Virginia Commonwealth University Massey Cancer Center

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Phase 1 Study of the Pan-DAC Inhibitor AR-42 and Pazopanib in Advanced Soft Tissue Sarcoma and Renal Cell Carcinoma

Sponsor-Investigator
Andrew Poklepovic, MD
VCU Massey Cancer Center

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ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BP	blood pressure
CR	complete response
CrCL	creatinine clearance
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTRL	Clinical and Translational Research Laboratory
DLT	dose-limiting toxicity
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HDAC	histone deacetylase
HR	heart rate
HSP	heat shock protein
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
LVEF	left ventricular ejection fraction
MCC	Massey Cancer Center
MI	myocardial infarction
MTD	maximum tolerated dose
OHRP	Office for Human Research Protections
Pan-DAC	pan-deacetylase
PBMC	peripheral blood mononuclear cell
PO	by mouth (per os)
PPE	palmar-plantar erythrodysesthesia
PR	partial response
QTc	corrected QT interval
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RP2D	recommended phase 2 dose
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	serious adverse event
SAR	suspected adverse reaction
SEM	standard error of the mean
SSAR	serious suspected adverse reaction
SIIT	Solid Tumor Investigator-Initiated Trial
STS	soft tissue sarcoma
ULN	upper limit of normal
UP	unanticipated problem
VEGF	vascular endothelial grown factor
WCBP	woman of childbearing potential
WNL	within normal limits

1 BACKGROUND

1.1 Renal Cell Carcinoma and Soft Tissue Sarcomas

This clinical trial is focused on 2 disease groups, renal cell carcinoma (RCC) and soft tissue sarcoma (STS).

1.1.1 Renal Cell Carcinoma

RCC originates within the renal cortex and is by far the most common primary renal neoplasm. In the United States, there are approximately 62,000 new cases and almost 14,000 deaths from RCC each year (1). Treatment for localized RCC (ie, stages IA, IB, II, and III) is surgical resection. Surgery still has a role in a small portion of patients with stage IV RCC. Specifically, if the tumor directly involves the ipsilateral adrenal gland and a radical nephrectomy (including adrenalectomy) is possible or if there is a solitary metastasis, metastasectomy can sometimes be curative. All other cases are not considered curable even with surgery.

Treatment options for advanced RCC include high-dose interleukin-2 (IL-2) therapy, immune checkpoint inhibition, and molecularly-targeted therapy. IL-2 can induce durable long-term remissions in a minority of patients, but, due to the rigors of treatment, patients must have an excellent performance status and intact organ function (2, 3). Given the small number of patients who are eligible for IL-2 therapy and the small minority of eligible patients who will respond to therapy, most patients will receive molecularly-targeted therapy. Immune checkpoint inhibitors and specifically anti-PD1-based therapy have been shown to improve survival as well. However, durable benefit is only seen in a minority of patients (4). Outside of immunotherapy, treatment for RCC is either an anti-angiogenic, targeting the vascular endothelial growth factor (VEGF) pathway, or a mammalian target of rapamycin (mTOR) inhibitor (5). Additional advances in therapeutic options are needed.

1.1.2 Soft Tissue Sarcoma

Sarcomas are a rare and heterogeneous group of tumors with mesenchymal origin, accounting for approximately 1% of all human tumors. Sarcomas are categorized into 2 major groups according to primary tumor location: STS and bone sarcomas. The yearly incidence of STS cases in the United States is roughly 11,930, with an overall mortality of 4,870 deaths per year (1).

STS can arise almost anywhere in the body. Approximately 40-60% occur in the extremities, 20-30% occur in and around the internal organs (eg, uterus, heart); 10% occur in the trunk (eg, chest, back); and 10% occur in the head and neck (6). STS tumors comprise more than 50 different tumor entities that can exhibit significant differences in terms of genetic alterations, pathogenesis, and clinical behavior.

Local control of STS can be obtained through the use of surgery and radiotherapy. In approximately 30-40% of patients, disease will recur at distant sites, and of these, more than 90% ultimately will die from metastatic disease. Surgical resection of

isolated metastases can lead to cure in some patients. The probability of the tumor to metastasize is directly correlated with the histological grade, which is the most important predictive factor for distant metastases. In advanced and/or metastatic STS, the median overall survival of about 12 months has remained unchanged during the last 20 years. Only 2 agents have been approved in the past 30 years for progressive STS, signifying the dire need for novel therapies and combinations. In the vast majority of cases, both anthracyclines (epirubicin or doxorubicin) and ifosfamide remain the backbone of chemotherapy in patients with locally advanced or metastatic STS. Given the heterogeneous nature of this disease, advances in therapeutic options have been slower to progress compared to other cancers. New agents and regimens are urgently needed.

1.2 Pazopanib in RCC and STS

Pazopanib is an oral multikinase inhibitor approved by the Food and Drug Administration (FDA) for the treatment of patients with advanced (ie, unresectable or metastatic) RCC and patients with advanced STS who have previously received chemotherapy.

1.2.1 Pazopanib in RCC

In RCC, systemic treatment for many patients who have metastatic disease involves drugs targeting angiogenesis. High-dose interleukin 2 in the front-line setting is still recommended for patients with Karnofsky performance status of > 80%, and other immune-based therapies with immune checkpoint inhibitors are showing promise. However, agents targeting angiogenesis remain a cornerstone in the management of this disease. Two different approaches have demonstrated clinical activity in blocking the VEGF pathway. Clinical anticancer activity has been observed with small molecule tyrosine kinase inhibitors (TKIs) (eg, pazopanib, sunitinib, sorafenib, and axitinib) which block the intracellular domain of the VEGF receptor, as well as the monoclonal antibody bevacizumab which can bind circulating VEGF and prevent activation of the VEGF receptor. Among the TKIs, pazopanib and sunitinib are accepted first-line treatment options (7).

In a randomized phase 3 study of pazopanib versus sunitinib in 1,110 previously untreated patients with advanced RCC, partial responses were observed in 170 patients in the pazopanib group (31%), and one patient had a complete response (7). The median progression-free survival was 8.4 months with pazopanib (95% confidence interval [CI], 8.3 to 10.9), and the median duration of treatment was 8.0 months (range, 0 to 40) in the pazopanib group. Regarding tolerability, 44% of patients treated with pazopanib had a dose interruption of 7 days or more and 44% of patients had a reduction in the dose. The proportion of patients who discontinued the study drug because of adverse events was 24%. These data demonstrate a favorable pazopanib safety profile compared to sunitinib, with similar efficacy. The results of this study established pazopanib as an acceptable front-line choice in the treatment of RCC with TKI-based therapy.

1.2.2 Pazopanib in STS

The interaction between VEGF and its receptors involved in angiogenesis plays a role in STS tumor progression and prognosis (8). Two studies found that high VEGF serum levels correlated strongly with the most poorly differentiated STS (9, 10).

The randomized multicenter phase 3 “PALETTE” study evaluated pazopanib compared to placebo in 369 patients with STS that had progressed following front-line therapy (11). In this study, the best overall response for patients taking pazopanib was a partial response in 14 of 246 (6%), stable disease in 164 (67%), and progressive disease in 57 (23%). Median progression-free survival was 4.6 months (95% CI 3.7-4.8) for pazopanib compared to 1.6 months (95% CI 0.9-1.8) for patients who received placebo, and median overall survival was 12.5 months (10.6-14.8) compared to 10.7 months (8.7-12.8) for the placebo arm.

1.3 AR-42

AR-42, the investigational agent in this study, is an orally bioavailable, small molecule, broad-spectrum inhibitor of histone deacetylase (HDAC) and non-histone protein deacetylation (pan-DAC) which has also been shown to inhibit Akt by a deacetylation-independent mechanism. HDAC inhibitors are a class of anticancer agents that suppress tumor cell growth via a broad spectrum of mechanisms including the ability to induce growth arrest, differentiation, and apoptosis in cancer cells (12-14).

AR-42, a class I and class II HDAC inhibitors, belongs to a novel class of potent phenylbutyrate-based HDAC inhibitors possessing submicromolar HDAC-inhibitory activity. In addition to HDAC inhibition, AR-42 has also been shown to work via histone-independent mechanisms including acetylation of tubulin (affects cytoskeletal integrity), Ku70 (inhibits DNA double-strand break repair), and Hsp90 (chaperone protein) (15-17). AR-42 also works via a deacetylation-independent pathway inhibiting Akt by increasing protein phosphatase I activity. Studies of AR-42 in a number of in vitro and in vivo models across a broad range of tumor types, both as a single agent and in combination, have shown AR-42 to be a potent HDAC inhibitor which targets multiple aspects of cancer cell survival including Akt signaling, mitochondrial integrity, and caspase activity.

