with saracatinib did not lead to changes in cell proliferation in vitro as determined by MTT assays. This is similar to results found in breast, colon, lung and prostate tumor cell lines (33). However, treatment of both murine and human osteosarcoma cell lines with saracatinib led to inhibition of tumor cell migration as determine by a wound-healing assay and migration through a porous membrane. Again, this effect is in concordance with data obtained using MDA-MB231 and MCF-7 breast cancer cell lines (33).

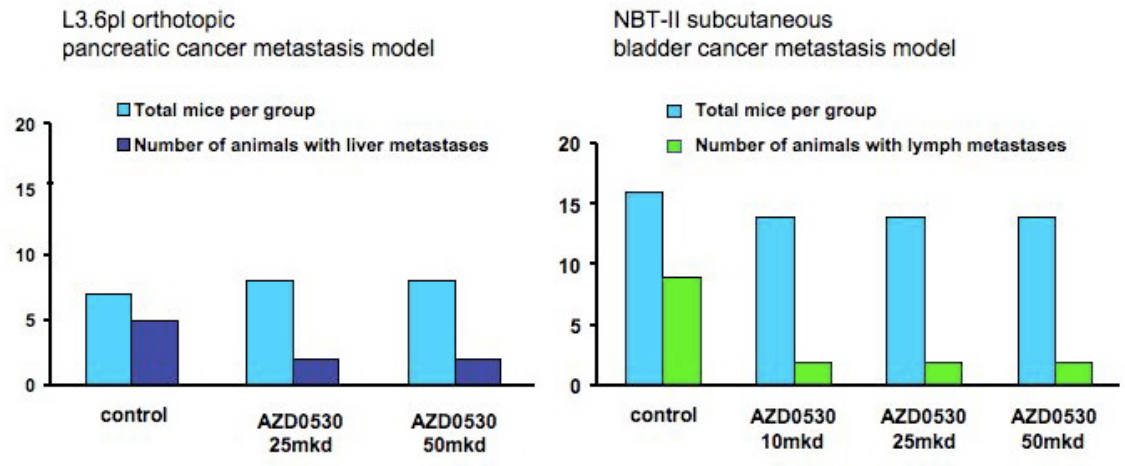
The photograph on the right demonstrates that treatment of osteosarcoma cell lines with saracatinib led to a marked decrease in phosphorylation levels of both Focal Adhesion Kinase (FAK) and Paxillin. This occurred most markedly at a concentration of 10 uM, but even as low as 0.1 uM, in MNNG/HOS cells. A similar result was obtained with K7M2 cells. The results of immunohistochemistry (IHC) studies using phospho-FAK and phospho-paxillin are pending. However, marked decrease in phospho-paxillin has been detected by IHC in Calu-6 human lung cancer xenografts following a single dose of saracatinib (33).



Many pre-clinical in vivo studies point to the ability of saracatinib to inhibit primary tumor growth. NIH3T3 fibroblasts that overexpress a constitutively active human c-src construct, form primary tumors in athymic mice following subcutaneous implantation. Mice that were treated with saracatinib (6 mg/kg) by once daily gavage had >95% inhibition of tumor volume and tumor weight after 18 days of treatment (27). Mice treated with saracatinib at a slightly higher dose of 10 mg/kg had almost complete inhibition of tumor growth, depicted in the figure on the right.



Shown below are results demonstrating reduced metastases in an orthotopic pancreatic cancer model and a subcutaneous bladder cancer model. In both cases, there was marked decrease in the number of animals that developed metastatic disease when treated with saracatinib (33).



In total, these findings suggest that saracatinib markedly inhibits Src substrates in vitro, by altering pathways unrelated to proliferation. The anti-metastatic activity of saracatinib may be linked to its anti-migratory property seen in vitro. These features make saracatinib a very attractive biological agent to move forward in advanced clinical trials.

1.2.7 Clinical Pharmacokinetics of Saracatinib

The initial evaluation of saracatinib was carried out in healthy male volunteers (33). Following single oral doses between 2.5 mg and 1000 mg, saracatinib was relatively slowly absorbed (median tmax of 5 hours), extensively distributed outside the blood, and cleared moderately slowly. After Cmax, the disposition was biphasic with a terminal phase from 24 hours after dosing, having a $t_{1/2}$ of approximately 40 hours. The increase in exposure with the dose tended to be slightly greater than proportional. Across the dose range, a doubling of the dose led to a 30% higher than proportional increase in both Cmax and the area under the curve (AUC).

Saracatinib, given at daily doses from 60 to 250 mg/day, resulted in steady state levels after 10 to 12 days. At steady state, the plasma concentrations of saracatinib in an individual remained within a 2-3 fold range. The degree of accumulation (6-8 fold) was greater, and the time to steady state was longer, than predicted from the single dose pharmacokinetics (PK). Also, at steady state, the exposure was greater than proportional to the dose. A doubling of the dose resulted in a 3-fold increase in exposure to saracatinib. The average urinary recovery of saracatinib at steady state ranged from 8% to 14% across the dose groups.

The most likely reason for these pharmacokinetic changes with dose and time appeared to be increased bioavailability. This may be the result of saturation of efflux transporters or metabolizing enzymes. However, the possibility of a reduction in systemic clearance of saracatinib cannot be ruled out. These changes in the pharmacokinetics of saracatinib were observed as a result of the relatively wide dose ranges employed in the studies. Non-proportionality is easier to observe when a wide range of doses is employed. It is

unlikely that non-proportionality would be relevant for a patient taking a fixed dose of saracatinib.

In patients with advanced cancer, the pharmacokinetic profile of saracatinib, at doses between 50 mg and 250 mg, was generally similar to that observed in healthy volunteers. However, there was a tendency for patients to have slightly higher plasma concentrations. Exposure to saracatinib increased in an apparently dose-proportional manner after a single dose. Accumulation with once daily dosing was 4-6 fold across the dose levels. Steady state was achieved after 10 days, at which point the increase in exposure with the dose was proportional, up to the 175mg dose. The table below summarizes the results of this two-part study.

	Demographics and drug exposure				Steady State Pharmacokinetics (geometric mean)			
Dose (mg/day)	N	Time on Treatment (days)	Age (years)	Weight (kg)	N	Css,max (ng/mL)	AUCss (ng.h/mL)	CL/F (L/h)
Part B								
50	16	9-51	40-72	49-92	11	95	1597	31.3
125	16	22-210	42-75	34-88	15	247	3691	34
175	19	7-45	20-71	35-110	16	444	7588	23.2
Part A								
175	5	11-65	49-73	37-98	4	484	7911	22.2
250	7	6-61	23-70	52-88	2	493, 1090	9070, 198000	28.7, 12.6

N	Number of patients providing data for the particular endpoint
Css, max	Maximum plasma concentrations at steady state
AUCss	Area under the plasma concentration curve during the dosing interval at steady state
CL/F	Oral drug clearance

To determine saracatinib levels in tumors, tissue was homogenized, subjected to solvent extraction and analyzed by high performance liquid chromatography with mass spectrometric detection. At steady state, the concentrations of saracatinib in tumor tissue were approximately 70 times greater than in plasma, in human patients.

Saracatinib is an inhibitor of CYP3A4 in vitro. The relevance of this finding was examined in a clinical study using midazolam, a recognized substrate of CYP3A4. Saracatinib, at a dose of 125 mg/day, resulted in an average increase in the plasma AUC of midazolam of 2.7-fold. This observation classifies saracatinib as a moderate inhibitor of CYP3A4 and suggests the possibility that it could affect the exposure and effects of co-administered drugs. Medications that are contra-indicated (see Section 4.5) and recommendations regarding the use of drugs known to be sensitive to inhibition of this enzyme are included in this protocol (see Section 4.6). A list of contra-indicated foods is also provided (see Section 4.7).

The early studies with saracatinib were conducted using a provisional tablet formulation (the "Phase I" formulation). The performance of a tablet with less mannitol that is more resistant to physical damage (the "Phase II" tablet) was examined in a clinical study. Based on the pharmacokinetic profile, the new tablet is considered interchangeable with the saracatinib "Phase I" formulation. Thus, the data generated with the early formulation is of direct relevance. The effect of food on the bioavailability of saracatinib in the "Phase II" tablet was examined in the same study. These results led to the recommendation that saracatinib can be taken with or without food. The "Phase II" tablet will be used in this study.

1.2.8 Phase I Trials of Saracatinib

Saracatinib has been evaluated in healthy volunteers and patients with advanced cancer. Single oral doses of up to 1000 mg and multiple, oral daily doses of up to 500 mg have been administered.

The results of a single-dose, ascending study of saracatinib in healthy adult volunteers showed that doses between 2.5 mg to 500 mg were well tolerated (33). However, at 1000 mg, patients experienced severe vomiting and diarrhea. Multiple daily doses for 14 days were also well tolerated from 60 mg to 185 mg. The next dose, 250 mg, was also tolerated. However, adverse effects (influenza-like syndrome and diarrhea) were more frequent and severe at this dose level. Dose escalation was stopped and the maximum tolerated dose (MTD) was defined as 250 mg. Other side effects observed were as follows: acneform rash (125 mg), loose stools and mild diarrhea (185 mg), muscular shoulder pain (185 mg), mild flu-like symptoms (185 mg) and elevated C-reactive protein (CRP) (250 mg).

A monotherapy study has also been performed in 81 patients with advanced solid malignancies refractory to or unsuitable for standard therapy, or for whom no standard therapy existed. In this study, patients received saracatinib continuously, every day, without any breaks between cycles. This was a two-part, Phase 1, open-label, multi-center study. Part A had the aim of establishing the appropriate dose of saracatinib monotherapy for use in future studies of patients with advanced solid malignancies. Part B had the aim of evaluating the effect of saracatinib on c-Src kinase activity in human cancers over a range of doses. In Part A, 30 patients received daily doses of saracatinib from 60 mg to 250 mg. The duration of therapy ranged from 6 to 150 days, with a median of 23 days. Dose limiting toxicity (DLT) was defined using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3 (http://ctep.cancer.gov/forms/CTCAEv3.pdf). Part A defined the MTD in the patient population who participated as 175 mg daily. DLTs at 250 mg were as follows: grade 5 septic shock with grade 3 renal failure, grade 3 fatigue and grade 3 leucopenia. DLTs at 200 mg were grade 3 febrile neutropenia and grade 3 dyspnea. In Part B, 51 patients were randomized in a parallel-group cohort-expansion phase of three doses of saracatinib previously declared tolerable in Part A. In Part B of the study, 16 patients received 50 mg saracatinib daily, 16 patients received 125 mg saracatinib daily and 19 patients received 175 mg saracatinib daily. The duration of therapy ranged from 7 to 210 days, with a median of 25 days.

The patient who developed grade 5 septic shock was a 55 year old female, who had been heavily pre-treated for breast adenocarcinoma, metastatic to multiple sites. This patient developed renal failure (oligouria, increased creatinine, maximum CTCAEv3 grade 2) on day 9 of treatment with saracatinib at 250 mg. On day 12 of treatment, she developed pyrexia and septic shock (maximum CTCAEv3 grade 4) and saracatinib was discontinued. On day 13, the renal failure worsened to grade 3. Despite antibiotics, the patient deteriorated and died 4 days following treatment discontinuation (septic shock worsening to grade 5). The investigator felt that the renal failure was causally related to a study procedure (administration of intravenous radiological contrast medium and dehydration) and was not causally related to treatment with saracatinib. AstraZeneca felt that the relationship to treatment to saracatinib could not be excluded.

There were two additional pulmonary serious adverse events (SAEs) in this trial. One patient had rapidly progressive colorectal cancer with extensive metastatic burden in the lungs and liver. The patient had been taking saracatinib at 200 mg. On day 18, the patient presented with acute onset dyspnea, and had an arterial oxygen saturation of 70% on room air. Despite the use of oxygen, morphine and corticosteroids, this patient died on the same day. At autopsy, histopathology demonstrated diffuse alveolar damage, consistent with acute respiratory distress syndrome. In the second case, a minimally symptomatic patient, with locally advanced malignant melanoma and metastases to the lung pleura, had diffuse pulmonary findings on a planned follow-up CT scan following 21 days of treatment with saracatinib at 175 mg once daily. These findings resolved following discontinuation of saracatinib and the start of steroid therapy.

Two other pulmonary SAEs have been recorded in subsequent trials of saracatinib in combination with chemotherapy. The third patient had been taking 175 mg of saracatinib daily and paclitaxil weekly for approximately 4 months for metastatic gastric adenocarcinoma. She had a complex treatment history that included recurrent urinary tract infections. She developed cough and dyspnea and a thoracic CT scan revealed patchy ground glass opacities in all lobes of the lung, at which time saracatinib was stopped. Her symptoms progressed despite treatment with steroids and antibiotics and the patient died 10 days later. The fourth patient was receiving 175 mg of saracatinib daily and gemcitabine on days 1, 8 and 15 for metastatic pancreatic cancer. During cycle 2, worsening of flu-like symptoms prompted a thoracic CT scan that revealed diffuse ground glass opacities consistent with interstitial lung disease. Both the symptoms and the radiographic findings resolved after saracatinib was stopped. In all four cases, the pulmonic events were considered to be possibly related to treatment with saracatinib, even though it was not possible to establish a clear etiology. The common finding of diffuse interstitial lung changes in these patients has prompted early monitoring to detect these changes using thoracic CT scans (see Sections 2.2, 3.4 and 4.4).

Other events, irrespective of reported causality, that have been seen in greater than 10% of the study population (healthy volunteers and patients with advanced cancer) included anemia, neutropenia, fatigue, pyrexia, dyspnea, anorexia, nausea, diarrhea, vomiting and constipation. The most common treatment-related adverse events reported in the Phase I population of patients with advanced caner were: anemia, anorexia, nausea, diarrhea and vomiting. Decreases in total white cell counts and platelet counts, and increases in serum

creatinine (within the normal range) have also been seen in some healthy volunteers and patients, and are described below.

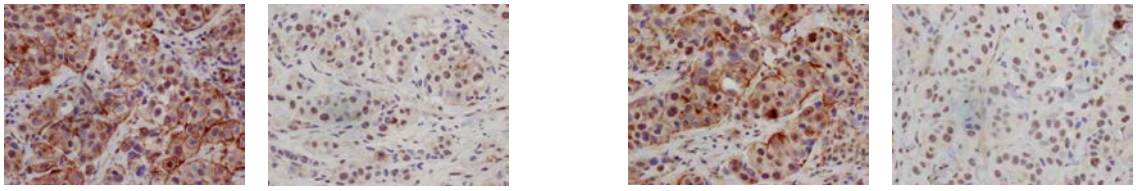
A dose related effect of saracatinib on neutrophil and platelet counts in healthy volunteers has been identified. These effects are seen following multiple dosing (up to 14 days has been evaluated in healthy volunteer studies) but were not apparent following single dose administrations of up to 1000 mg. In all cases within healthy volunteers, neutrophil and platelets counts returned to near baseline values within a period of time that drug levels may be considered pharmacologically relevant (within 3 days, $t_{1/2}$ of saracatinib is 40 hours) or during therapy. Moderate declines in neutrophil counts were also observed in patients with advanced cancer, with a nadir at 10 to 25 days of continuous saracatinib treatment. However, the majority of these declines were not clinically significant, with counts recovering without the need for dose interruption or the addition of supportive care.

Declines in hemoglobin levels were observed in patients with advanced cancer. The majority of these declines were of little clinical significance with counts recovering without the need for dose interruption or dose reduction. These declines occurred in patients with multiple confounding factors (treatment with multiple cytotoxic agents, administration of non-steroidal anti-inflammatory drugs for analgesia, previous history of peptic ulcer disease, prior blood transfusions to permit entry into the study), thus making evaluation difficult. No overt effect on platelet values has been identified in patients with advanced cancer. No evidence of cumulative hematological toxicity has been observed in either healthy volunteers or patients with advanced cancer.

Moderate rises in plasma creatinine by 5% to 30% have been observed in both healthy volunteers and patients with malignancies. These rises appear to be dose related and occur after a single dose, before rapidly reversing. With multiple dosing, the rise occurs rapidly following commencement of saracatinib, reaches a plateau and falls rapidly when dosing is stopped. No patient or healthy volunteer experienced an initial rise in serum creatinine that exceeded the upper limit of normal, and no clinical sequelae have been apparent. A study of renal function in healthy volunteers who have received up to 14 days continuous saracatinib dosing has been undertaken with the aim of clarifying the mechanism underlying the observed moderate and reversible rise in serum creatinine. The report for this study is currently being prepared. However, it is clear that saracatinib does not affect glomerular filtration rate (GFR), and that increases in serum creatinine consequent to saracatinib treatment are the result of inhibition of tubular secretion of creatinine. No evidence of tubular damage has been observed and no cumulative effect on renal function or changes in serum creatinine have been recorded. Such changes in serum creatinine have been observed with a number of medications, including cimetidine and trimethoprim (34).

Evaluations of saracatinib monotherapy in healthy volunteers and patients with advanced cancer have, therefore, demonstrated that dosing of saracatinib is associated with a manageable safety and tolerability profile, which in patients with advanced cancer is generally consistent with the underlying disease state.

In addition, examination of tumor samples from patients in Phase I trials, before and after the initiation of saracatinib, have shown decreases in phosphorylation of the downstream targets of Src, namely FAK and paxillin. Shown below are immunohistochemistry results in a patient with breast carcinoma, one day prior to, and 28 days after, treatment with saracatinib at 125mg (21).



Day -1 Day 28 Day -1 Day 28

p-FAK p-paxillin

To date, no formal analysis of the efficacy evaluations of saracatinib have been performed. In the Phase 1 multiple ascending dose and cohort expansion study conducted in 81 patients with advanced cancer, 11 patients experienced a best objective response of stable disease, with 11 others having unconfirmed stable disease. There were no complete responses or confirmed partial responses. Thirteen out of 81 (16%) patients who participated in the Phase 1 study received saracatinib therapy for over 12 weeks.

1.2.9 Rationale for the Use of Saracatinib in Recurrent Osteosarcoma

There is a large body of in vitro data showing Src plays an important role in the motility of osteosarcoma cells, a function that can be abrogated by the use of Src inhibitors. More importantly, Src and other genes that are involved in the Src pathway are activated in 95% of patients with osteosarcoma. These data suggest that saracatinib represents a promising candidate for the treatment of patients with recurrence of osteosarcoma.

We propose to utilize a newly described type of study, coined a Phase II.5 study (35). Phase II.5 studies examine outcome differences using a one-sided 0.10 alpha level significance test, rather than the traditional value of 0.05. The benefits of this type of study include enrollment of a fewer number of patients, which is important since patients with recurrent osteosarcoma are rare. In addition, it is a randomized, placebo-controlled trial, thus precluding the need to compare to historical controls, which is important since patients with recurrent osteosarcoma have previously received many different treatment modalities. The purpose of this design is to provide a sufficiently large, controlled, comparative evaluation to determine whether a sufficient effect is noted. Although the results are not definitive, if merited, they can then be used to estimate the parameters to design a definitive subsequent trial.

The trial objective is to perform a randomized, double-blinded, placebo-controlled study to evaluate the addition of saracatinib to pulmonary metastasectomy, versus placebo and pulmonary metastasectomy, in patients with relapsed osteosarcoma, localized to the lung. Currently, patients who achieve a surgical second remission have a progression free survival rate of 33% at two years and an overall survival rate of 45% at three years. An important caveat to this statement is that these patients have received a multitude of

different treatments, including surgery alone, and/or radiation, and/or chemotherapy, and/or high dose chemotherapy with stem cell rescue. Therefore, historical data do not give a true indication of actual survival rates. This study will try to determine whether patients who receive saracatinib will experience a 60% relative increase in progression free survival. Secondary objectives will determine whether patients who receive saracatinib will experience a 56% relative increase in overall survival and an increase in the time to treatment failure. Any adverse event, including toxicity, disease progression and death, that result in discontinuation of either saracatinib or placebo will be considered a treatment failure. The randomized nature of this study will allow us to determine the actual survival rates in these two cohorts, thereby assessing the efficacy of saracatinib in this patient population. Forty-four patients will need to be randomized in each arm, for a total of 88 patients, over a 48-month accrual period. Follow-up for survival of the last patient randomized must continue for an additional year. Patients who recur in the lung while on-study and who are thought to be amenable to complete surgical resection will be unblinded. Those who were receiving placebo will be given the option of undergoing surgical resection. If fully resected, they will be given the option to begin oral therapy with saracatinib.

2 Eligibility Assessment and Enrollment

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

Patients who have recurrence of osteosarcoma, localized to the lungs, who have had complete surgical removal of all lung nodules, are eligible for enrollment.

OR

Patients with suspected recurrence of osteosarcoma but have not had surgery are eligible for enrollment but will not be randomized until inclusion criteria (a) and exclusion criteria (b) are confirmed after surgery. If these are not confirmed, patient will be considered a screen failure and will not be randomized.

Other inclusion criteria are as follows:

a. Histological diagnosis of osteosarcoma of the recurrent sample (histology types must be osteoblastic, chondroblastic, fibroblastic or telangiectatic). For patients enrolled prior to surgery, this criterion can be confirmed after consent, enrollment and surgical resection.
b. Recurrence of osteosarcoma in the lung following standard chemotherapy including: adriamycin, cisplatin, ifosphamide and methotrexate (or provide justification why any of these agents were not received, for example, previous toxicity with methotrexate, or methotrexate not routinely given for adult patients)
c. Age $\geq$15 and <75 years of age
d. Weight $\geq$34 kg
e. ECOG performance score of 0, 1 or 2 (0 = asymptomatic, 1 = symptomatic but fully ambulatory, 2 = symptomatic in bed <50% of the day)
f. Adequate bone marrow function (ANC $\geq$1500/uL, Hb $\geq$9.0 g/dL, platelets $\geq$100,000/uL)
g. Adequate renal function (serum creatinine $\leq$1.5 or a creatinine clearance $\geq$50 mL/min/1.73m^2)
h. Adequate hepatic function (ALT/AST $\leq$2.5X normal, total bilirubin $\leq$2 mg/dl with the exception of patients with Gilbert's syndrome)
i. Adequate cardiac function (ECHO or MUGA with shortening fraction $\geq$27% or ejection fraction $\geq$45%) and (EKG with QTc $\leq$480 msec)
j. Negative pregnancy test for women of childbearing potential, $\leq$7 days prior to enrollment, and the willingness to use an acceptable method of contraception during participation in the study and for 3 months after the last dose

k. Randomization must occur ≤6 weeks after complete surgical resection of all tumor nodules
l. Informed consent: all patients, or their legal guardian if the patient is less than 18 years of age, must sign a document of informed consent indicating their awareness of the investigational nature and the risks of this study

2.1.2 Exclusion Criteria

a. Presence of metastatic disease in other locations in addition to the lung
b. Extensive disruption of the lung pleura by tumor. For patients enrolled prior to surgery, this criterion can be confirmed after consent, enrollment and surgical resection. This does not include solitary nodules that involve the lung pleura, but that have been completely resected, with no evidence of additional pleural involvement.
c. Paget's disease
d. Current use, or previous use within the specified time period, of medications that are potent inducers, inhibitors or substrates of CYP3A4, (see Section 4.5)
e. Known hypersensitivity to other Src/Abl non-receptor kinase inhibitors
f. Any evidence of interstitial lung disease (bilateral, diffuse, parenchymal lung disease)
g. Any concurrent condition which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol. These include conditions that are severe and/or inadequately uncontrolled, such as severe or worsening hepatic, respiratory and cardiac impairment.
h. Myocardial infarction within one year prior to study entry
i. Bleeding diathesis, resulting in symptomatic bleeding
j. Pregnant women or breast-feeding or nursing women
k. Any agent (chemotherapy, biological or investigational) administered ≤ 28 days prior to enrollment
l. Unresolved toxicity ≥ CTCAEv3 grade 2 (except alopecia) from previous agents

The reasoning for the above criteria is that patients who meet exclusion criteria a-c have an extremely poor five-year survival rate (3). Since some patients will meet one of the above criteria, it is possible that a true survival advantage with adjuvant saracatinib treatment may go undetected if the above patients are included.

2.2 Screening

For patients who are enrolled prior to surgery, if there is a significant change in a patient health status post-operatively, appropriate screening studies should be repeated based on the judgment of the treating investigator.

- History and Physical Examination
  - vital signs, weight, height, ECOG score

- Laboratory Studies (within 7 days prior to enrollment)
  - urine or serum pregnancy test (for females of childbearing potential)

- Laboratory Studies (within 14 days prior to enrollment)
  - white blood cell count with differential
  - hemoglobin and hematocrit
  - platelet count
  - prothrombin time, partial thrombin time, INR
  - sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose
  - calcium, magnesium, phosphorus
  - ALT, AST, total bilirubin, direct bilirubin
  - alkaline phosphatase, lactate dehydrogenase, total protein, albumin
  - urinalysis
  - urine or serum pregnancy test (for females of childbearing potential)

- Functional Studies (within 14 days prior to enrollment)
  - EKG

- Radiographic Studies (within 6 weeks prior to definitive resection or within 6 weeks prior to randomization)
  - Thoracic CT scan with contrast (unless patient cannot tolerate contrast) */**
  - Bone scan **

- Functional Studies (within 28 days prior to enrollment)
  - echocardiogram or MUGA
  - creatinine clearance (if serum creatinine is >1.5)

* The thoracic CT scan must be performed at a slice thickness of 5 mm or less. If there is any suspicion of interstitial lung disease, the patient must undergo high-resolution CT imaging to exclude interstitial lung disease. Any evidence of interstitial lung disease will make the patient ineligible for the study (see Exclusion Criteria in Section 2.1.2.f). The suggested parameters for the high-resolution thoracic CT scan are as follows: position (supine), slice thickness (≤1.25 mm), slice spacing (10 mm), start location (10 mm below the apices), end location (10 mm above the costophrenic angles).

** There will be instances when patients have very small indeterminate nodules on the CT scan. Sometimes it will be difficult to determine if these are tumor nodules or not. For the purposes of this protocol, the oncologist, radiologist and surgeon will have to use their best judgment to decide if the patient is fully resected of tumor. The same applies for nonspecific uptake on bone scans.

2.3 Patient Enrollment

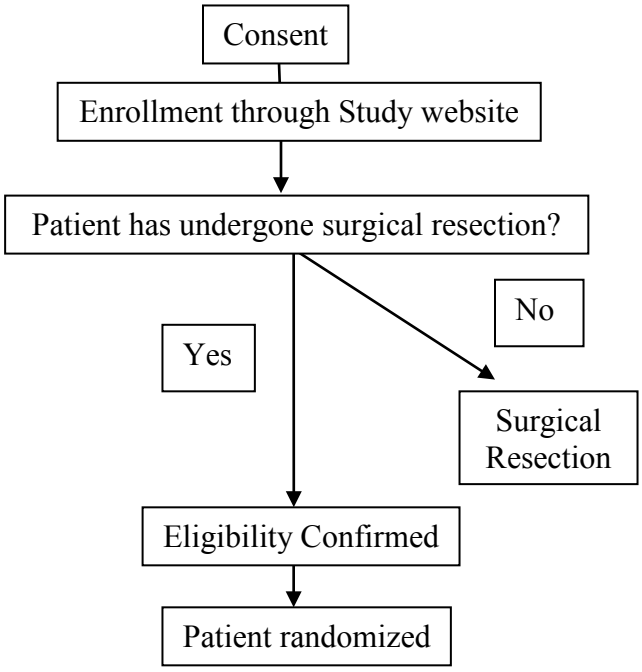
A signed informed consent document will be obtained prior to entry onto the study. Following consent, patient information is entered in the eCRF database. All patients must have histological verification of recurrent osteosarcoma in the lung prior to randomization. A copy of the pathology report documenting histologic confirmation should be sent to the SARC RPM prior to randomization.

Enrollment will be centrally managed by the trial coordinating center, SARC. Patient data will be entered electronically by the participating institutions through the study website:

https://velos.med.umich.edu/eres/jsp/ereslogin.jsp

Each patient will be assigned a patient identification number automatically following enrollment. Patients can be enrolled at any time of the day, any day of the week, via the website.

Once the patient has undergone complete surgical resection and the institutional PI determines that all of the criteria for inclusion have been met per protocol Section 2.1, the eligibility CRF will be completed in the database. The patient can then be randomized.