1.3.1 AR-42 Preclinical Data

AR-42 has been studied in several cancer models including prostate, hepatocellular, and ovarian (16, 18). Antiproliferative effects via HDAC inhibition and apoptosis induction mechanisms were confirmed in both tumor cell lines and tumor xenograft studies. The effect of AR-42 on hematologic malignancies, including lymphocytic leukemia, mantle cell leukemia, and acute myelogenous leukemia, has also been studied.

Safety studies to assess potential adverse effects on the central nervous system (CNS) (rats), the cardiovascular system (dogs), and the respiratory system (rats) are completed (19). There were no adverse effects on respiration rate or tidal volume in rats after oral administration of AR-42. At normal doses there were no CNS effects noted in rats, whereas at high doses there were mild and reversible depressive effects noted. There was a lower-than-expected prolongation of the QT interval in comparison to other HDAC inhibitors.

In the most sensitive animal model (beagle dogs), an AR-42 dose of 1 mg/kg (20 mg/m^2) was not toxic when given every other day PO for 7days or 28 days. Even at 3 mg/kg (60 mg/m^2), AR-42 resulted in slight decrements in weight and some decrease in red and white blood cell counts, some vomiting, and some diarrhea.

1.3.2 AR-42 Clinical Data

Two clinical studies have been conducted with AR-42: a first into man (FIM) study and a pharmacodynamics study in combination with decitabine (19). The FIM study enrolled 44 patients with multiple myeloma, chronic lymphocytic leukemia, lymphoma, and solid tumors. AR-42 was administered at doses of 20-70 mg/day, 3-times-per-week for 3 weeks, followed by 7 days off treatment. Another study looked at AR-42 plus decitabine (20 mg/m^2) in 13 adult patients with relapsed or refractory AML. Doses of AR-42 ranging from 10-40 mg/day administered with decitabine on days 6-15 were used. To date, a total of 57 patients have been treated with AR-42 in these 2 clinical trials.

Of the 44 patients enrolled in the FIM study, approximately half of the treatment-emergent adverse events were considered to be related to AR-42 by the study investigator (661 events of a total of 1295 treatment-emergent AEs). There were 4 deaths reported within 30 days of AR-42 being discontinued. One death in the hematologic cancer group was considered to be related, but the other 3 deaths were considered to be unrelated to AR-42. The related death occurred at the 50 mg dose during cycle 2 in a patient with cutaneous T-cell lymphoma. The patient developed the following AEs: thrombocytopenia (grade 3 during cycle 1; grade 2 during cycle 2), increased creatinine (grade 2), and hypotension (grade 2). AR-42 was held on day 8 of cycle 2. The patient was found unresponsive 2 days later, and the investigator considered the event a dose-limiting toxicity (DLT).

Eight serious adverse events (SAEs) were considered to be related to AR-42. The SAEs included a psychiatric disorder (grade 4), lung infection (2 events, both grade 3), a thromboembolic event (grade 3), hematuria (grade 3), increased creatinine (grade 1), anemia (grade 3), and decreased platelet count (grade 3). All SAEs were reported to be possibly related to AR-42 except for grade 3 thrombocytopenia which was reported with probable attribution to AR-42. Both lung infections were seen in patients at the 40 mg dose. The psychiatric disorder was seen in a patient at the 80 mg dose and was considered a DLT. All other SAEs occurred in patients at the 60 mg dose level, 4 of which occurred in the same patient (hematuria, increased creatinine, anemia, and thrombocytopenia).

QTc interval was also monitored in the FIM study. Seven out of the 27 patients with hematologic malignancy had QTc prolongation-related events. All events were grade 1 with no significant cardiac toxicities. None of the patients with solid tumors experienced prolongation of the QTc interval.

Three patients died within 30 days of drug being stopped in the study of AR-42 and decitabine combination treatment. One of these deaths was considered to be related to study medication. A patient with refractory AML developed febrile neutropenia (grade 3), dyspnea (grade 2), catheter-related infection (grade 3), hypoxia (grade 3), lung infection (grade 3), and gram-negative bacteremia. The patient expired from complications of lung infection and pseudomonas sepsis. This death, which occurred in cycle 1, was deemed a DLT by the data safety monitoring board.

The most common drug-related AEs were cytopenias (ie, decreased platelet, neutrophil, white blood cell, and lymphocyte counts), anemia, fatigue, nausea, and diarrhea.

1.4 Combination of Pazopanib and HDAC Inhibitors

1.4.1 Mechanisms of Action

Pazopanib and HDAC inhibitors interact in an additive to a greater than additive fashion to kill sarcoma and kidney cancer cells in vitro. In prior studies using the multikinase inhibitor sorafenib, Virginia Commonwealth University (VCU) investigator Paul Dent, PhD and colleagues have shown that knock down of PDGFRβ can stimulate the number of autophagosome vesicles in cells. Pazopanib is an inhibitor of PDGFRβ, therefore, Dent hypothesized that autophagy plays a role in the survival/killing of pazopanib-treated cells (20, 21). Treatment of HT1080 cells with pazopanib + valproate, another HDAC inhibitor, increased the number of LC3-GFP and LC3-RFP vesicles, indicating increased autophagy (Figure 1) (22).

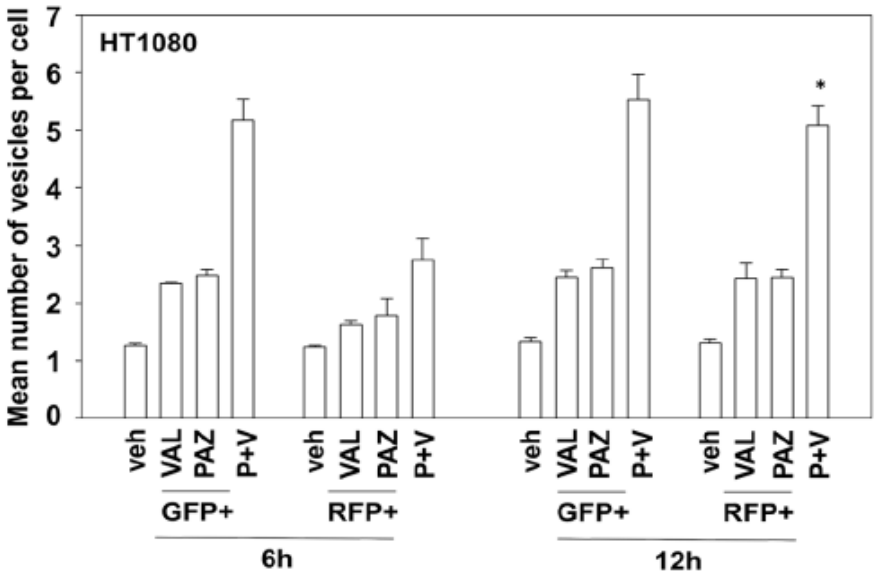

Figure 1. Regulation of Autophagy by Pazopanib and Valproate

HT1080 cells were transfected with a plasmid to express LC3-GFP-RFP. Twenty-four hours after transfection cells were treated with vehicle (DMSO), pazopanib (PAZ, 5.0 μM), and/or valproate (VAL, 500 μM). Cells were microscopically examined 6 hours and 12 hours after exposure and the number of GFP and RFP punctae determined in at least 40 random cells per condition (n=3, ± SEM). *P < 0.05 greater than the value at 6 hours (22).

Chloroquine treatment, which inhibits autophagosome fusion with lysosomes, decreased the numbers of LC3-RFP+ vesicles (data not shown). Collectively, these data demonstrate that autophagic flux was being stimulated. The multikinase inhibitor pazopanib increased the levels of LC3-GFP+ vesicles and in a chloroquine-dependent and time-dependent manner to a lesser extent LC3-RFP+ vesicles, indicating that autophagic flux was occurring. Knock down of either Beclin1 or ATG5 blocked drug-induced LC3-GFP+/LC3-RFP+ vesicle formation and protected cells from the toxic effects of treatment with pazopanib + HDAC inhibitor (Figure 2).