Patients will be registered and then stratified based on the number of recurrences (FIRST versus SECOND versus THIRD or MORE) and the number of recurrent nodules (ONE or TWO versus THREE or MORE).

SARC will possess separate randomization sheets for each stratum. Patient treatment assignment will be kept confidential and will not be shared with the treating physician(s) or any other site team staff involved in the care of the patient, except in the event of a medical emergency where unblinding is necessary to ensure patient safety (See Operation Manual for details), or at the time of recurrence if the recurrence is in the lung. (See Section 7.4.2).

Any questions regarding eligibility or the randomization process can be addressed to the SARC Operations Office:

SARC Research Project Manager
24 Frank Lloyd Wright Dr.
PO Box 406
Lobby A, 3rd Floor, Suite 3100
Ann Arbor MI, 48105
Phone: 734-930-7600
Fax: 734-930-7557
Email: sarc@sarctrials.org

SARC, the study Principal Investigator and the Principal Investigators at each participating institution will have access to this website to review data regarding this clinical trial.

For patients at the National Cancer Institute, in addition to the required enrollment procedure described above, the following are also required prior to initiation of therapy. Patients must register with the NCI Central Registration Office (CRO, phone number 301-402-1732, fax number 301-480-0707). A completed eligibility checklist and a signed consent form must be on file prior to entry onto the study. Research nurses in the Pediatric Oncology Branch will facilitate this process.

3 Study Implementation

3.1 Study Design

The primary objective of this study is to determine whether pulmonary metastasectomy and treatment with saracatinib, versus pulmonary metastasectomy and treatment with placebo, results in an increase in progression free survival. A secondary objective is to determine whether pulmonary metastasectomy and treatment with saracatinib, versus pulmonary metastasectomy and treatment with placebo, results in an increase in overall survival. Patients will be eligible for the study following the histological verification of recurrent osteosarcoma. Patients will be stratified based on the number of recurrences (FIRST versus SECOND versus THIRD or MORE) and the number of recurrent nodules (ONE or TWO versus THREE or MORE).

Randomization will occur following complete resection of all lung nodules and the histological verification of recurrent osteosarcoma.

Patients who are randomized to the saracatinib arm will receive saracatinib, 175 mg, orally, once daily, for a 28-day cycle, with no breaks between cycles. The total duration of treatment with saracatinib will be **thirteen 28-day cycles** (364 days total). Patients will receive one 125 mg tablet (9.5 mm diameter) and one 50 mg tablet (7 mm diameter).

Patients who are randomized to the placebo arm will receive placebo, orally, once daily, for a 28-day cycle, with no breaks between cycles. The total duration of treatment with placebo will be **thirteen 28-day cycles** (364 days total). Patients will receive one 9.5 mm tablet and one 7 mm tablet. These tablets will be indistinguishable from saracatinib.

Patients who recur in the lung while on-study and who are thought to be completely resectable will be unblinded. Those patients who were receiving placebo will be offered the opportunity to undergo additional surgical resection, followed by treatment with Saracatinib. If fully resected, they will then begin oral therapy with saracatinib. Saracatinib will be administered as a once daily, oral dose of 175 mg, for a 28-day cycle, with no breaks between cycles. The duration of treatment with saracatinib will be thirteen 28-daycycles (364 days total).

Patients will be followed for the duration that this study is open. If accrual rates proceed as projected, the total duration of this study will be six years.

3.2 Treatment Administration

3.2.1 Administration and Commencement of Oral Therapy

Patients will receive two bottles that contain either saracatinib or placebo. One bottle will contain 125 mg tablets (or a similar placebo tablet) and the other bottle will contain 50 mg tablets (or a similar placebo tablet).

Patients will take one 125 mg tablet and one 50 mg tablet, once every day, for the duration of the trial. The tablets can be taken at any time of the day, with or without food. See Sections 4.5, 4.6 and 4.7 for a list of medications and food products that should be avoided while on study. Patients will also be asked to keep a daily diary of the time and dose of the drug ingested. (see Appendix B).

There are three possibilities for disease burden in our study population. First: patients who had very few nodules at recurrence, may have had resection of all of the nodules at the time of the biopsy. Second: patients who had biopsy of one nodule and require one additional surgery for complete resection of any remaining nodules. Third: patients who had biopsy of one nodule who have bilateral disease that requires a staged thorocotomy to obtain surgical remission. The timing of enrollment, randomization and commencement of oral therapy, with either saracatinib or placebo, is detailed below for all three of these possibilities.

3.2.2 Distinction between Enrollment and Randomization

This protocol distinguishes between enrollment and randomization. Patients with suspected or confirmed recurrence of osteosarcoma localized to the lung will be enrolled in the study following informed consent. This allows for the collection of tumor samples (for patients with suspected recurrence of osteosarcoma who have not yet undergone surgical resection), and their subsequent examination, which is an important objective in this protocol. However, randomization will not occur until the patient has had complete surgical resection of all recurrent tumor nodules.

There will be several patients who are deemed fully resectable based on a CT scan. In a few cases, at the time of definitive surgery, the surgeon will find more tumor burden than was expected. At that point, if total tumor resection is not possible, the procedure may be stopped due to high morbidity risk.

Patients who have been enrolled in the study, but subsequently are not fully resected of tumor will not be randomized and therefore, they will not be included in any efficacy or toxicity studies. However, their tumor samples can still be analyzed (see Section 3.6.1 and Operations Manual). These patients will be followed for overall survival only. Their primary oncologist will manage their medical care. The continued monitoring for overall survival on this study does not preclude them from any other trials or treatments that these patients will undergo.

3.2.3 Regimen for Patients Who Have Been Fully Resected

Patients who had resection of all tumor nodules at the time of their biopsy will be eligible for randomization after definitive histological diagnosis of recurrent osteosarcoma. Once the treating physician decides that the patient is able to tolerate oral therapy, the patient will be randomized to either the saracatinib arm or the placebo arm. Following randomization, tablets will be dispensed by the hospital pharmacy.

Cycle 1 Day 1 must commence no later than 6 weeks after the time of the definitive mestastasectomy. Patients who cannot commence oral therapy within these time frames will be removed from the study.

3.2.4 Regimen for Patients Who Require Definitive Resection

Patients who underwent biopsy of a nodule but have remaining nodules will be eligible for randomization after definitive histological diagnosis of recurrent osteosarcoma. These patients should undergo definitive pulmonary metastasectomy as soon as possible. Following definitive surgical resection of all metastatic nodules, and once the treating physician decides that the patient is able to tolerate oral therapy, the patient will be randomized to either the saracatinib arm or the placebo arm. Following randomization, tablets will be dispensed by the hospital pharmacy.

Cycle 1 Day 1 must commence no later than 6 weeks after the time of the definitive metastasectomy. Patients who cannot commence oral therapy within these time frames will be removed from the study.

Biological studies to determine the etiology of recurrent osteosarcoma are an important component of this protocol. Prior to metastasectomy, every attempt should be made to insure that the tumor sample is handled properly, so that all of the biological studies can be performed (see Sections 3.6.1 and Operations Manual).

3.2.5 Regimen for Patients Who Require Staged Thoracotomies

Patients with extensive bilateral disease that requires staged thoracotomies will be eligible for enrollment. These patients should undergo resection of one side as soon as possible. Resection of the other side should be performed at a time determined by the surgical oncologist. Following definitive surgical resection of all metastatic nodules, histologic confirmation of osteosarcoma, and once the treating physician decides that the patient is able to tolerate oral therapy, the patient will be randomized to either the saracatinib arm or the placebo arm. Following randomization, tablets will be dispensed by the hospital pharmacy.

Cycle 1 Day 1 must commence no later than 6 weeks after the time of the definitive metastasectomy. This will allow for the resolution of any complications that may arise as a result of the procedure, prior to administration of oral therapy. Patients who cannot commence oral therapy within these time frames will be removed from the study.

Biological studies to determine the etiology of recurrent osteosarcoma are an important component of this protocol. Prior to BOTH surgeries, every attempt should be made to insure that the tumor sample is handled properly, so that all of the biological studies can be performed (see Sections 3.6.1 and Operations Manual).

3.2.6 Cross-over Regimen for Patients Who Recur in the Lung While On-Study

Patients who recur in the lung while on study, and who are thought to be amenable to complete surgical resection of the recurrent tumor will be unblinded. Those patients who were receiving placebo will then have the option of undergoing surgical resection; if fully resected they will be given the option to begin oral therapy with Saracatinib.

Saracatinib will be administered as a once daily, oral dose of 175 mg, for a 28-day cycle, with no breaks between cycles. The duration of treatment with saracatinib will be thirteen 28-day cycles (364 days total). Cycle 1 Day 1 must commence no later than 6 weeks after the time of the definitive metastasectomy. Patients who cannot commence oral therapy within 6 weeks will be removed from the study.

Biological studies to determine the etiology of recurrent osteosarcoma are an important component of this protocol. Prior to metastasectomy, every attempt should be made to

insure that the tumor sample is handled properly, so that all of the biological studies can be performed (see Sections 3.6.1 and Operations Manual).

Patients who recur in locations other than the lung while on-study will be taken off study and will not be unblinded.

3.3 Treatment Modifications

3.3.1 Dose Modification Criteria

Dose reductions should be applied if any of the following toxicities occur

Hematological

- Any CTCAEv3 grade 4 hematological toxicity of any duration (With the exception of CTCAEv3 grade 4 neutropenia ≤6 days duration. For CTCAEv3 grade 4 neutropenia ≤6 days duration, oral therapy will be held until the neutropenia recovers to CTCAEv3 grade 1 or less, at which time oral therapy will resume at the same dose)

- Febrile neutropenia (CTCAEv3 grade 3 neutropenia with temperature ≥38.5°C or CTCAEv3 grade 4 neutropenia with temperature ≥38.0°C)

- CTCAEv3 grade ≥3 neutropenia requiring hospitalization

- CTCAEv3 grade ≥3 thrombocytopenia associated with non-traumatic bleeding (with the exception of patients on therapeutic anti-coagulation)

Non-Hematological

- Any CTCAEv3 grade ≥3, non-hematological toxicity (with the exception of alopecia, nausea and vomiting)

- CTCAEv3 grade ≥3, hypophosphatemia (see section 3.3.3 for modified dose reduction schema)

- CTCAEv3 grade ≥3 nausea or CTCAEv3 grade ≥3 vomiting, lasting >24 hours despite IV fluids, anti-emetic therapy and adequate supportive care

- Chronic CTCAEv3 grade 2 nausea or vomiting

In the event of any toxicity, of any grade, that the treating physician suspects is due to disease progression, re-evaluation of tumor status is indicated, irrespective of scheduled clinic visits.

3.3.2 Dose Reduction of Oral Therapy

If a patient experiences any of the toxicities defined in section 3.3.1, or another unacceptable toxicity occurs, and the investigator considers that the event is related to the study drug, oral therapy will be stopped for a maximum of 21 days, and supportive therapy will be administered as required. If the toxicity resolves or reverts to a CTCAEv3 grade 0 or grade 1 or to the baseline (pre-study) grade within 21 days of onset, oral therapy will be restarted at a lower dose as follows:

If a patient is currently taking 175 mg, the lower dose will be 125 mg.
If a patient is currently taking 125 mg, the lower dose will be 100 mg.

A maximum of two dose decreases, for any individual patient, can be made during the study period, down to the lowest dose of 100 mg of saracatinib or placebo.

If a patient experiences any of the toxicities defined in Section 3.3.1, or another unacceptable toxicity occurs, while taking 100 mg, then the patient must be withdrawn from the study. For all patients who experience any of the toxicities defined in Section 3.3.1, or another unacceptable toxicity occurs during the study, if the toxicity does not resolve to CTCAEv3 grade 0 or grade 1 or to the baseline (pre-study) grade within 21 days of onset, then the patient must be withdrawn from the study. Patients will continue to be monitored until the toxicity has resolved.

Patients will continue to be monitored for overall survival for the duration of the study. If patients have toxicity that requires their removal from the study prior to ascertainment of disease progression, then these patients will be considered treatment failures in the time to treatment failure analysis and the duration of total treatment will be included in the time to treatment failure. However, for the progression free survival analysis, withdrawals due to toxicity will be censored, as the subject has not progressed.

3.3.3 Dose Reduction of Oral Therapy for Hypophosphatemia

Hypophosphatemia may be encountered for reasons that are unrelated to the study drug, such as vitamin D deficiency. Prior to beginning oral therapy, treating physicians should obtain a full work-up to evaluate low or borderline low levels of phosphorus. In addition, additional time to allow hypophosphatemia to normalize will be allowed.

If a patient experiences CTCAEv3 grade 3 hypophosphatemia, dose reduction will occur as per section 3.3.2. However, oral therapy may be stopped for a maximum of 35 days, and supportive therapy will be administered as required. If the toxicity resolves or reverts to a CTCAEv3 grade 0 or grade 1 or to baseline (pre-study) grade within 35 days of onset, oral therapy will be restarted at a lower dose. If the toxicity does not resolve to CTCAEv3 grade 0 or grade 1 or to baseline within 35 days of onset, then the patient must be withdrawn from the study.

3.4 On Study Evaluations

Treatment with saracatinib or placebo will be given for **thirteen 28-day cycles (364 days)**. Patients will be required to return for routine follow-up visits as indicated in the chart below.

For patients enrolled on this study, evaluations must be administered at the study site for the pre-treatment evaluation and for the 3, 6, 9, and 13 cycle visits. For all other study evaluations (including specified follow up evaluations), the investigator may determine in the best interest of the patient that those evaluations may be safely conducted at a local, competent, referring oncologist's office. The institutional principal investigator is responsible for the timely and accurate reporting of data to the SARC Operations Center.

Treatment Evaluations (also available in table form, see Appendix A)

All treatment evaluations/procedures should be performed within a +/- 7 day window, with the exception of week 1 and week 3-4 which should be done within +/- 3 day window.