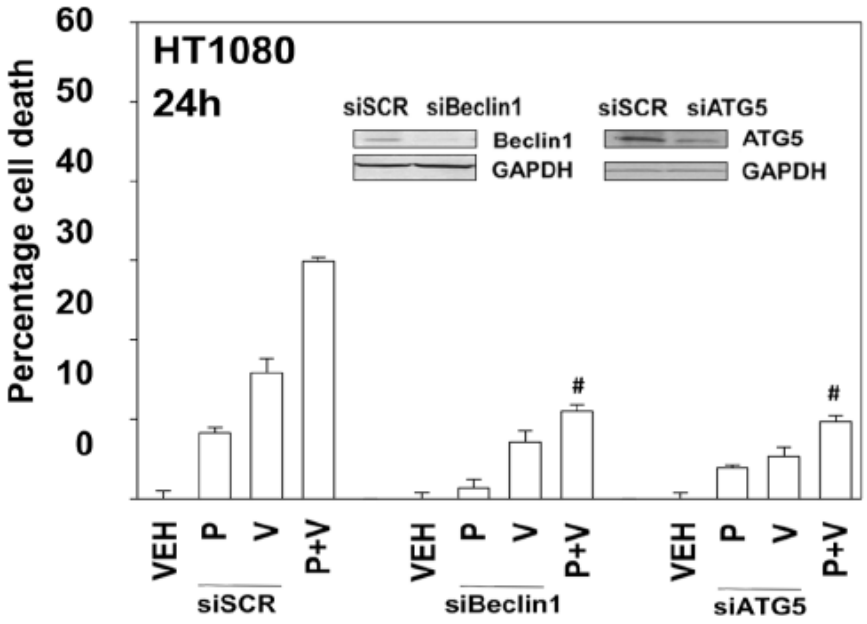

Figure 2. Knockdown of Beclin1 or ATG5 Protects Cells from Pazopanib and Valproate Toxicity

HT1080 cells were transfected with scrambled control siRNA (siSCR) or siRNA molecules to knock down expression of Beclin1 (siB1) or ATG5 (siA5). Thirty-six hours after transfection cells were treated with vehicle (DMSO), pazopanib (P, 5.0 μM), and/or valproate (V, 500 μM). Cells were isolated 24 hours after exposure and viability determined by trypan blue exclusion (n=3, ± SEM). #P < the corresponding value in siSCR cells (22).

Autophagy data using pazopanib, which were similar to our own, were recently reported in bladder cancer cells (23). In addition to autophagy, the intrinsic or extrinsic apoptosis pathways played a role in cell killing caused by the pazopanib/HDAC inhibitor drug combination. Overexpression of the mitochondrial protective protein BCL-XL or the caspase 8 inhibitor c-FLIP-s significantly reduce drug combination lethality. As caspase 8 appeared to be playing a role in cell death, we determined whether death receptor signaling was involved. Knockdown of the death receptor CD95 or the death receptor/caspase 8 docking protein FADD also significantly reduced cell killing caused by the drug combination. Expression of both activated Akt and activated MEK1 was required to strongly suppress drug combination lethality. The drug combination inactivated mTOR, and expression of activated mTOR strongly suppressed drug combination lethality (Figure 3).

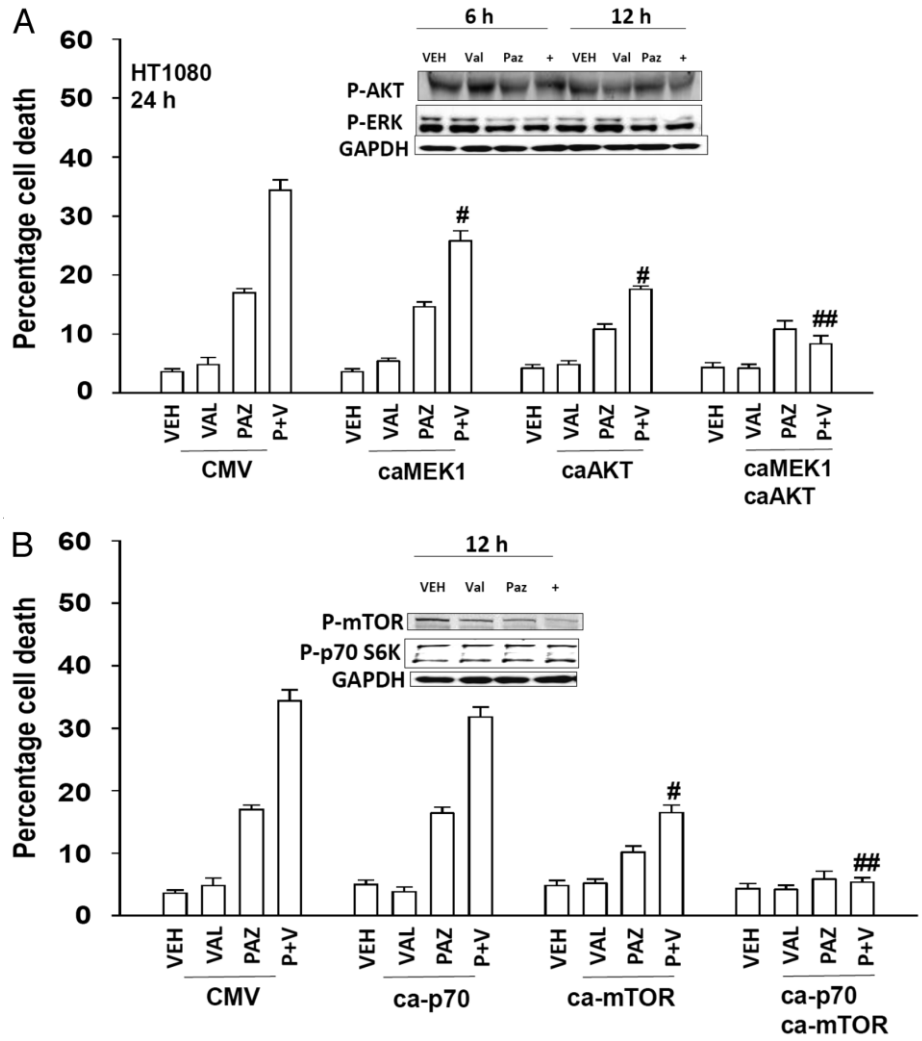

Figure 3. Expression of Activated Akt and MEK1 Suppresses Toxicity of Pazopanib and Valproate

(A) HT1080 cells were infected (50 minimum effective MOI) with empty vector control virus (CMV) or with viruses to express activated MEK1 (caMEK1), activated Akt (caAkt), or caMEK1 and caAkt together. Twenty-four hours after infection, cells were treated with vehicle (DMSO), pazopanib (PAZ, 5.0 μM), and valproate (VAL, 500 μM). Cells were isolated 24 hours after exposure and viability determined by trypan blue exclusion (n=3, ± SEM) #P < the corresponding value in CMV infected cells; ##P < the corresponding value in caAkt infected cells. (B) HT1080 cells were transfected with empty vector plasmid (CMV), with a plasmid to express activated p70 S6K (ca-p70), with a plasmid to express activated mTOR (ca-mTOR), or with both plasmids together. Twenty-four hours after infection, cells were treated with vehicle (DMSO), pazopanib (PAZ, 5.0 μM), and valproate (VAL, 500 μM). Cells were isolated 24 hours after exposure and viability determined by trypan blue exclusion (n=3, ± SEM) #P < the corresponding value in CMV transfected cells; ##P < the corresponding value in ca-mTOR transfected cells (22).

1.4.2 Inhibition of Chaperone Protein Function

In several 2015 studies conducted after publication of the initial pazopanib + HDAC inhibitor manuscript, we have shown that pazopanib can alter the tertiary conformation of chaperone proteins at their NH2-termini, as judged by occlusion of the antibody epitope and using in situ immunofluorescence on native proteins (unpublished data). Pazopanib reduced the immunofluorescence detection of HSP90, HSP70, and GSP78 using an NH2-terminal-specific antibody but not using antibodies directed against epitopes in the middle and COOH-terminal portions of the proteins. This altered detection effect was observed in multiple other chaperone proteins (Figure 4). AR-42 has also been shown to potentially disrupt heat shock protein 90 (HSP90) chaperone function (24). Modulation of HSP protein function has been explored as an anticancer therapeutic approach for years, and this approach has demonstrated antitumor activity in a variety of malignancies (25).

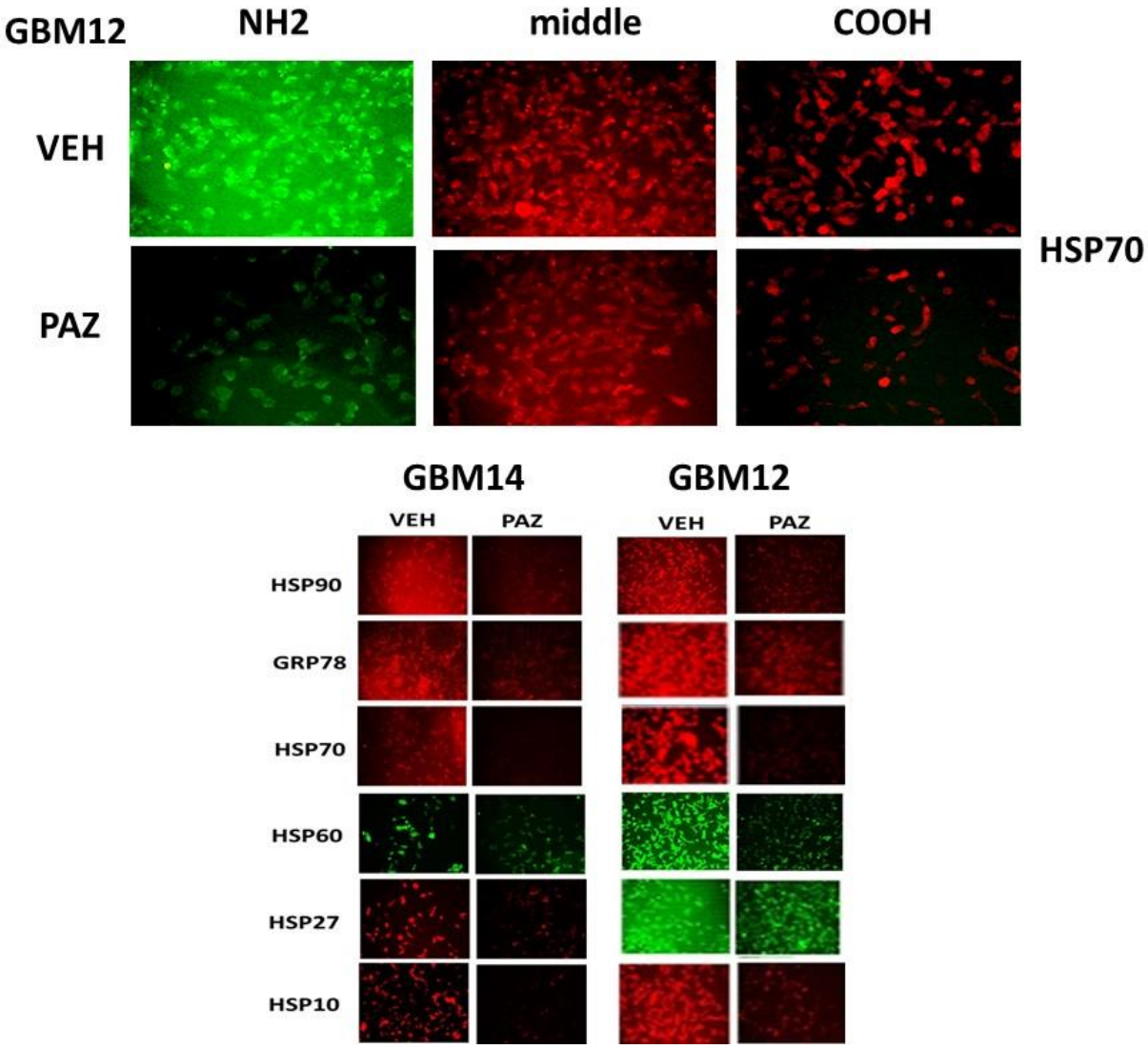

Figure 4. Modulation of HSP70 NH2-terminal Detection by Pazopanib

Upper: GBM12 cells were treated with vehicle or pazopanib (2 μM) for 2 hours. Cells were fixed in place and permeabilized using 0.5% Triton X100. Immunofluorescence was performed to detect the expression levels of HSP70 using antibodies raised to detect the NH2-terminus; the middle; and COOH terminus of the protein.
Lower: GBM14 and GBM12 cells were treated with vehicle or pazopanib (2 μM) for 2 hours. Cells were fixed in place and permeabilized using 0.5% Triton X100. Immunofluorescence was performed to detect the expression levels of the indicated chaperone proteins.

In agreement with the altered ability to detect chaperone NH2-termini, pazopanib (and other drugs) inhibited the chaperone ATPase activities of HSP90 and HSP70 (Figure 5).

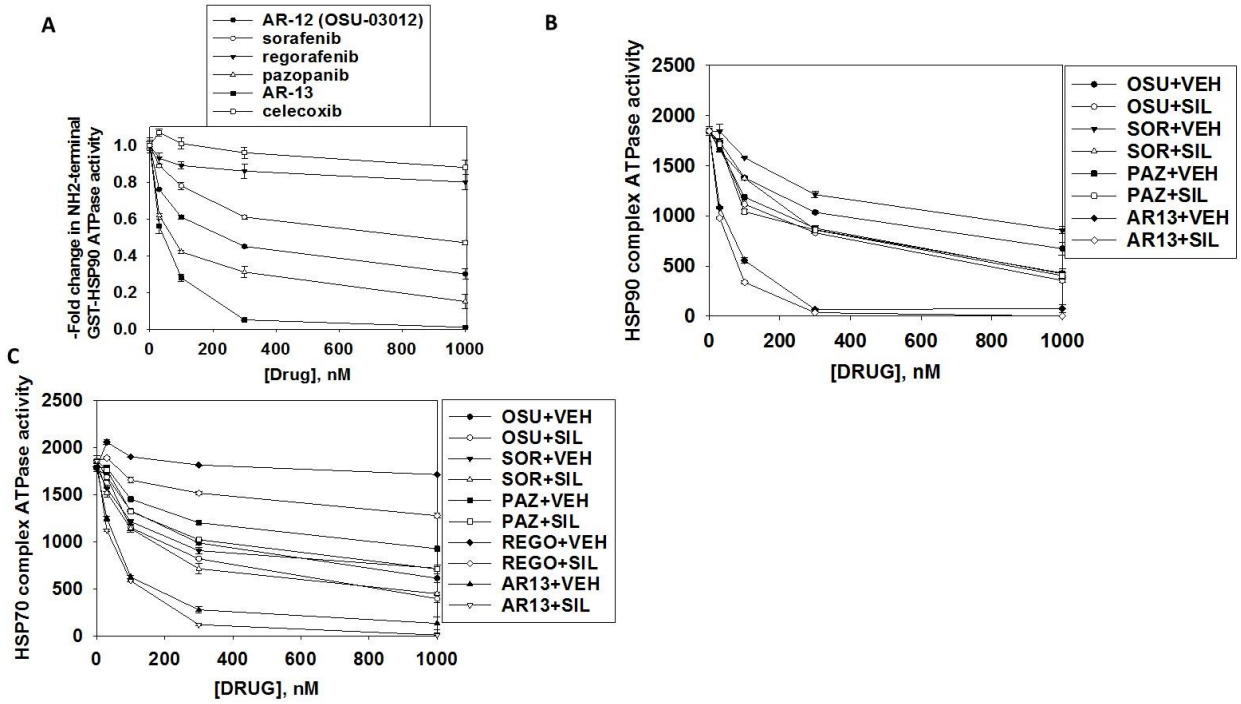

Figure 5. Sildenafil Enhances the ATPase Inhibitory Effects of Regorafenib, Sorafenib, Pazopanib, AR-13, and OSU-03012

A. A GST-HSP90 NH2-terminal fragment containing the ATP-binding domain of the chaperone was synthesized in *E. coli* and purified from other bacterial proteins using glutathione sepharose. The GST-HSP90 NH2-terminal fragment protein *was not* eluted off the sepharose beads. Equal portions of beads were immediately aliquoted into individual wells in a 96-well plate. Beads were resuspended in kinase reaction buffer containing vehicle control; OSU-03012; sorafenib tosylate; regorafenib; pazopanib; AR-13; celecoxib (30 nM; 100 nM; 300 nM; 1 μM) in triplicate, and incubated for 30 minutes at 37 °C. The reaction was started by addition of ATP-lite substrate. The plate was removed from the incubator and placed into a Vector 3 plate reader to determine the luminescence of the reactions under each treatment condition (n=3 (x 3) +/- SEM).
B. and C. GBM12 cells were transfected with a plasmid to express HSP70-GFP or to express FLAG-tagged HSP90. Twenty-four hours after transfection cells were treated with vehicle control or sildenafil (2 μM) for 1 hour. Chaperone proteins were immunoprecipitated using their tags in the presence of phosphatase inhibitors. Equal portions of precipitate sepharose beads were immediately aliquoted into individual wells in a 96-well plate. Beads were resuspended in ATPase reaction buffer containing vehicle control; OSU-03012; sorafenib tosylate; regorafenib; pazopanib; AR-13; (30 nM; 100 nM; 300 nM; 1 μM) in triplicate, and incubated for 30 minutes at 37 °C. The reaction was started by addition of ATP-lite substrate. The plate was removed from the incubator and placed into a Vector 3 plate reader to determine the luminescence of the reactions under each treatment condition (n=3 (x 3) +/- SEM).

In further agreement with pazopanib acting as a chaperone inhibitor, the association of chaperone proteins in complexes with other chaperone proteins was disrupted by pazopanib as judged after immunoprecipitation of endogenous chaperone proteins (Figure 6).