Pre-treatment	history, physical, vital signs, laboratory tests
Day 1	**BEGIN oral therapy of saracatinib or placebo**
Week 1	history, physical, vital signs, laboratory tests *
Week 3-4	history, physical, vital signs, laboratory tests * thoracic CT */**
Week 6-8	history, physical, vital signs, laboratory tests * thoracic CT */**
Week 9	history, physical, vital signs, laboratory tests *
3 months/Cycle 3	history, physical, vital signs, laboratory tests thoracic CT EKG ***
4 months/Cycle 4	history, physical, vital signs, laboratory tests *
5 months/Cycle 5	history, physical, vital signs, laboratory tests *
6 months/Cycle 6	history, physical, vital signs, laboratory tests thoracic CT
7 months/Cycle 7	history, physical, vital signs, laboratory tests *
8 months/Cycle 8	history, physical, vital signs, laboratory tests *
9 months/Cycle 9	history, physical, vital signs, laboratory tests thoracic CT
10 months/Cycle 10	history, physical, vital signs, laboratory tests *
11 months/Cycle 11	history, physical, vital signs, laboratory tests *
12 months/Cycle 12	history, physical, vital signs, laboratory tests
13 months/Cycle 13	perform thoracic CT and bone scan within 14 days after the last dose
	DISCONTINUE oral therapy of saracatinib or placebo after thirteen 28-day cycles (364 days of therapy) ****
15 months	history, physical, vital signs *
18 months	history, physical, vital signs, laboratory tests

	thoracic CT
21 months	history, physical, vital signs *
24 months	history, physical, vital signs, laboratory tests thoracic CT
30 months	history, physical, vital signs *
36 months	history, physical, vital signs, laboratory tests thoracic CT

Laboratory tests are as follows:

- white blood cell count with differential
- hemoglobin and hematocrit
- platelet count
- sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose
- calcium, magnesium, phosphorus
- ALT, AST, total bilirubin,
- alkaline phosphatase, lactate dehydrogenase, total protein, albumin

* At the discretion of the treating physician, these visits do not need to be performed at the study center. However, a document containing the interim history, physical examination, weight and height, vital signs, laboratory tests, and CT scan results when appropriate, must be sent to the treating physician at the study center as soon as they are available.

** The purpose of the two additional thoracic CT scans is to monitor for interstitial lung disease, which has been seen in 2% of patients taking saracatinib. If there is any suspicion of interstitial lung disease on any CT scan, the patient must undergo high-resolution CT imaging to exclude interstitial lung disease. Any evidence of interstitial lung disease will lead to removal of the patient from the study (defined in the Exclusion Criteria in Section 2.1.2.f). The suggested parameters for the high-resolution thoracic CT scan are as follows: position (supine), slice thickness (≤1.25 mm), slice spacing (10 mm), start location (10 mm below the apices), end location (10 mm above the costophrenic angles).

*** Previous studies have not demonstrated prolonged QTc intervals in patients treated with saracatinib. A 12-lead EKG should be obtained after the patient has rested in a supine position for at least five minutes. The treating physician should review the EKG. Any abnormality of clinical significance should result in medical management of the patient as clinically indicated. The abnormality should be reported as an adverse event or a serious adverse event (see Section 7.2).

**** Saracatinib or placebo will be discontinued after thirteen 28-day cycles (364 days) of therapy.

3.5 Concurrent Therapies

Chemotherapeutic agents, radiation therapy, immunotherapy or investigational anti-cancer agents cannot be administered to patients enrolled on this protocol. If these therapies are administered, the patient will be removed from the study.

3.5.1 Surgical Guidelines

Surgery will play an important role in the management of patients enrolled on this protocol. Only patients who have been fully resected, or who are deemed fully resectable, will be eligible to enroll. The surgical oncologist will determine the approach for resection. Oral therapy with saracatinib or placebo will begin following complete resection of all recurrent lung nodules. For patients with bilateral disease who require staged thoracotomies, oral therapy will begin only after the second thoracotomy and only if all nodules have been resected. Patients who recur in the lung while on study and who are thought to be amenable to complete surgical resection will be unblinded. Those patients who were receiving placebo may then have the option of undergoing surgical resection. If fully resected, they will be given the option to begin oral therapy with Saracatinib.

Biological studies to determine the etiology of recurrent osteosarcoma are an important component of this protocol. Prior to any surgery, every attempt should be made to insure that the tumor sample is handled properly, so that all of the studies can be performed (see Sections 3.6.1 and Operations Manual).

3.6 Biological Studies

All institutions will send fresh frozen tissue, a corresponding H+E slide, and a blood sample for microarray and sequencing analysis from biopsy and/or time of surgery for patients who have consented, if available (see Sections 3.6.1, 3.6.4, and Operations Manual). Other biological studies will be performed only at the NIH (see Sections 3.6.2 and 3.6.3).

The molecular changes that underlie tumorigenesis have been well studied in many tumor types due to the availability of tumor samples. For pediatric cancers such as leukemia and neuroblastoma, this has resulted in a dramatic improvement in overall survival and marked decrease in treatment related toxicities. The latter is a direct consequence of molecular studies that have resulted in the ability to stratify patients into high-risk, standard-risk and low-risk groups. Overall survival rates in osteosarcoma have also increased remarkably in the last 40 years. However, the identification of biological and genetic surrogates for prognosis, progression and metastasis has been lacking. One of the major reasons for this has been the overwhelming use of neo-adjuvant chemotherapy to treat patients. Initial biopsy samples are so small that the entire sample is usually needed for diagnosis. Samples taken at the time of definitive surgery are large. However, very few samples contain high numbers of viable tumor cells due to the effects of chemotherapy, and many times the sample consists only of a dense non-cellular stroma.

This has greatly hindered the ability to study molecular changes associated with osteosarcoma.

The tumor samples that we expect to analyze will form the largest collection of recurrent osteosarcoma patient samples that have not been subjected to any form of therapy. Many of the studies we have planned can only be performed if the sample is freshly frozen. We therefore request, that treating physicians use the guidelines in this protocol for sample preparation and shipping whenever possible (see Operations Manual).

3.6.1 Microarray Analysis

The expression pattern of genes in tumors can provide a wealth of knowledge, especially when they are tied to outcome data. Microarray analysis makes it possible to study the expression of tens of thousands of transcripts. This study will provide the opportunity to increase the biological data for patients with osteosarcoma. Specifically, the large number of untreated samples will make it easier to identify a gene signature to predict for recurrence of osteosarcoma. In addition, the outcome of patients, irrespective of whether they received saracatinib or placebo, will also be known. This allows for the possibility of determining an additional gene signature that predicts for survival. Understanding gene signatures using a large population will help elucidate the pathophysiology of recurrent osteosarcoma and may lead to improvements in the treatment of this disease.

In general, the methodology relies on preparation of RNA, followed by cDNA. Fluorescent labeling followed by hybridization to a DNA chip allows for quantitative scanning for hybridized complexes. The complexity and density of the microarray chips is increasing exponentially, as are the software programs used to analyze these large result files. Therefore, specifics of this experiment will not be addressed, since the technology may improve markedly prior to the point that samples are available for analysis.

For all patients who have consented, samples will be collected, consisting of flash frozen tumor (see Operations Manual, for preparation and shipping instructions) and a corresponding H+E slide. In addition, peripheral blood will also be collected for the preparation of normal DNA from leukocytes. These assays will be performed at the NCI under the guidance of Dr. Paul Meltzer. To maintain the integrity of the blind, at no point, will clinical investigators have access to the results of these studies.

3.6.2 Biomarkers Related to Activation of Src and Src Substrates

For patients who are treated at the NIH, immunohistochemistry will be utilized to study the expression of Src and phosphorylated Src in tumor samples. More importantly, the downstream targets of Src will also be examined. These include FAK and paxillin and their phosphorylated forms. Samples will consist of paraffin blocks of tumor tissue. The

assay will be performed under the direction of Dr. Mark Raffeld at the NCI. To maintain the integrity of the blind, at no point, will clinical investigators have access to the results of these studies.

3.6.3 Establishment of Cell Lines and Murine Xenografts

For patients who are treated at the NIH, the establishment of cell lines and murine xenografts will be attempted when there is a sufficient amount of tumor sample. Cell lines are a valuable reagent that allow for in vitro and in vivo experiments. These cell lines can be targeted for introduction of exogenous DNA sequences or disruption of endogenous DNA sequences, allowing investigators to verify that distinct genetic changes are causative for tumor progression and metastases. The paucity of human osteosarcoma cell lines testifies to the difficulty in establishing them. In addition, only a handful of osteosarcoma cell lines that grow in cell culture form primary tumors in immunocompromised mice.

The successful generation of a cell line requires immediate processing of the sample. At the NIH, as soon as a surgical sample is removed from the operating room, a pathologist places the sample in media and delivers it to a laboratory technician who has expertise in tissue culture. The sample is minced and added to a tissue culture flask and allowed to propagate. Overgrowing fibroblasts are allowed to grow and detach as they become over-confluent. In several instances, osteosarcoma cells begin to grow rapidly, but this may take up to one year of tissue culture.

Another useful reagent is a primary tumor that forms following surgical implantation of tumor fragments into immunocompromised mice. At the NIH, a protocol has been approved by the animal care committee, allowing for such studies. Tumor samples will be minced and added to a tissue culture flask containing tissue culture media for overnight propagation. The following day, tumor samples will be surgically implanted in the area of the tibia. In several instances, a primary tumor will form at the implantation site. Although it will be impossible to determine the type of treatment that a patient is receiving based these results, at no point will clinical investigators have access to the results of these studies.

3.6.4 Sequencing Analysis

Technology is improving so rapidly, that we now have the capability to perform sequencing analysis with the samples that are left over following microarray analysis (see section 3.6.1). In addition to RNA, DNA will also be prepared after comparison to an H+E slide of the corresponding tumor. We will then perform transcriptome sequencing, exon re-sequencing and mate-pair end sequencing, allowing us to detect translocations. The availability of matched normal DNA in the blood will allow us to determine which changes are unique to the tumor. The rapid improvements in genomic sequencing technology makes it impossible to predict what will be the state of the art methodology at the time that the samples are actually tested. Therefore, specifics of this experiment are not addressed.

These tests will be performed for research purposes. All samples will be de-identified prior to submission. Although it is impossible to determine the type of treatment that a patient is receiving based on these results, to maintain the integrity of the blind, at no point will clinical investigators have access to the results of these studies. The results of these tests will not be divulged to the patient or any physician who is involved in clinical care.

3.7 Off Study Criteria

3.7.1 Definition of Disease Progression

Disease progression is defined as recurrence of osteosarcoma based on radiographic evidence or histologic verification of the recurrent lesion. Disease progression is one of the criteria that results in removal from the protocol.

Patients who recur in the lung while on study and who are thought to be amenable to complete surgical resection will be unblinded.
(see Section 7.4.2).

Those who were receiving Saracatinib will be taken off study due to disease progression.

Those patients who were receiving placebo, whose recurrence is localized to the lung and who are thought to be completely resectable, will be offered the option of undergoing further surgery followed by therapy with Saracatinib (see Section 3.2.6).

The only curative therapy for patients who have progression of disease, which in this case, is recurrence of tumor, while on saracatinib or placebo, is surgical resection of all recurrent nodules. Therefore, every attempt at complete surgical resection should be attempted in any patient who progresses/recurs. Biological analysis of these tumor samples may prove very informative in determining the etiology of osteosarcoma recurrence. Therefore, at the time of surgery every attempt should be made to send the recurrent tumor sample for biological studies (see Operations Manual). Blood sample for microarray analysis should be collected at time of recurrence only if it was not obtained at baseline. Even though patients who were receiving Saracatinib will be off study due to disease progression, if the patient consents the recurrent tumor sample should still be collected for biological studies if possible.

The date that the patient is randomized will be used as the starting date for measurements of overall survival, progression free survival and time to treatment failure. For cross-over patients, the date that Saracatinib is started will be used as the starting date for measurements of overall survival, progression free survival and time to treatment failure. Progressive disease will be defined as recurrence of osteosarcoma based on radiographic evidence of recurrent nodules. In many cases, initial radiographic scans may not provide clear evidence of recurrence, especially if an infectious etiology is also possible. Once recurrence is verified, either by conclusive radiographic evidence or by histologic

diagnosis, the earliest date of the abnormal radiologic finding will be used as the ending date for measurement of progression free survival and time to treatment failure. Any adverse event that results in discontinuation of either saracatinib or placebo will be considered a treatment failure. This includes toxicity, disease progression or death. The time to treatment failure will begin on the day of randomization, and end on the day of discontinuation of either saracatinib or placebo.

3.7.2 Criteria for Removal from Protocol

Patients will be taken off study for any of the reasons listed below. The reason for removal from the protocol must be noted in that patient's medical record, the case report form and the SARC Operations Office must be notified.

SARC Research Project Manager
24 Frank Lloyd Wright Dr.
PO Box 406
Lobby A, 3rd Floor, Suite 3100
Ann Arbor MI, 48105
Phone: 734-930-7600
Fax: 734-930-7557
Email: sarc@sarctrials.org

Criteria for Removal from Protocol:
Administrative

- Protocol violations, such as non-compliance with treatment, or required follow-up evaluation, as determined by the Principal Investigator (Contact SARC for non-compliance issues; study PI will review on a case-by-case basis)
- Refusal of further treatment or withdrawal of consent by the patient
- Patient is lost to follow-up

Medical

- Patients with radiographic or histologic evidence of disease progression who were receiving Saracatinib (see section 7.4.2)
- All patients with radiographic or histologic evidence of disease progression that is not confined to the lung(s)
- Patients with radiographic or histologic evidence of disease progression who were receiving placebo and are not amenable to surgical resection
- If the treating physician decides that it is in the best interest of the patient to be taken off the study
- Development of any concurrent medical condition that might preclude or contra-indicate the further administration of saracatinib/placebo
- Pregnancy
- Death

Toxicity

- Life threatening toxicity as a result of saracatinib/placebo
- Patients who have persistent toxicity despite appropriate dose modifications
- Any unacceptable toxicity in the opinion of the Principal Investigator

Patients who are taken off study will continue to be monitored for survival determination, annually by contacting the referring/treating physician, for the duration that this study is open or a maximum of 3 years follow up.

3.8 Post-Study Evaluation

The following tests or procedures should be performed, if possible, at the time a patient is taken off of the study, regardless of the reason, unless the test or procedures have been performed within a period of four weeks.

- Physical examination
- ECOG performance status
- Assessment of clinical toxicity or adverse events
- Radiologic evaluation of progressive disease
- Laboratory studies
  - white blood cell count with differential
  - hemoglobin and hematocrit
  - platelet count
  - sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose
  - calcium, magnesium, phosphorous
  - ALT, AST, total bilirubin
  - alkaline phosphatase, lactate dehydrogenase, total protein, albumin

4 Supportive Care

4.1 General

The appropriate surgical care, antibiotics, blood product support and general supportive care measures will be administered by the treating physician, as clinically indicated.

4.2 Management of an Overdose with Saracatinib

There is no known antidote for saracatinib and management of overdose should consist of symptomatic and supportive treatment. In view of the slow absorption rate of saracatinib, measures such as gastrointestinal lavage or administration of an emetic agent such as

activated charcoal or Ipecac syrup may be helpful if a patient is seen within two hours of taking an overdose.

Should an overdose occur, it must be recorded in accordance with the procedures described (see Section 7.2) regardless of whether the overdose was associated with any symptoms or not. All symptoms associated with the overdose should be recorded as adverse events. Oral therapy with saracatinib or placebo will re-commence at a time decided by the treating physician.

4.3 Procedures in Case of Pregnancy

All patients must use adequate contraception during the study. However, should pregnancy occur, the patient will be removed from the study. Patients will be advised that the possible effects of saracatinib on the fetus are unknown.

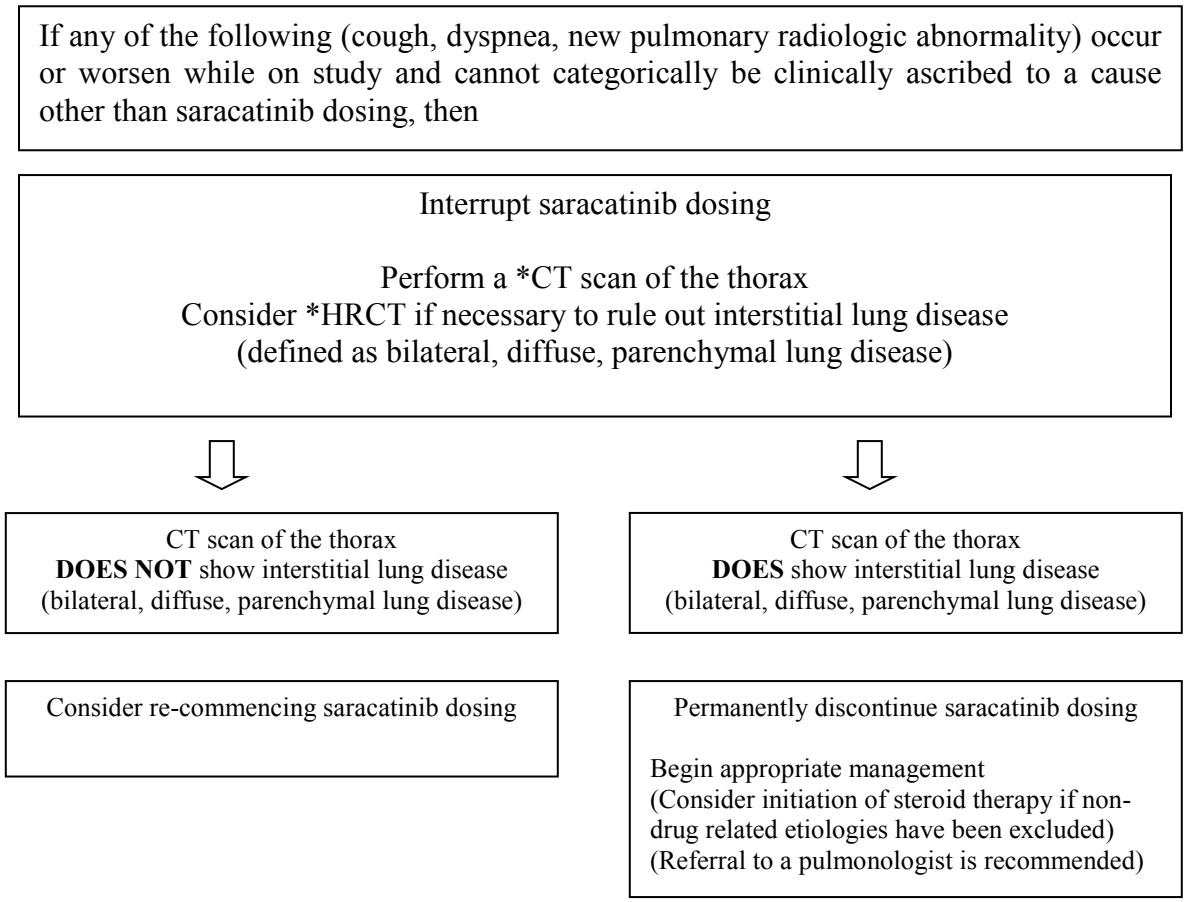
Rodent reproductive toxicology studies have found that the administration of saracatinib resulted in effects on embryonic survival and fetal malformations at dose levels that were similar or lower than those likely to be achieved in humans. Some of the malformations included anophthalmia, microphthalmia, aglossia, micrognathia, cleft palate, kinked tail and hind paw hyperextension (33).

Should a pregnancy occur, it must be recorded in accordance with the procedures described (see Section 7.2). Pregnancy in itself is not regarded as an adverse event, unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

4.4 Respiratory Care

As described previously (Section 1.2.8), four adult patients developed pulmonary adverse events, possibly due to concurrent treatment with saracatinib. The development of any pulmonary symptom, no matter how minimal it may be, must be investigated immediately. Patients who have cough or slight discomfort in association with an upper respiratory infection may be monitored clinically, if the symptoms resolve or improve within a period of seven days.

Any patient who develops a pulmonary symptom, or has worsening of symptoms, will undergo thoracic CT as soon as possible. Pulmonary symptoms include, but are not limited to the following: cough, dyspnea, pain, hemoptysis, or oxygen saturation <94%. Oral therapy will be stopped immediately and the algorithm below should be followed.



*CT scan of thorax to be performed with slice thickness ≤ 5mm
*HRCT scan recommended parameters:

position	supine
slice thickness	≤1.25 mm
slice spacing	10 mm
start location	10 mm below the apices
end location	10 mm above costophrenic angles

4.5 List of Contra-Indicated Medications

Saracatinib is substrate of CYP3A4 in humans. There are many drugs that either inhibit or induce CYP3A4 metabolism. This may result in increased or decreased exposure to saracatinib. The following tables list the drugs that are contra-indicated. In addition, the tables also list the minimum time period that the contra-indicated drug must be stopped, prior to the initiation of oral therapy with saracatinib or placebo.

Potent CYP3A4 inhibitors (may result in a 3-fold increase in exposure to saracatinib)

Contraindicated Drugs	Minimum period of discontinuation
Diltiazem	14 days
Clarithromycin (250 mg or 500 mg bid)	7 days
Erythromycin	7 days
Fluconazole 400 mg - lower doses (200 mg and 100 mg) are allowed	7 days
Itraconazole	7 days
Voriconazole	7 days
Ketoconazole	7 days
Indanavir	2 days
Nefazodone	2 days
Ritonavir	2 days
Saquinavir	2 days

Potent CYP3A4 inducers (may result in a 3-fold decrease in exposure to saracatinib)

Contraindicated Drugs	Minimum period of discontinuation
Barbiturates	14 days
Carbamazepine	14 days
Phenytoin	14 days
Rifabutin	14 days
Rifampicin	14 days
St John's Wort	14 days

Saracatinib is a moderate inhibitor of CYP3A4 in humans. There are many drugs that are CYP3A4 substrates. Therefore, patients who are receiving saracatinib may have increased exposure, pharmacological action or toxicity to CYP3A4 substrate medications due to inhibition of CYP3A4 by saracatinib. The following table lists the drugs that are contra-indicated. In addition, the table also lists the minimum time period that the contra-indicated drug must be stopped, prior to the initiation of oral therapy with saracatinib or placebo.

Contraindicated Drugs	Minimum period of discontinuation
Carbamazepine	14 days
Alfentanil	7 days
Cyclosporin	7 days
Tacrolimus	7 days
Atorvastatin	7 days
Lovastatin	7 days
Simvastatin	7 days

In addition, all of the medications listed above should not be restarted until 14 days after the last dose of oral therapy with saracatinib or placebo. They should never be restarted as long as the patient remains on oral drug therapy.

4.6 Use of Concomitant Medications

The following table is a list of medications that are moderate inhibitors of CYP3A4. It is possible that the concomitant use of these items may result in an increase in exposure to saracatinib. If possible, these medications should be avoided. However, they are not contra-indicated, but care must be taken to monitor closely for possible drug interactions.

Moderate CYP3A4 inhibitors (may result in an increase in exposure to saracatinib)

Drugs with possible interactions	
Fluconazole (200 mg or 100 mg) - 400 mg is contraindicated	Monitor closely
Verapamil	Monitor closely
Nelfinavir	Monitor closely

The following table is a list of medications that are CYP3A4 substrates, but are allowed to be taken in conjunction with oral therapy with saracatinib or placebo. Again, when at all possible, these drugs should be avoided, due to the possibility of increased exposure to these drugs. The following is a list of some medications that may be affected by saracatinib that may be more commonly used in this study population.

Drugs with possible interactions	
Alprazolam Midazolam Triazolam	Monitor closely
Felodipine Isradipine Nifedipine Other calcium antagonists	Monitor closely
Methylprednisolone	Monitor closely
Pimozide	Monitor closely
Quinidine	Monitor closely

This list is by no means complete. Treating physicians should determine the toxicity and interaction profile of all medications that her/his patient is taking.

4.7 List of Contra-Indicated Foods

The following is a list of food products that are moderate inhibitors of CYP3A4. It is possible that the concomitant use of these items may result in an increase in exposure to saracatinib. The following food products must not be taken while the patient is on study: grapefruits, grapefruit juice, star fruits, Seville oranges (also known as Chinese Bitter Oranges) and Seville orange marmalade.

5 Data Collection and Evaluation

5.1 Data Collection

This is a multi-institutional study. The data from all participating institutions will be stored electronically at the Michigan Institute for Clinical and Health Research (MICHR) Specific forms for registration, adverse event reporting, non-adverse event data collection, and documentation of shipment and receipt of biological specimens will be developed by SARC and the study Principal Investigator. The data manager at participating institutions will complete these online forms. Patients will be identified by their unique patient identification number on these forms. Only persons directly involved in this clinical trial will have access to the data stored at MICHR.

Electronic case reports are available at: https://velos.med.umich.edu/eres/jsp/ereslogin.jsp

Please contact the SARC Operations Office with any questions.

SARC Research Project Manager
24 Frank Lloyd Wright Dr.
PO Box 406
Lobby A, 3rd Floor, Suite 3100
Ann Arbor MI, 48105
Phone: 734-930-7600
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Email: sarc@sarctrials.org

Required forms should be submitted electronically within two weeks of the required visit (see Section 3.4). The SARC Research Project Manager will review the receipt of all required forms and contact any institution directly if data entry is delinquent.

In addition to electronic data submission, participating institutions will print copies of completed forms, which will be kept with source documentation, in the patient study binder.

5.2 Toxicity Criteria

Toxicity will be graded according to the CTEP CTCAE version 3.0 for toxicity and adverse event reporting. A copy of the Common Terminology Criteria for Adverse Events Version 3.0 (http://ctep.cancer.gov/forms/CTCAEV3v3.pdf) is available and is included in the study database. All appropriate treatment areas should have access to a copy of this document. Dose modifications will be made based upon the parameters defined previously (see Section 3.3.1).

5.3 Statistical Considerations

The primary goal of this study is to determine whether the addition of saracatinib to surgery will result in an improvement in progression free survival (PFS). The sample size will be based on being able to detect a 60% relative improvement (from 33% to 53%) in PFS probability at two years. The current 2-year PFS probability is 33%, when a second surgical complete remission is achieved (3). Assuming exponential survival curves, the hazard rate corresponding to this 2-year PFS probability for the control arm is 0.0462, which is defined as approximately a 0.0462 probability of failing each month when the 2-year PFS probability is 33%. If we assume that the 2-year PFS probability may be 53% for the saracatinib arm, the hazard is 0.0265, which then results in a hazard ratio of 1.75. Forty-four patients will need to be randomized in each arm of the study, for a total of 88 patients, over a 48-month accrual period. Follow-up of the last patient randomized must continue for an additional year. Since this study follows a phase II.5 design (35), this provides 80% power to detect a difference between the two resulting actuarial curves with a one-sided 0.10 alpha level log-rank test.

A secondary goal of this study is to determine whether the addition of saracatinib to surgery will result in an improvement in overall survival (OS). The sample size selected to evaluate PFS will also be adequate to detect a 56% relative improvement (from 45% to 70%) in OS probability at three years. The current 3-year OS probability is 45%, when a second surgical complete remission is achieved (3). Assuming exponential survival curves, the hazard rate corresponding to this 3-year OS probability for the control arm is 0.0222, which is defined as approximately a 0.0222 probability of failing each month when the 3-year OS probability is 45%. If we assume that the 3-year OS probability may be 70% for the saracatinib arm, the hazard is 0.0099, which then results in a hazard ratio of 2.24. Evaluation of the 88 patients who are randomized, over the same time frame, will provide 85% power to detect a difference between the two resulting actuarial curves with a one-sided 0.10 alpha level log-rank test.

As explained in section 3.2.6, a subset of patients who recur while receiving placebo will be given the opportunity to receive saracatinib. Since patients on both arms will have received this agent, although at different times in the natural history of their disease, this may result in a lessening of the difference in survival between the arms compared to the case when only patients on one arm received the agent. However, since development of a recurrence may still be associated with overall survival duration, the magnitude of the impact may be limited.

An additional secondary goal is to determine if the addition of saracatinib to pulmonary metastasectomy, versus placebo and pulmonary metastasectomy, results in an increase in the time to treatment failure (TTF). Any adverse event that results in discontinuation of either saracatinib or placebo will be considered a treatment failure. This includes toxicity, disease progression or death.

Again, the randomized nature of the Phase II.5 study will allow us to determine the actual 2-year PFS and 3-year OS rates in patients who receive surgery and placebo, or surgery in combination with saracatinib.

Patients will be stratified based on the following criteria:

Number of Recurrences: FIRST versus SECOND versus THIRD or MORE

Number of Recurrent Nodules: ONE or TWO versus THREE or MORE

The date that the patient is randomized will be used as the starting date for measurements of overall survival, progression free survival and time to treatment failure. Progressive disease will be defined as recurrence of osteosarcoma based on radiographic evidence or histologic verification of the recurrent lesion.