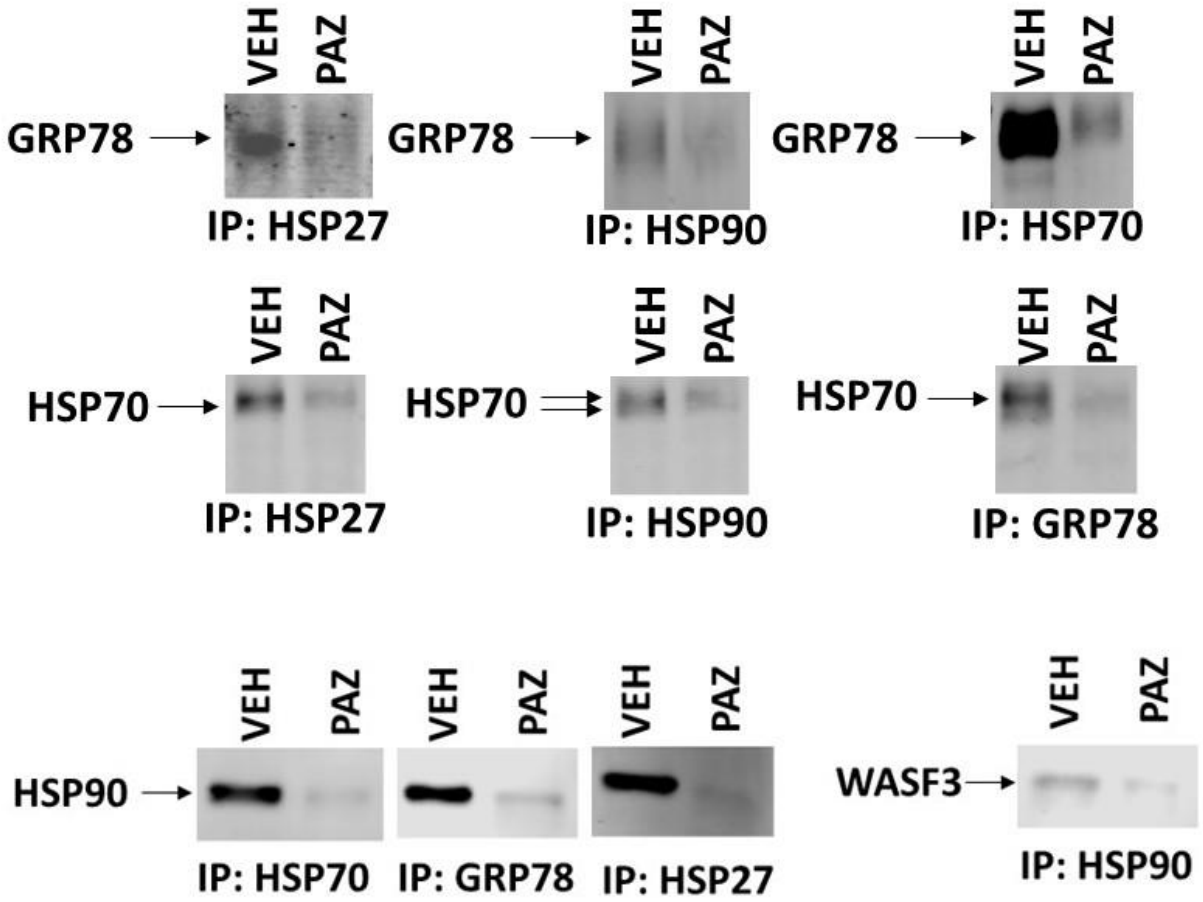

Figure 6. Pazopanib Alters Chaperone–Chaperone Interactions Assessed after Immunoprecipitation

GBM12 cells were treated with vehicle or with pazopanib (2 μM); for 10 minutes and then lysed. Immunoprecipitation of HSP90, GRP78, HSP27, and HSP70 was performed in the presence or absence of each drug individually (2 μM) for 3 hours. Cells were washed with lysis buffer in the presence or absence of each drug individually (3 x 1 hour, each). Immunoprecipitates were then boiled in SDS PAGE buffer containing glycerol and bromophenol blue. Proteins were separated on SDS PAGE (12% and 14% gels) and immunoblotting performed for the proteins as indicated.

1.4.3 In Vivo Data

In vitro findings were translated into an animal model system. At the doses of drug used and for the treatment time, neither pazopanib nor valproate caused a large reduction in tumor mass. However, treatment of the animals with the drug combination resulted in a significantly reduced rate of tumor growth (Figure 7).

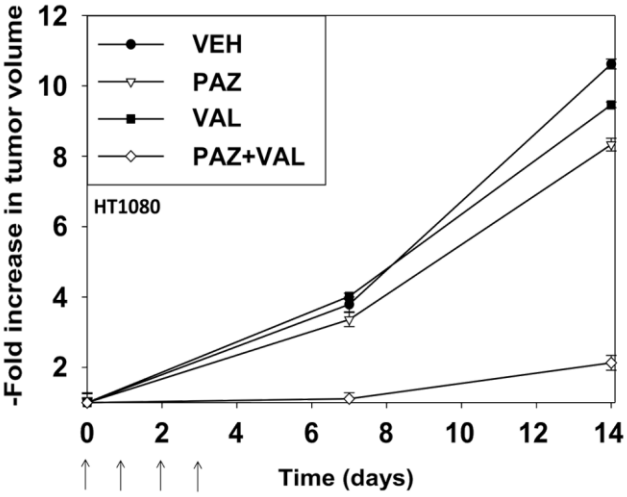

Figure 7. Pazopanib and Valproate Interact to Suppress the Growth of Established HT1080 Tumors

Mice were injected in the rear flank with 1.0×10^7 HT1080 cells in 100 µl of growth medium. Fourteen days after tumor cell implantation when tumors had grown to ~50 mm^3 (defined as 1.00 in the graph) mice were PO administered vehicle diluent, pazopanib (25 mg/kg, QD), valproate (50 mg/kg BID), or the drugs in combination for 4 days. Animals were monitored daily and tumor volumes measured every 7 days. (Values plotted are the fold change in mean tumor volume at each time point; ± SEM, 8 mice per treatment condition.) (22)

1.4.4 Combination of Pazopanib and AR-42

In multiple sarcoma and kidney cancer cell lines, at clinically achievable doses, pazopanib and an HDAC inhibitor (including valproate, vorinostat, and AR-42) interacted in an additive to greater than additive fashion to cause tumor cell death (Figure 8, Figure 9, Figure 10, and Figure 11). The antitumor effects seen with the combination of pazopanib with AR-42 was more pronounced than with the other HDAC inhibitors used in laboratory models.

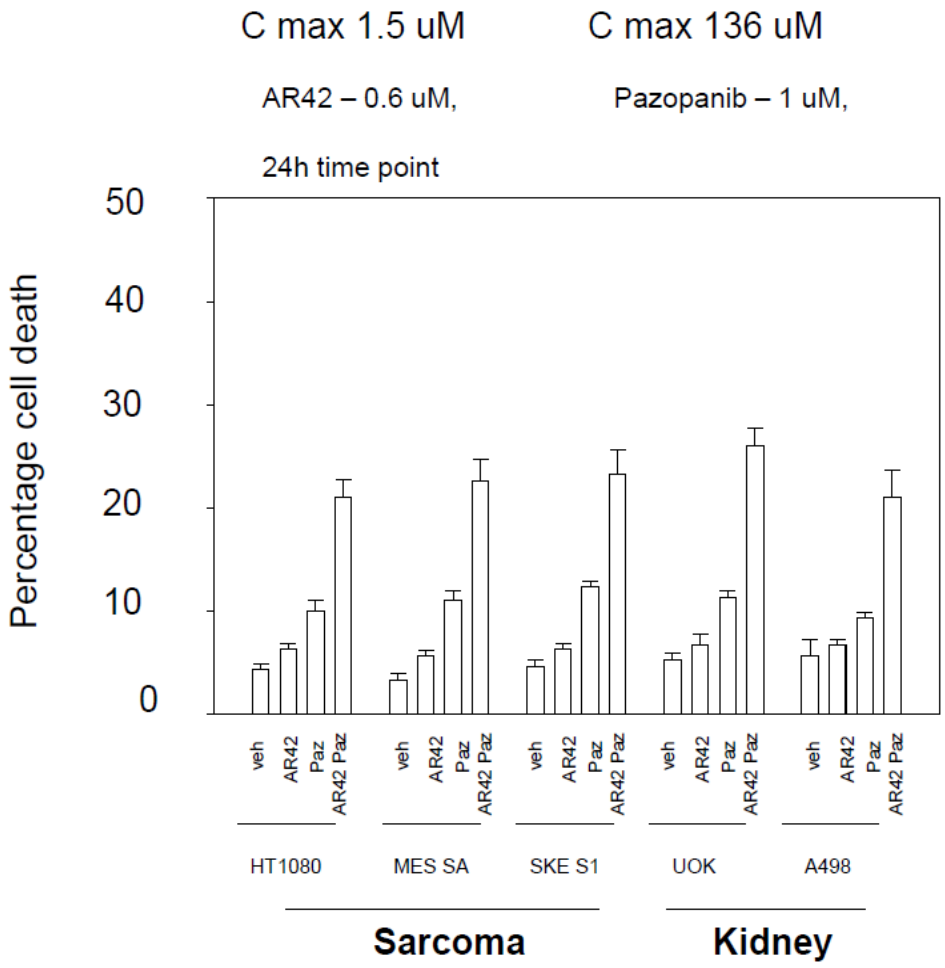

Figure 8. AR-42 and Pazopanib (1 μM) Interact to Kill Sarcoma and Kidney Cancer Cells at the 24-Hour Time Point

Tumor cells were treated with vehicle (VEH, DMSO), pazopanib (PAZ, 1.0 μM), and/or AR-42 (600 nM) as indicated. Cells were isolated 24 hours after exposure and viability determined by trypan blue exclusion (n=3, ± SEM).