At the first annual opportunity following the point at which 20 patients per arm have been randomized (40 total) and potentially followed for at least 12 months, an interim evaluation for futility will be performed.

The futility evaluation will be performed as follows. Based upon the full data available at that time, a conditional power analysis will be performed to determine if the trial is

unlikely to find an effect at the 0.10 one-sided level with continued accrual, based on the PFS endpoint. Since the goal is to detect a difference between two year PFS of 33% and 53%, an early evaluation will be performed based on the binomial probabilities at the 12-month point, which reflect the same objective. A PFS of 33% at 2 years would be equivalent to a 1 year PFS of 57.4% and a PFS of 53% at two years is equivalent to a 1 year PFS of 72.8%. Using these as the values under the alternative, and using the actual proportions without progression at 1 year based on the observed fractions based on the expected sample size at 1 year, the conditional power of the trial assuming accrual of however many patients would remain to be entered will be computed. If the conditional probability of finding a difference at the one-sided 0.10 level at the end of the trial is less than 20%, then it will be reasonable to recommend that no further patients will be enrolled. Alternatively, an evaluation based on exponential distribution of PFS may be substituted for the binomial evaluation.

At the first annual point after which 30 patients per arm (60 total) have been accrued and potentially followed for at least 12 months, a very stringent interim monitoring rule will be used to determine if superiority is identified early. If at this single interim efficacy evaluation for superiority, the log-rank p-value for the difference (one-tailed) is <0.001, then accrual will stop. Otherwise, enrollment will continue as planned.

5.3.1 Patient Randomization

Details of patient randomization are described in the Operations Manual.

Dr. Seth Steinberg, the NCI statistician, will generate randomization assignment sheets. The sheets will be based on a stratified randomization, which will be created using software that generates randomized blocks of varying sizes as directed by Dr. Steinberg. He will provide these sheets directly to the SARC Operations Office, where they will be maintained in a confidential manner.

After the patient is registered and enrolled electronically by the site through the SARC study website, the site will contact the SARC Operations Office to obtain patient randomization treatment assignment.

The site pharmacy will be notified of the assigned randomization treatment (i.e. saracatinib or placebo). After confirmation of receipt of treatment assignment by the site pharmacy, labeled, blinded medication will be dispensed for the patient. This will consist of saracatinib in 125 mg and 50 mg tablets, or placebo 125-like and 50-like tablets, in accordance with the protocol.

The randomization assignment should be kept confidential and should not be shared with the treating physician(s) or any other site team staff involved in the care of the patient, except in the event of a medical emergency where unblinding is necessary for patient care (see section 7.4) or for disease recurrence (see section 7.4.2)

5.4 Multi-Institutional Guidelines

The trial coordinating center will be SARC. Patients will be registered electronically via the study website (see Section 2.3) and adverse events (see Section 7.2) will be reported to SARC.

SARC Research Project Manager
24 Frank Lloyd Wright Dr.
PO Box 406
Lobby A, 3rd Floor, Suite 3100
Ann Arbor MI, 48105
Phone: 734-930-7600
Fax: 734-930-7557
Email: sarc@sarctrials.org

5.4.1 IRB Approvals

The protocol must be approved at the participating institution prior to enrolling patients. Documentation of individual institutional IRB approval for the current protocol must be sent to SARC along with IRB approved consent.

5.4.2 Amendments and Consents

Institution informed consent form must be sent to SARC for review and approval prior to submission to their IRB. All amendments must be submitted to institutional IRB for review and approval. Documentation of approval of amendments and of yearly continuing review must be sent to SARC to permit site continued enrollment and treatment of patients on this study.

5.4.3 Data Collection and Toxicity Reporting

Weekly registration and reports will be generated by SARC to monitor patient accrual and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies by the Research Project Manager at SARC.

A monthly telephone conference will be held between the study Principal Investigator and the research project manager at SARC to address any issues that arise pertaining to this study.

Unexpected CTCAEv3 grade 3 or grade 4 toxicities (see Section 8.1.5 for known toxicities of saracatinib) and all grade 5 toxicities must be reported to the research project manager at SARC within 24 hours of the occurrence (see Section 7.3.1). All serious adverse events will be submitted to the National Heart, Lung and Blood Institute (NHLBI) IRB (see Section 7.3.2).

5.4.4 Data and Participating Institution Audits

SARC research project manager will review data entered into the electronic data capture system on a weekly basis and generate queries as needed. No on site audit will be performed for this study. Selected source documents will periodically be requested by SARC for verification of data entered into the electronic data capture system. All source documents submitted to SARC will be marked with the patient initials and patient unique study number. All other patient identifiers will be redacted.

5.5 Data and Safety Monitoring Plan

The SARC Executive Committee will convene monthly via teleconference to review with the study principal investigator the study accrual, adverse events, serious adverse events, protocol violations and/or deviations. Data provided to this committee will be blinded as to the treatment arm for the events reported. Any concerns related to patient safety will be referred to the NCI DSMB as they will have access to unblinded data.

A NCI-created DSMB will monitor this trial for toxicity, as well as clinical endpoints relative to early termination, in its annual meetings. As noted above (see Section 5.3), clinical evaluations of endpoints will be formally evaluated beginning after 40 to 60 total patients have accrued and potentially followed for 12 months.

6 Human Subjects Protections

6.1 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 (see Section 2.1). No groups are being excluded from participation in this trial. To date, there is no information that suggests differences in the effectiveness of saracatinib between genders or among racial or ethnic groups in any patient with cancer, indicating that the results of this trial will be applicable to all groups. Efforts will be made to extend the accrual to a representative population. Patients with recurrent osteosarcoma are rare and our hope is to enroll every patient in the United States. Since recurrent osteosarcoma affects both genders and all racial and ethnic groups, almost equally, this trial should be composed of a representative population. All participating institutions will need to have IRB approval prior to registering a subject for this trial.

6.2 Participation of Children

Pediatric subjects ≥15 years of age are eligible for this trial. Patients with recurrent osteosarcoma are typically adolescents or older. Until the safety/efficacy of this approach is established, children <15 years of age will not be included in this study.

6.3 Evaluation of Benefits and Risks/Discomforts

The primary risk to patients participating in this research study is from toxicity of anticancer drugs and the agents used to alleviate the toxicities of the anticancer drugs. For patients with recurrent osteosarcoma, there is no salvage regimen that offers a good response rate. The current standard of care is to resect all recurrent nodules, if this is possible. The primary objective of this study is to assess the ability of saracatinib, versus placebo, to increase progression free survival in patients who have undergone complete resection of recurrent nodules. Saracatinib has been tolerated in patients with advanced cancers, but it is still an investigational agent. As such, an additional risk to patients participating in this trial may be that saracatinib may have an increased incidence of side effects. Potential benefits for patients who participate in this study include a possible increase in progression free survival. Since the standard of care is surgical resection, patients who are randomized to receive placebo, will be receiving the standard of care.

The medical, hospital and research records associated with this study are considered confidential. Members of the treating team and designated research study assistants will have access to the records as required to administer treatment and comply with the protocol. Neither the name nor other identifying information for an individual will be used in any reports or publications concerning this study. Patient records may be inspected by auditing agencies, including the NCI, the FDA, SARC (the study sponsor) and AstraZeneca (the distributor of saracatinib) to satisfy regulatory requirements.

6.4 Risks/Benefits Analysis

This protocol provides for detailed and careful monitoring of all patients to assess for toxicity and response to treatment. Patients will be treated with therapeutic intent and response to the therapy will be closely monitored. The potential benefit from this therapy is to improve progression free survival. Therefore, this protocol involves greater than minimal risk to subjects, but presents the potential for direct benefit to individual subjects.

6.5 Consent and Assent Processes and Documentation

A signed informed consent document will be obtained prior to entry onto the study. The investigational nature and research objectives of this trial, the procedures and treatments

involved and their attendant risks and discomforts and potential benefits, and alternative therapies will be carefully explained to the patient and/or the patient's parents or guardians if she/he is a child. The investigators are requesting a waiver from the NCI IRB to allow only one parent or guardian to sign the informed consent to enter a child on the protocol. Because many patients must travel to the NIH from long distances at substantial expense, requiring both parents to be present for the consent process may adversely impact other children at home and pose financial hardship due to loss of work-related income. Other participating centers will have patients in similar circumstances and may request a similar waiver from their IRB.

The institutional Principal Investigator, or their designee, will meet with the patient, or the patient's parents or guardian, and other family members, to discuss the protocol treatment and alternative options. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. The patient and family members will be encouraged to ask questions, and additional meetings to discuss the treatment options will be arranged if necessary. The institutional Principal Investigator, or their designee, will then obtain consent from the patient. For patients who are <18 years of age, where deemed appropriate by the clinician and the child's parents or guardian, the child will also be included in all discussions about the trial and verbal or written assent will be obtained. The parent or guardian will sign the designated line on the informed consent form attesting to the fact that the child has given assent.

6.6 Handling of Research Samples

This study is being conducted and coordinated by SARC. Collection of blood can occur any time prior to the first dose of oral therapy. A blood specimen should be collected regardless of whether there is tissue to be submitted. Collection of tumor tissue for research purposes will occur at the time the tumor is resected (see Sections 3.6.1 and Operations Manual). A corresponding H+E should also be prepared and sent to the NIH. Every attempt will be made to obtain tissue samples and to combine the collection of research samples with the collection of specimens for clinical care purposes. If there is not a tissue sample available the patient is still eligible to participate in the trial.
Research specimens will be evaluated for the following:

Microarray analysis (for all patients)
Biomarkers related to activation of Src and Src substrates (for NIH patients)
Establishment of cell lines and murine xenografts (for NIH patients)
Sequencing analysis (for all patients)

Samples will be transported in a manner that complies with current regulatory guidelines for transport of specimens. All samples will be labeled with a protocol-specific patient tracking number that was generated for the patient at the time of randomization. Sample labeling, collection and initial processing will be conducted as described in the Operations Manual. Unintentional loss or destruction of any sample will be reported to the National Cancer Institute (NCI) IRB and the IRB of the responsible Institutional

Principal Investigator as part of annual continuing reviews. Unexpected problems such as, but not limited to, natural disaster, equipment malfunction, and human error, will be reported to the IRB in written form. Any use of these samples for purposes not described in this section will require prospective NCI IRB review and approval.

For all fresh frozen tumor samples submitted, microarray studies and corresponding normal lymphocytes will be performed in the laboratory of Dr. Paul Meltzer (see Sections 3.6.1 and Operations Manual for details). Participating institutions are requested to send fresh frozen tissue, a corresponding H+E slide, and peripheral blood to the NIH. Samples will be tracked and considered the responsibility of the Institutional Principal Investigator, until they are received by the designated recipient at the NIH. Samples will then be logged into a database on a secured computer. Tumor samples will be stored in a designated monitored -80°C freezer. Peripheral blood will be processed for isolation of white blood cells which will then be stored in a designated monitored -80°C freezer associated with Dr. Paul Meltzer's laboratory until analyzed. After the samples have been analyzed and the results published, any remaining samples will be transferred anonymously to a research sample protocol. To maintain the integrity of the blind, at no point, will clinical investigators have access to the results of these studies.

For all fresh frozen tissue samples received from patients who are treated at the NIH, activation of Src and Src substrates will be determined by immunohistochemistry in the laboratory of Dr. Mark Raffeld (see Sections 3.6.2 for details). Samples will be logged into a database on a secured computer, and stored at room temperature and secured in Dr. Mark Raffeld's laboratory. After the samples have been analyzed and the results published, any remaining samples will be transferred anonymously to a research sample protocol. To maintain the integrity of the blind, at no point, will clinical investigators have access to the results of these studies.

For all tissue samples received from patients who are treated at the NIH, tumor samples will be minced and cultured in media in an effort to obtain a stable cell line in the laboratory of Dr. Chand Khanna (see Sections 3.6.3 for details). These samples will only be obtained if extra samples are available. Sterile resection samples are sent to pathology. After samples are sent for clinical analysis and other requirements of this protocol, any extra tumor samples will be added sterilely into a 50 cc conical tube containing 20 ml of tissue culture media. The sample will be minced and added to a tissue culture flask containing tissue culture media. Samples will then be logged into the NCI LabMatrix database on a secured computer. Tissue culture samples will be propagated in a tissue culture incubator associated with Dr. Chand Khanna's laboratory. In most cases, a cell line will not result and the sample will be destroyed. In the rare event that a cell line does result, the cell line will be renamed in the following format (NCI-OST-last two digits of the year-random one digit check number). The cell line will then be aliquoted and frozen in liquid nitrogen. Two aliquots will be deposited with ATCC with only the renamed identifier and the following description: "recurrent osteosarcoma tumor isolated from the lung." At no point will any other clinical information be given to ATCC. Although it will be impossible to determine the type of treatment that a patient is receiving based these results, at no point will clinical investigators have access to the results of these studies.

For all tissue samples received from patients who are treated at the NIH, tumor samples will be minced and injected into immuno-compromised mice to obtain xenografts in the laboratory of Dr. Chand Khanna (see Sections 3.6.3 for details). These samples will only be obtained if extra samples are available. Sterile resection samples are sent to pathology. After samples are sent for clinical analysis and other requirements of this protocol, any extra tumor samples will be added sterilely into a 50 cc conical tube containing 20 ml of tissue culture media. The sample will be minced and added to a tissue culture flask containing tissue culture media. Samples will then be logged into the NCI LabMatrix database on a secured computer. Tissue culture samples will be propagated overnight in a tissue culture incubator associated with Dr. Chand Khanna's laboratory. The following day, tumor samples will be surgically implanted in the area of the tibia. In most cases, a primary tumor will not form and the mouse will be euthanized. In the rare event that a primary tumor does form, the resulting tumor will be renamed in the following format (XEN-OST-last two digits of the year-random one digit check number). The tumor will be harvested, minced and frozen in liquid nitrogen. Although it will be impossible to determine the type of treatment that a patient is receiving based these results, at no point will clinical investigators have access to the results of these studies.

For all patients for whom frozen tissue is available, sequencing analysis of DNA and RNA from tumor samples and corresponding normal lymphocytes will be performed in the laboratory of Dr. Paul Meltzer. This will include transcriptome sequencing, exon re-sequencing and mate-pair end sequencing. These studies will be performed on material that is left over following microarray analyses (see Sections 3.6.1, 6.6 and Operations Manual for details). The logistics have been described previously.

7 Data Reporting

7.1 Patient Registration and Case Report Forms

This is a multi-institutional study. The data from all institutions will be stored in the database at the Michigan Institute for Clinical and Health Research (MICHR). All case report forms (CRFs) should be filed electronically within two weeks of the scheduled visit

Electronic case reports are available at: https://velos.med.umich.edu/eres/jsp/ereslogin.jsp

Please contact the SARC Operations Office with any questions.

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Ann Arbor MI, 48105
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7.2 Adverse Event Recording

7.2.1 Definitions

ADVERSE EVENT: An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event 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 the event is considered causally related to the use of the product. Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

SERIOUS ADVERSE EVENT OR SERIOUS SUSPECTED ADVERSE REACTION: A serious adverse event (SAE) is considered 'serious' if, in the view of the investigator or sponsor it results in any of the following outcomes:

- Death
- is life-threatening
- requires inpatient hospitalization, or prolongs an existing hospitalization
- causes persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- results in congenital anomalies or birth defects
- Important medical events which in the judgment of the investigators may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SUSPECTED ADVERSE REACTION: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For purpose of safety reporting, "reasonable possibility' means there is evidence to suggest causal relationship between the drug and the adverse event. SUSPECTED ADVERSE REACTION implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

EXPECTED ADVERSE EVENT: An expected adverse event (EAE) is an adverse event with a non-fatal outcome that is described in section 5.4 of the Investigator's Brochure or in section 8.1.5 of this protocol.

UNEXPECTED ADVERSE EVENT: An unexpected adverse event (UAE) is any adverse event that is not described at the specificity and severity that has been observed and described in section 5.4 of the Investigator's Brochure or in section 8.1.5 of this protocol, or an event described in these sections that has a fatal outcome.

ATTRIBUTION: The relationship of adverse events to the study medication will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the study medication?" The Institutional Principal Investigator well answer: Yes or No. If there is a reasonable possibility that the event is related to study drug, then Yes would be designated for causality to study drug. If there is clearly no possibility that the event is related to the study drug then No would be designated for causality to study drug.

7.2.2 Recording Procedures for All Adverse Events

All observed or volunteered adverse events, regardless of treatment group or suspected causal relationship to study drug, will be recorded as an Adverse Event in the case report forms at each study visit. Adverse events should be collected from the time the patient provides informed consent to participate in the study until 30 days after the last dose of study medication. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbation of pre-existing illnesses should be recorded. Objective test findings (e.g., abnormal laboratory test results) that result in a change in study drug dosage should also be recorded.

All AEs will be recorded on the CRFs provided. A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, the date it became serious, seriousness criteria (e.g fatal, life-threatening, hospitalization, disability, congenital anomalies), any action taken (e.g., changes to study treatment, other treatment given and follow-up tests) and outcome should be provided along with the Investigator's assessment of causality to the study drug, study medication and study procedure.

It will be left to the treating physician's clinical judgment whether or not an adverse event is of sufficient severity to require that the subject should be removed from treatment. A subject may also voluntarily withdraw from treatment due to what she/he perceives as an intolerable adverse event. If either of these occurs, the subject will be given appropriate care under medical supervision until the symptoms cease or until the condition becomes stable.

The severity of toxicities will be graded in accordance with the Common Terminology Criteria for Adverse Events Version 3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf). A link to CTCAE v3 is also provided in the study database in the adverse event CRFs.

7.3 Adverse Event Reporting

7.3.1 Reporting Procedures for Serious Adverse Events

Reporting of SAEs will be managed by SARC. Full details for the procedures to be adopted will be documented in the Safety Reporting Plan approved by the responsible parties.

Initial notification of serious adverse events

The treating physician or other site personnel must report all serious adverse events within 24 hours to the study coordinator at SARC.

All SAEs must be reported, whether or not considered causally related to the investigational product or to the study procedure/s. All SAEs will be recorded in the CRF.

All serious AEs (SAEs), whether considered related or unrelated to investigational product, must be reported immediately (**within 24 hours of awareness)** by the investigational site to SARC, the Study Principal Investigator, and AstraZeneca Patient Safety by confirmed facsimile transmission. 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 should be reported on the MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/MedWatch/. The MedWatch form must be completed using the following guidelines:

- The date the site notified SARC and AstraZeneca of the SAE must be specified in the "Describe event" narrative section.
- Initial and follow-up MedWatch reports should be numbered either in the narrative section or in section G.7 of the MedWatch form.
- If more than one SAE is listed on the MedWatch form, each event should be numbered.
- Institutional Principal Investigator must designate causality to study drug for each SAE and must be specified in both the "Describe event" narrative section of the MedWatch form and the SARC012 SAE Fax Coversheet.
- There will be 2 causality designations: Yes = Related to study drug, No = Unrelated to study drug
    - If there is any possibility that the SAE is related to study drug, then designate Yes for causality.
    - If there is clearly no possibility that the SAE is related to study drug, then designate No for causality.
- If the SAE is considered to be related to a study procedure, this should also be indicated in the narrative section

For all SAEs, completed MedWatch forms along with a completed SAE Fax Coversheet (Appendix C) should be faxed to SARC, the Study Principal Investigator, and AstraZeneca Patient Safety **within 24 hours** of awareness of the event. The SAE Fax

Coversheet must be completed with Site and Subject Identifiers, SAE CTCAE version 3.0 terms with a causality assessment to study drug, to other medication and to study procedure for each SAE term, Grade, and whether the notification concerns any event that is fatal or life-threatening. The fax date and whether the notification constitutes an initial or follow-up report (with follow-up number) should also be noted on the SAE Fax Coversheet.

Contact details for reporting SAEs are documented on the SAE Fax Coversheet and are as follows:

- SARC
  SARC Research Project Manager
  Fax Number: (734) 930-7557
- Study Principal Investigator, Scott Okuno, MD
  Email: okuno.scott@mayo.edu
- AstraZeneca, Patient Safety
  Fax Number: +1 302 886 4114
  Back up Fax Number: +1 302 886 5886
  Email back-up in the event of fax failure (this is not a secure e-mail connection): PatientSafety.ClinicalTrialTemplatesWilm@astrazeneca.com (include in subject line: Study D8180C00039, SARC012, Patient number)

SARC will review the SAE report for completeness and accuracy and will work with the Investigator to compile all the necessary support information to provide full written reports, and will record the SAE on the safety database.

Reporting of serious adverse events

SARC will determine the reportability of the event and will send expeditable reports to the FDA within the required timelines. The Research Project Manager at SARC will be responsible for sending these expeditable reports to the Study Leader at AstraZeneca at the same time that they are reported to the FDA.

SARC will also provide full written reports of all SAEs to:

- STUDY PRINCIPAL INVESTIGATOR. Scott Okuno (okuno.scott@mayo.edu).
- INSTITUTIONAL PRINCIPAL INVESTIGATOR.
- SARC will email expedited reports to all local sites involved in the study within 2 business days of receipt, and local sites will process per institutional policy.

SARC will send Safety Reports received from AstraZeneca to all sites involved in the study within the timelines required by the FDA, and local sites will process per institutional policy.

7.3.2 Adverse Event Reporting Procedures to the Investigator's IRB

The Principal Investigator of each participating site is responsible for reporting to their local IRB all events that occur in participants enrolled at the site according to the policies and procedures of the institutional IRB.

7.4 Treatment Regimen Unblinding

See Operations Manual for process to request patient treatment regimen unblinding.

7.4.1 Criteria for Unblinding for Serious Adverse Events

The following events require unblinding of treatment assignments in this study:

1. The occurrence of a serious adverse event that is both unexpected and considered by the reporting investigator to be associated with the use of study drug, and the knowledge of the treatment assignment is deemed essential for the patient's care.
2. An unexpected serious adverse event occurs and the intervention must be made known for purposes of reporting to the FDA (SARC responsibility as Study Sponsor).

Unblinding of treatment assignments for patients on this study will be performed by authorized SARC personnel, upon approval from the SARC Medical Officer or designee.

Requests for unblinding by the site should be only for urgent patient safety issues.

Note: To ensure patient safety, if need be, all discussions can be done verbally with written documentation to follow once patient safety secured.

Any patient whose treatment assignment is unblinded because of a serious adverse event(s) will be removed from study treatment and followed only for survival. The site should continue to follow the patient status regarding the serious adverse event(s) for which the patient's treatment was unblinded until resolved or improved to baseline and the patient can receive additional off-study treatment as necessary.

7.4.2 Unblinding for Disease Recurrence in the Lung

Patients who recur in the lung while on-study and who are thought to be amenable to complete surgical resection will be unblinded. Those patients who were receiving placebo may then have the option of undergoing surgical resection. If fully resected,

the patient will be given the option to begin oral therapy with Saracatinib. Patients who recur in sites other than the lung while on-study will be taken off study and will not be offered the opportunity to be unblinded.

Requests for unblinding by the site should be made at the time of recurrence, only if the recurrence is in the lung, and only if the recurrence is thought to be amenable to complete surgical resection. Authorized SARC personnel will perform unblinding of the treatment assignment. Those patients who were receiving Saracatinib will be taken off-study for disease progression (see Section 3.7). Those patients who were receiving placebo will be offered the option of undergoing surgical resection. If complete resection is achieved, the patient will be given the opportunity to receive Saracatinib (see Section 3.2.6).

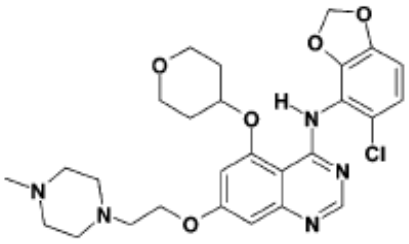
8 Pharmaceutical Information

8.1 Saracatinib (AZD0530)

8.1.1 Chemical Information

Chemical Name : *N*-(5-Chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-4-amine

Chemical Structure :



Molecular Formula : $C_{27}H_{32}ClN_5O_5$

Molecular Weight : 542.04 as free base

Half-life 40 hours in humans

8.1.2 Supplier and Trial Sponsor

AstraZeneca will supply saracatinib and placebo for this trial. SARC (Sarcoma Alliance for Research through Collaboration) will sponsor this trial, which will be conducted under an IND held by SARC (IND #103,268).

8.1.3 Preparation and Storage

Saracatinib tablets will be prepared by AstraZeneca and supplied by a third party vendor to the hospital pharmacy for subsequent distribution to the patient. The tablets are round, pink, film-coated and come in 50 mg and 125 mg doses. Tablets will be packed in child-resistant, tamper-evident, high-density, polyethylene (HDPE) bottles with child-resistant closures. Packaging includes bottles, caps and labels.

Bottle labels will be available for the two different strengths of saracatinib. Saracatinib is presented in plain, round, biconvex, pink, film-coated tablets that contain 50 mg or 125 mg of saracatinib in free base form. The 50 mg tablets have a diameter of 7 mm and the 125 mg tablets have a diameter of 9.5 mm.

Both 50 mg and 125 mg tablets contain saracatinib, mannitol, dibasic calcium phosphate anhydrous, crospovidone, hypromellose and magnesium stearate. The film-coat contains hypromellose, macrogol 400, red iron oxide, black iron oxide and titanium dioxide.

The tablets should be stored at room temperature in the pack provided. The expiration date will be listed on the product label. For further information, investigators should refer to the investigational product label.

8.1.4 Administration of Saracatinib

Saracatinib will be administered orally, once daily, every day, until the patient comes off study. The tablets can be taken at any time of the day, with or without food. See sections 4.5, 4.6 and 4.7 for a list of medications and food products that should be avoided while on study.

Each cycle will consist of 28 days, but there will be no breaks between cycles.

Should emesis occur after swallowing the saracatinib tablet, an additional dose is not to be given. The only exception is when emesis occurs immediately after swallowing the saracatinib tablet, and a fully intact, regurgitated, tablet is recovered.

For patients who cannot swallow tablets, the following guideline must be followed to crush either the 50 mg or the 125 mg tablets.

- Ensure that the crusher is clean and thoroughly dry (Ezy Dose Tablet Crusher with Pill Container, stock number 71091 from Apothecary Products Inc, Minneapolis or equivalent).

- Place the crusher on its base on a flat surface, insert the tablet and screw down the crusher cap to crush the tablet.

- Rotate the crusher cap repeatedly backwards and forwards (about one quarter turn in each direction).

- Unscrew the cap by about one half turn, then tap the crusher sharply on the table, to redistribute the powder. Do not shake or invert the crusher.

- Repeat the crushing process until a fine powder has been produced. Note that the pink coating on the tablet may remain as flakes. This is not critical. As long as the inside of the tablet has been ground to a fine powder, this is sufficient.

- Unscrew the crusher cap and transfer the powder into an appropriate glass container. If any significant amounts of tablet remain stuck to the crusher, these should be scraped or tapped out and added to the container.

- Add 50 ml of water to the crushed tablet in the glass container and drink immediately.

- Clean and dry the tablet crusher in preparation for the next dose.

  Should emesis occur after swallowing the saracatinib suspension, an additional dose is not to be given, since it is impossible to estimate the amount of saracatinib that has been delivered.

For patients who require administration of saracatinib through a gastrostomy tube, the following guideline must be followed.

- Note: The elapsed time from the first addition of water to the crushed tablet to the administration of rinse through the gastrostomy tube should not exceed 4 hours.

- Stir the water and tablet powder together for 15 seconds. Then promptly draw the suspension into the syringe.

- Administer through the gastrostomy tube.

- Add 50 ml water to the glass container as a rinse, stir for 15 seconds and draw into the syringe.

- Administer through the gastrostomy tube.

- Clean and dry the tablet crusher in preparation for the next dose.

- Rinse the syringe with water.

8.1.5 Known toxicities of Saracatinib

For further information regarding saracatinib, please refer to the Investigator's Brochure.