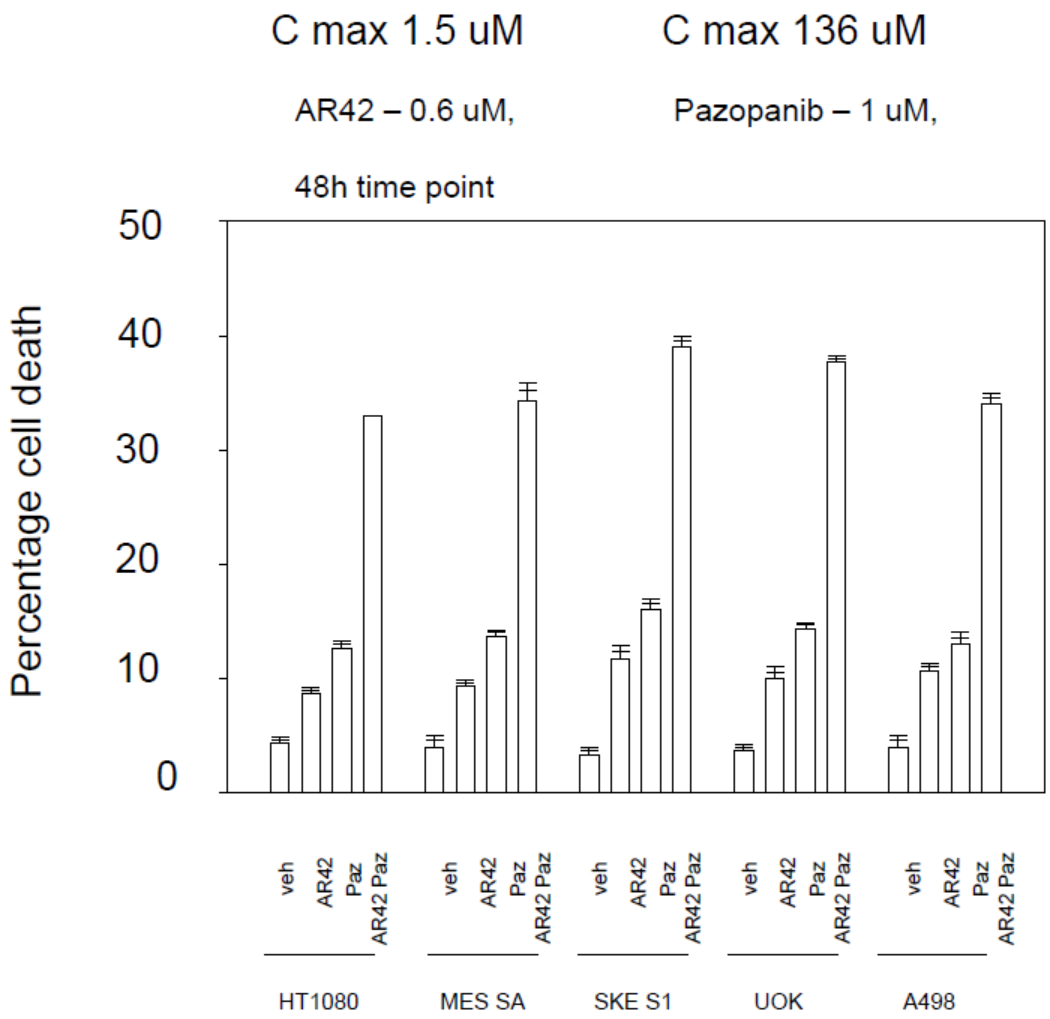

Figure 9. AR-42 and Pazopanib (1 μM) Interact to Kill Sarcoma and Kidney Cancer Cells at the 48-Hour Time Point

Tumor cells were treated with vehicle (VEH, DMSO), pazopanib (PAZ, 1.0 μM), and/or AR-42 (600 nM) as indicated. Cells were isolated 48 hours after exposure and viability determined by trypan blue exclusion (n=3, ± SEM).

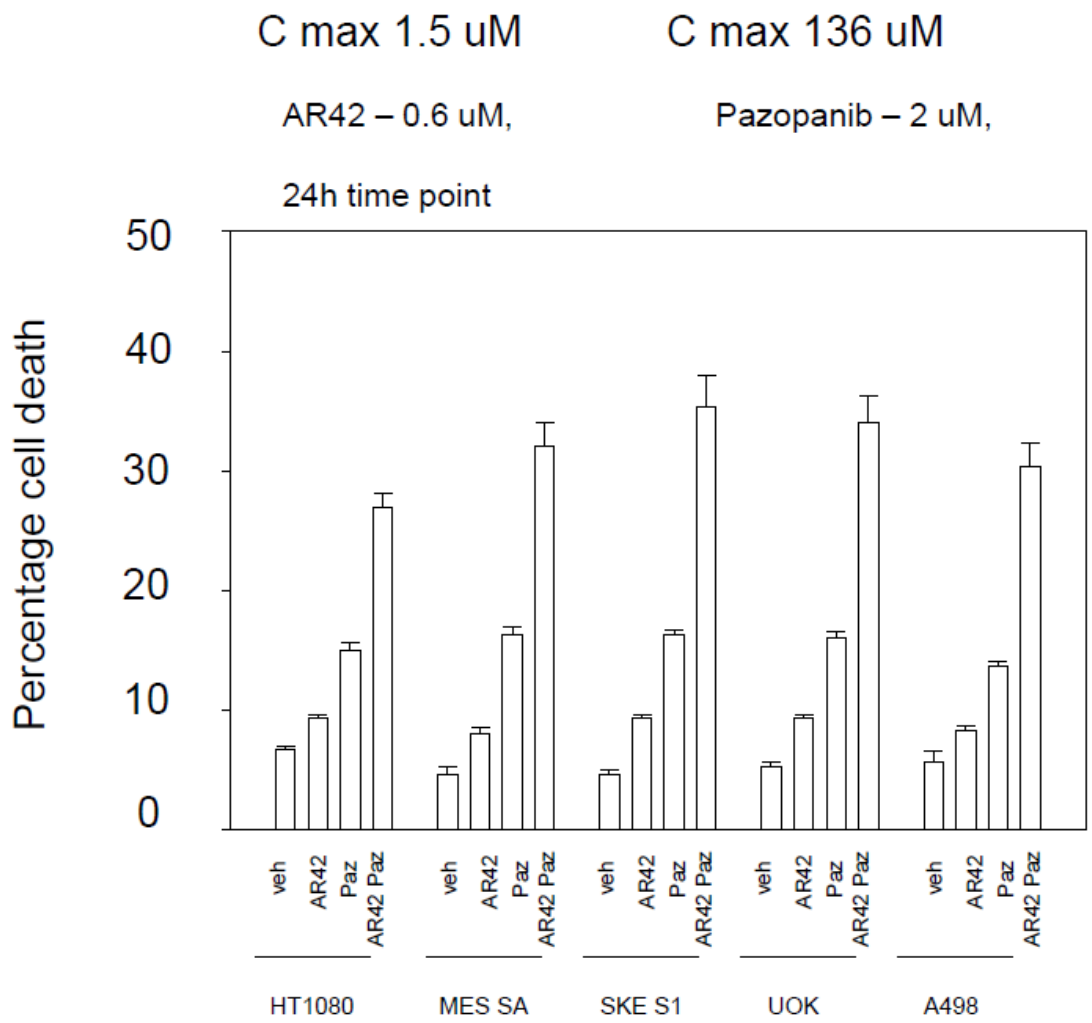

Figure 10. AR-42 and Pazopanib (2 μM) Interact to Kill Sarcoma and Kidney Cancer Cells at the 24-Hour Time Point

Tumor cells were treated with vehicle (VEH, DMSO), pazopanib (PAZ, 2.0 μM) and/or AR-42 (600 nM) as indicated. Cells were isolated 24 hours after exposure and viability determined by trypan blue exclusion (n=3, ± SEM).

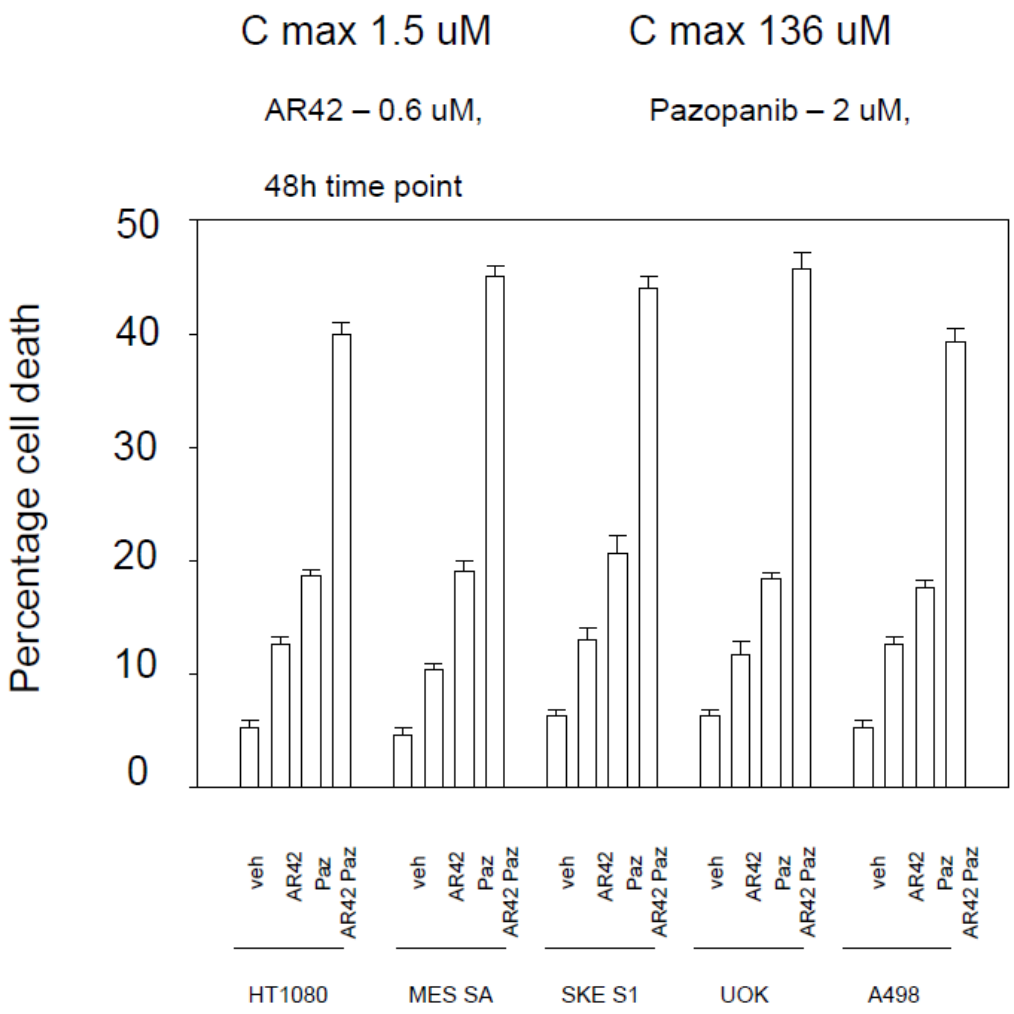

Figure 11. AR-42 and Pazopanib (2 μM) Interact to Kill Sarcoma and Kidney Cancer Cells at the 48-Hour Time Point

Tumor cells were treated with vehicle (VEH, DMSO), pazopanib (PAZ, 2.0 μM), and/or AR-42 (600 nM) as indicated. Cells were isolated 48 hours after exposure and viability determined by trypan blue exclusion (n=3, ± SEM).

1.5 Rationale for the Study

Most highly active cancer chemotherapy regimens involve multiple agents. Pazopanib is an FDA-approved agent for the treatment of both advanced RCC and STS. AR-42 is a broad-spectrum inhibitor of HDAC and non-histone protein deacetylation (pan-DAC inhibitor) which has also been shown to inhibit Akt by a deacetylation-independent mechanism. Preclinical studies in both tumor cell lines and animal tumor models have shown promising anticancer effects of the combination of AR-42 and pazopanib suggesting that the combination should be tested clinically. Preclinical studies also suggest that these promising anticancer effects may be related to modulation of tumor cell autophagy. This phase 1 study will identify recommended phase 2 doses (RP2Ds) of AR-42 and pazopanib when given in combination for subsequent clinical trials and may potentially identify candidate pharmacodynamic and predictive biomarkers.

1.6 Correlative Studies

Archived tumor samples from the most recent biopsy or surgery will be used to correlate expression of CD95 and other cellular proteins of interest with response to AR-42 and pazopanib exposure.

2 OBJECTIVES

2.1 Primary Objective

To determine the recommended phase 2 doses (RP2Ds) of AR-42 and pazopanib when given in combination

2.2 Secondary Objectives

2.2.1 To evaluate the safety and toxicity of AR-42 and pazopanib when given in combination

2.2.2 To explore the antitumor effects of the AR-42 and pazopanib treatment regimen in patients with advanced RCC or STS

2.3 Exploratory Objective

To correlate expression of CD95 and other cellular proteins of interest with response to AR-42 and pazopanib treatment

3 STUDY DESIGN

3.1 General Description

This study is a single-arm, open-label, phase 1 trial to determine the RP2Ds of AR-42 and pazopanib when given in combination to patients with advanced RCC or STS. Eligible patients will have recurrent, unresectable, or metastatic RCC or STS for which pazopanib is an appropriate therapy.

AR-42 will be taken orally once per day on 3 non-consecutive days each week during the first 3 weeks of each 4-week cycle. Pazopanib will be taken by mouth once daily continuously during each cycle.

A modified 3+3 dose-escalation design will be followed until the maximum tolerated doses (MTDs) have been determined. Additional patients will be enrolled until a total of 12 patients have been treated at the MTDs. The maximum number of patients needed is 51 with an expected sample size of 29-35 patients enrolled over a period of about 15-35 months.

Correlative studies will be conducted using samples of tumor that were archived following the most recent surgery or biopsy.

3.2 Primary Endpoint

RP2Ds for AR-42 and pazopanib that are the same as or less than the MTDs

3.3 Secondary Endpoints

3.3.1 AEs characterized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0) to determine the safety and toxicity of the combination of AR-42 and pazopanib

3.3.2 Tumor response based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

3.4 Exploratory Endpoint

Expression of CD95 and other proteins of interest by immunohistochemical (IHC) analysis using archived tumor samples from the most recent diagnostic biopsy or surgery (performed before initiation of study treatment) correlated with response to study treatment

4 PATIENT SELECTION

4.1 Inclusion Criteria

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

4.1.1 Recurrent, unresectable, or metastatic RCC or STS (any histologic type) for which pazopanib is an appropriate therapy

4.1.2 Measurable or evaluable disease by RECIST v1.1

4.1.3 Age ≥ 18 years

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

4.1.5 Adequate bone marrow function as defined below:

- Absolute neutrophil count (ANC) ≥ 1200/mm^3
- Platelets ≥ 120,000/mm^3
- Hemoglobin ≥ 9.5 g/dL

4.1.6 Adequate renal function as defined below:

- Creatinine ≤ 1.5 x upper limit of normal (ULN) for the laboratory or calculated or actual creatinine clearance ≥ 60 mL/min (see Appendix 2 for the Cockcroft-Gault formula for calculating creatinine clearance)
- Proteinuria ≤ 2+ [100 mg/dL]) using a random urine sample or < 3.0 gm using a 24-hour sample)

  Note: If urine sample indicates ≥ 2+ [100 mg/dL]), a 24-hour urine sample must be collected and tested; urine protein in the 24-hour sample must be < 3.0 gm/24 hours.