The following events are to be regarded as expected for regulatory reporting purposes:

General symptoms	flu-like symptoms - including fever, fatigue, musculoskeletal pain, headache fatigue

Hematological symptoms	mild bleeding (such as epistaxis) mild bruising (such as bruising at a venipuncture site)
Respiratory symptoms	pneumonitis
Gastrointestinal symptoms	nausea vomiting diarrhea
Skin symptoms	rash, generally papular
Laboratory findings	decrease in neutrophil count including neutropenia decrease in platelet count including thrombocytopenia increase in serum creatinine increase in serum C-reactive protein positive protein on urinalysis positive heme or RBCs on urinalysis

8.2 Placebo

Placebo tablets contain mannitol, microcrystalline cellulose, sodium starch glycolate and magnesium stearate. The drug substance is substituted with an equal quantity of mannitol. Placebo tablets are provided to match the active tablets in size, shape and color. The tablets should be stored at room temperature in the pack provided. The expiration date will be listed on the product label. For further information, investigators should refer to the investigational product label. Placebo tablets will be prepared by AstraZeneca and supplied by a third party vendor to the hospital pharmacy for subsequent distribution to the patient. The same instructions as described above (see Section 8.1.4), should be used for patients who are not able to swallow the tablets whole, or who require administration through a gastrostomy tube.

Since this is a double-blinded, placebo-controlled study, patients must refrain from taking certain medications and food products (see Sections 4.5, 4.6 and 4.7).

8.3 Drug Ordering

See Operations Manual for details of Drug supply/ordering.

8.3.1 Initial Supply

The investigational drug will be supplied by AstraZeneca and will be distributed to individual sites by a third party vendor.

Initial drug supply is provided to maintain a minimum inventory at the site to avoid delays in starting patient treatment.

The drug order supply form must be faxed or emailed to SARC. Upon confirmation that SARC has received all necessary regulatory documents, the contract is fully executed, and the site initiation meeting completed, SARC will authorize the initial drug supply shipment.

Requests should be submitted at least 5-7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.

Please complete the Saracatinib (AZD0530) Drug Supply Form (see Appendix D for drug supply form). Fax or email the form to SARC Operations Office:

SARC Research Project Manager
SARC operations office fax: 734-930-7557 or
Email: sarc@sarctrials.org

8.3.2 Re-Supply

Re-supply requests can be obtained by completing the saracatinib Drug Supply Form (see Appendix D for drug supply form). Fax or email the form to SARC as above.

Requests should be submitted at least 5-7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.

8.4 Investigational Product Records at Investigational Site(s)

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number and use date or expiry date.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area/site for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount destroyed at study site.

Investigational product dispensing record/inventory logs and copies of signed packing lists must be maintained at the investigational site. Batch numbers for saracatinib must be recorded in the drug accountability records.

8.5 Destruction of Investigational Product

It is the Institutional Principal Investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained. Unused drug and empty bottles will not be returned to AstraZeneca.

A copy of the institutional drug disposal policy should be sent to SARC for retention in the Trial Master File.

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10 Appendices

Appendix A – On Study Evaluations

Study Month	screening	pre dose	day 1	week 1(g)	week 3-4 (g)	week 6-8 (h)	week 9 (h)
Interim History	X	X (d)		X (d)	X	X	X (d)
Physical Examination	X	X (d)		X (d)	X	X	X (d)
Weight, Height, Vital Signs	X	X (d)		X (d)	X	X	X (d)
Laboratory Tests (a, f)	X	X (d)		X (d)	X	X	X (d)
Thoracic CT (b)	X				X	X	
Bone Scan	X						
EKG	X						
Echocardiogram or MUGA	X						
Creatinine Clearance (c)	X						
Pregnancy Test	X						
ECOG Score	X						
Begin Oral Therapy			X ---------- >				

Study Month	3 Mo Cycle 3 (h)	4 Mo Cycle 4 (h)	5 Mo Cycle 5 (h)	6 Mo Cycle 6 (h)	7 Mo Cycle 7 (h)	8 Mo Cycle 8 (h)	9 Mo Cycle 9 (h)	10 Mo Cycle 10 (h)	11 Mo Cycle 11 (h)	12 Mo Cycle 12
Interim History	X	X (d)	X (d)	X	X (d)	X (d)	X	X (d)	X (d)	X
Physical Examination	X	X (d)	X (d)	X	X (d)	X (d)	X	X (d)	X (d)	X
Weight, Height, Vital Signs	X	X (d)	X (d)	X	X (d)	X (d)	X	X (d)	X (d)	X
Laboratory Tests (a)	X	X (d)	X (d)	X	X (d)	X (d)	X	X (d)	X (d)	X
Thoracic CT (b)	X			X			X			X
EKG	X									
Continue Oral Therapy	X ---------- >									

Suggested Follow-up

Study Month	End of Trmt 13 mo	15 mo	18 mo	21 mo	24 mo	30 mo	36 mo
Interim History	X	X (d)	X	X (d)	X	X (d)	X
Physical Examination	X	X (d)	X	X (d)	X	X (d)	X
Weight, Height, Vital Signs	X	X (d)	X	X (d)	X	X (d)	X
Laboratory Tests	X		X		X		X
Thoracic CT	X		X		X		X
Bone Scan	X						
EKG	X						
End Oral Therapy	X (e)						

(a) White blood cell count with differential, hemoglobin, hematocrit, platelet count, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, ALT, AST, total bilirubin, alkaline phosphatase, lactate dehydrogenase, total protein, albumin

(b) Thoracic CT scan must be performed at a slice thickness of 5 mm or less

(c) For patients with serum creatinine >1.5

(d) These visits do not need to be performed at the study center, however, documentation of the required items must be sent to the study center as soon as they are available

(e) Saracatinib or placebo will be discontinued after 13 cycles (364 days) of therapy

(f) Prior to beginning oral therapy, treating physicians should obtain a full work-up to evaluate low or borderline low levels of phosphorus. (See section 3.3.3)

(g) Treatment evaluations/procedures should be performed within +/- 3 days.

(h) Treatment evaluations/procedures should be performed within +/- 3 days.

Appendix B – SARC 012 Patient Pill diary

PATIENT INITIALS: _____ SUBJECT UNIQUE STUDY #_____

Please complete this chart each time you take study drug. You may take the study drug at any time of the day with or without food. Please contact the study staff before changing the dose of the study drug. Once completed, please return this chart to the study staff.

Study Drug Dose: 175 mg daily, 125 mg daily, or 100 mg daily

Note: Should vomiting occur after swallowing the saracatinib tablet, an additional dose is not to be taken. The only exception is when vomiting occurs immediately after swallowing the Saracatinib tablet, and a fully intact, regurgitated tablet is recovered. The following food products must not be taken while the patient is on study: grapefruits, grapefruit juice, star fruits, Seville oranges (also known as Chinese Bitter Oranges) and Seville orange marmalade.

Day	Date	Time	AM / PM	Dose of Study Drug	Comments
Day 1	/ /			mg	
Day 2	/ /			mg	
Day 3	/ /			mg	
Day 4	/ /			mg	
Day 5	/ /			mg	
Day 6	/ /			mg	
Day 7	/ /			mg	
Day 8	/ /			mg	
Day 9	/ /			mg	
Day 10	/ /			mg	
Day 11	/ /			mg	
Day 12	/ /			mg	
Day 13	/ /			mg	
Day 14	/ /			mg	
Day 15	/ /			mg	
Day 16	/ /			mg	
Day 17	/ /			mg	
Day 18	/ /			mg	
Day 19	/ /			mg	
Day 20	/ /			mg	
Day 21	/ /			mg	
Day 22	/ /			mg	
Day 23	/ /			mg	
Day 24	/ /			mg	
Day 25	/ /			mg	
Day 26	/ /			mg	
Day 27	/ /			mg	
Day 28	/ /			mg	

Patient Signature_____ Date _____

To be completed by Study Staff: Drug Bottle(s) Return Date:_____

# of 125 mg tablets dispensed _____ / returned _____

# of 50 mg tablets dispensed _____ / returned _____

Study Staff Signature_____ Date _____

Appendix C – SAE Fax Coversheet

SARC 012 SAE FAX COVERSHEET(To be retained with MedWatch form)

IND number: 103,268 AZ Study Code D8180C000039

Investigational Prooduct: Saracatinib (AZD0530)Please place a check mark below to indicate that you have faxed this form to all parties:

- ❒ SARC Research Project Manager: **(734) 930-7557**
- ❒ Scott Okuno, MD, Study PI: **(507) 266-9161**
- ❒ AstraZeneca, Patient Safety: (**302) 886-4114**

# of pages (incl. this page)	**Fax Date** (dd-mmm-yyyy)

Sender:

Investigator: **Site:**

Study Title: A Randomized, Double-Blinded, Placebo-Controlled, Multi-Institutional, Phase II.5 Study of Saracatinib (AZD0530), a Selective Src Kinase Inhibitor, In Patients with Recurrent Osteosarcoma Localized to the Lung

Subject Study ID:	**Subject Study Initials:**		
Type of Report: ❒ Initial ❒ Follow-up # _____			
Please list all AEs by unique term and CTCAE v3.0 grade. Use additional cover sheets if necessary:			
AE term 1:	**Grade**	Causality to study drug?	**Yes / No**
		Causality to other medication?	**Yes / No**
		Causality to study procedure?	**Yes / No**
AE term 2:	**Grade**	Causality to study drug?	**Yes / No**
		Causality to other medication?	**Yes / No**
		Causality to study procedure?	**Yes / No**
AE term 3:	**Grade**	Causality to study drug?	**Yes / No**
		Causality to other medication?	**Yes / No**
		Causality to study procedure?	**Yes / No**
AE term 4:	**Grade**	Causality to study drug?	**Yes / No**
		Causality to other medication?	**Yes / No**
		Causality to study procedure?	**Yes / No**
Is any AE listed above fatal or life-threatening? ❒ Yes ❒ No			
Photocopies of supportive documents; attach if relevant, tick those attached **❒ Lab report(s) ❒ Autopsy report ❒ Other: details _____**			

All serious adverse events will be reported and documented on MedWatch Form FDA 3500 A as follows:

- If more than one SAE is listed each event should be numbered.
- Investigator must designate causality as YES or NO for each SAE in the "Describe event" narrative section of the MedWatch form. If there is any possibility that the SAE is related to study drug, then designate Yes for causality. If there is clearly no possibility that the SAE is related to study drug, then designate No for causality.
- If causality is due to other medication or study procedure, please provide a clear description and reasoning in the narrative section of the MedWatch form.
- The date the site notified SARC and AstraZeneca of the SAE must be specified in the "Describe event" narrative section of the MedWatch form. Initial and follow-up MedWatch reports should be numbered either in the narrative section or in section G.7 of the MedWatch form.

Appendix D – Drug Supply Form

ASTRAZENECA
Saracatinib (AZD0530) DRUG SUPPLY FORM
FOR INVESTIGATOR SPONSORED STUDY - SARC 012 (D8180C00039)

REQUEST FOR DRUG SHIPMENT TO SITE (AZ)

AZ Protocol Number D8180C00039	**Group Protocol Number** SARC012	Site Name (as Institution) and Number:
Investigator Name: Dr.		Shipment Must Reach Destination By: DD/MM/YYYY *(Deliveries are not made on Monday: allow five (5) working days for resupply)*
Investigator Address: Telephone Number:		**Pharmacy Address - Where Supplies Should Be <u>Delivered</u>:** (If Different From Investigator Address and Contact) **Pharmacy Contact:** Telephone Number: E-mail (if available):

DRUG REQUIRED:		
Study Drug:	**Saracatinib (AZD0530)**	**Saracatinib (AZD0530)**
Strength/ Dose Form:	**50mg tablets/ 35 per bottle**	**125mg tablets/35 per bottle**
QUANTITY NEEDED	No. of bottles:	No. of bottles:
Study Drug:	**Placebo Saracatinib (AZD0530)**	**Placebo Saracatinib (AZD0530)**
Strength/ Dose Form:	**50mg tablets/ 35 per bottle**	**125mg tablets/35 per bottle**
QUANTITY NEEDED	No. of bottles:	No. of bottles:
Comments:		

Please fax or e-mail this document to the following:
Via email: sarc@sarctrials.org
Via FAX: 734-930-7557

For SARC Office use only:

SARC verifies that all required regulatory and contractual documentation for this Site/Study is complete:

Signature:_____ Date:_____

Appendix E – Local MD Guidelines

For patients enrolled on this study, evaluations must be administered at the study site for the pre-treatment evaluation and for the 3, 6, 9, and 13month visits (cycle 3, 6, 9 and end of cycle 13). For all other study evaluations, the investigator may determine in the best interest of the patient that those evaluations may be safely conducted at a local, competent, referring oncologist's office. The institutional principal investigator is responsible for the timely and accurate reporting of data to the SARC Operations Center.

- SARC institutional PI communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.
- A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care. (Sample letter- Appendix F).
- Protocol required evaluations outside the consortium site will be documented by telephone, fax, or e-mail. Fax or e-mail will be dated and signed by the SARC institutional PI, indicating that they have reviewed it.
- Documentation to be provided by the local physician will include all drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
- SARC institutional PI is responsible for all adverse event reporting, timely and accurate submission of serious adverse events reporting as outlined in Section 7.3

Appendix F – Local MD Agreement Letter

Date

Dear Doctor,

"Name" is a mutual patient of ours with sarcoma. He/she is participating in a multi-center randomized trial of Saracatinib (AZD0530). The study involves continuous study drug administration with interval lab studies, physical exams and CT scans. The cycle is repeated every 28 days, without any breaks between cycles. We are inquiring as to your willingness to supervise a portion of this patient's care while on the trial.

"Name" would like to be evaluated at XXXX and obtain the lab studies at your office. In order for this to be done, we will need the following:

- confirmation of your willingness to obtain lab studies
- ability to obtain thoracic CT scans and relay reports and images, if required, to the study center
- agreement to report all serious adverse events within 24 hours
- agreement to discuss and obtain approval prior to any change in drug dose and/or schedule
- a copy of your lab's certification
- a fax copy of the documented, dictated or handwritten, findings of patient visits, record of study doses and administration, lab results and documentation of any hospitalizations

If you agree to the above, we would ask you to sign and return this letter as confirmation that you will comply with the items as outlined above.

By signing below, I agree to perform all tests and evaluations as noted above, and fax all documentation to **name and fax number.**

_____ _____

Signature date

A copy of the abstract, study schema, and study calendar are included with this letter. Should you have any questions or need additional information, please do not hesitate to contact: **Name and Contact Information**

Sincerely,