4.1.7 Adequate hepatic function as defined below:

- Total bilirubin ≤ 1.5 x ULN for the laboratory

  Note: Patients with known Gilbert's Syndrome are **not** eligible for this study (Section 4.2.10).
- Aspartate aminotransferase (AST) ≤ 2.5 x ULN for the laboratory
- Alanine aminotransferase (ALT) ≤ 2.5 x ULN for the laboratory

4.1.8 Non-hematologic toxicities from previous cancer therapies resolved to ≤ grade 1

4.1.9 International normalized ratio (INR) ≤ 1.5

4.1.10 Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN for the laboratory

4.1.11 Left ventricular ejection fraction (LVEF) assessment (eg, echocardiogram, MUGA scan, first-pass technique) performed within 3 months prior to initiation of study treatment indicates an LVEF of ≥ 50%

4.1.12 A woman of childbearing potential (WCBP), defined as a woman who is < 60 years of age and has not had a hysterectomy, must have a documented negative serum pregnancy test within 7 days prior to initiating study treatment

4.1.13 A WCBP and a male patient with a partner who is a WCBP must agree to use a medically accepted method for preventing pregnancy for the duration of study treatment and for 2 months following completion of study treatment

4.1.14 Ability to understand and willingness to sign the consent form

4.2 Exclusion Criteria

A patient who meets any of the following exclusion criteria is not eligible to participate in this study.

4.2.1 Symptomatic or untreated brain metastasis

4.2.2 Leptomeningeal metastasis

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

4.2.4 Previous therapy with pazopanib

4.2.5 Inability to swallow medication

4.2.6 Known or suspected malabsorption condition or obstruction

4.2.7 Contraindication to antiangiogenic agents, including:

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

4.2.8 History of organ allograft including corneal transplant

4.2.9 Evidence of bleeding diathesis or coagulopathy

4.2.10 Documented Gilbert's Syndrome

4.2.11 Resting systolic blood pressure (BP) < 100 mmHg

4.2.12 Hypertension defined as systolic BP ≥ 140 mmHg **or** diastolic BP ≥ 90 mmHg despite optimal medical management

4.2.13 QTc interval > 450 ms on screening 12-lead electrocardiogram (ECG)

- If baseline QTc on screening ECG meets exclusion criteria:
  - Check calcium, potassium, and magnesium serum levels.
  - Correct any identified hypocalcemia, hypokalemia, and/or hypomagnesemia and repeat ECG to confirm exclusion of patient due to prolonged QTc interval.
- For patients with heart rate (HR) 60-100 bpm, manual read of QTc is not required.
- For patients with a baseline HR < 60 bpm or > 100 bpm, manual read of the QT interval by a cardiologist is required, with Fridericia correction applied to determine QTc (ie, QTcF).

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

- Unstable angina (eg, anginal symptoms at rest) or onset of angina within 3 months prior to initiating study treatment
- Myocardial infarction within 6 months prior to initiating study treatment
- Cardiac arrhythmias currently requiring anti-arrhythmic therapy other than beta blockers

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

Note: Patients with a tumor-associated thrombus of locally-involved vessels should not be excluded from participating in the study.

4.2.16 Active infection requiring treatment or chronic infection requiring suppressive therapy

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

4.2.18 Pleural effusion or ascites that causes respiratory compromise (eg, ≥ grade 2 dyspnea)

4.2.19 Required ongoing treatment with other drugs thought to potentially have adverse interactions with either of the medications included in the study treatment; if such medications have been used, patients must have discontinued these agents at least 1 week prior to initiating study treatment. Examples include:

- **Strong** CYP3A4 inhibitors and/or **strong** CYP3A4 inducers; the reference list of CYP isozymes and classification of strong, moderate, and weak interactions are available through the FDA website, Tables 5 and 6: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
- **Strong** inhibitors of P-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP); the reference list of strong inhibitors of P-gp and BCRP is available through the FDA website, Table 9: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
- Simvastatin and other HMG-CoA reductase inhibitors (ie, statins)
- Drugs that raise gastric pH including proton pump inhibitors and H2-blockers

  Note: Short-acting antacids, in place of PPIs and H2-blockers, are permitted.
- HDAC inhibitors

4.2.20 Pregnancy or breastfeeding

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

5 STUDY ENTRY AND WITHDRAWAL PROCEDURES

5.1 Study Entry Procedures

5.1.1 Required Pre-Registration Screening Tests and Procedures

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

5.1.2 Registration Process

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

- Completed registration cover sheet
- Completed, signed, and dated eligibility checklist
- Signed and dated consent form

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

Study treatment may not begin until the Confirmation of Registration assigning a study ID number has been received from the registrar. The registering study team will enter the patient’s initial enrollment data (eg, demographics, consent, eligibility, on-study, treatment assignment) into the OnCore database within 24 hours of registration (before study treatment begins).

5.2 Study Withdrawal

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

- Unacceptable toxicity defined as toxicity that requires holding one or both of the study medications for more than 21 consecutive days
- Consent withdrawal for study treatment and study procedures
- If, in the investigator's opinion, continuation of the study requirements would be harmful to the patient's well-being
- Patient is lost to follow-up

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

6 TREATMENT PLAN

6.1 Baseline Tests and Procedures

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

6.2 Administration of Study Treatment

6.2.1 AR-42 Administration and Treatment Schedule

- AR-42 tablets will be taken orally once per day on 3 non-consecutive days per week (eg, Monday, Wednesday, and Friday) during the first 3 weeks of each 4-week cycle (ie, a total of 9 doses). A 7-day "AR-42 rest period" during which AR-42 will not be taken is required at the end of each cycle (ie, AR-42 will not be taken by the patient during week 4 of each 4-week cycle).

- If treatment must be interrupted during the cycle, the cycle may be extended to a maximum of 5 weeks. If the cycle has been extended to 5 weeks, all doses of AR-42 (ie, a total of 9 doses) must be taken during the first 4 weeks of the extended cycle (ie, if the cycle was extended, AR-42 will not be taken by the patient during week 5 of the 5-week cycle).

- Patients will be instructed as follows:
  - Take AR-42 once per day on 3 non-consecutive days during the first 3 weeks of each 4-week cycle.
  - Take AR-42 tablets with water on an empty stomach, ideally the first thing in the morning at least 1 hour before breakfast. If necessary, doses can be taken at least 1 hour before or at least 2 hours following any meal.
  - Swallow the AR-42 tablets whole.

6.2.2 Pazopanib Administration and Treatment Schedule

- Pazopanib tablets will be taken orally once daily continuously during each treatment cycle. There are no scheduled breaks in pazopanib therapy.
- Patients will be instructed as follows:
  - Take pazopanib once daily during each 4-week cycle
  - Take pazopanib tablets with water on an empty stomach, ideally the first thing in the morning at least 1 hour before breakfast. If necessary, doses can be taken at least 1 hour before or at least 2 hours following any meal.
  - Swallow the pazopanib tablets whole.

6.3 Missed Doses

6.3.1 AR-42 Missed Doses

If an AR-42 dose is missed, the missed dose of AR-42 should be taken on the same day, as soon as the patient remembers. If the missed dose cannot be taken on the scheduled day, the patient should take the dose on the next day and adjust the schedule by one day (eg, from Monday, Wednesday, and Friday to Tuesday, Thursday, and Saturday) for the remainder of that cycle. The usual schedule should be resumed at the beginning of the next cycle as long as there has been a 7-day rest period.

6.3.2 Pazopanib Missed Doses

If a pazopanib dose of pazopanib is missed, the missed dose of pazopanib should be taken on the same day, as soon as the patient remembers. Two doses of pazopanib should not be taken on the same day to make up for doses that were missed on the previous day.

6.4 Monitoring Patient Compliance

Patients will be instructed to record the AR-42 and pazopanib doses they have taken on the study medication diary that will be provided. Also, patients will be instructed to bring their diary and any unused supply of AR-42 and pazopanib to each visit with their study team.

Patient reports of self-administration, review of the study medication diary, and pill counts will be used to assess the patient's compliance with the oral study treatment regimen.

6.5 Duration of Therapy

Treatment will continue until any of the following occurs (also see information regarding study withdrawal in Section 5.2):

- Interruption in either of the study medications due to unresolved toxicity for a period of more than 21 consecutive days
- AE that requires discontinuation of **both** study medications (see Section 7)
- Disease progression
- Patient decision to discontinue study treatment
- Investigator determination that discontinuation is in the patient's best medical interest
- Withdrawal of study sponsor support

6.6 AR-42 and Pazopanib Dose-Escalation Plan

The dose-escalation plan is based on the available dose levels listed on Table 1, the dose level instructions outlined on Table 2, and the modified 3+3 design on Table 3.

- The initial cohort of patients will be assigned to an AR-42 dose of 20 mg taken once per day on 3 non-consecutive days during the first 3 weeks of each 4-week cycle and a pazopanib dose of 600 mg once daily continuously.
- The treatment schedule as described in Section 6.2 will remain the same for all dose levels.
- The initial escalation will only affect the pazopanib dose so that the FDA-approved full dose of pazopanib (800 mg) is provided early in the dose-escalation plan. In subsequent dose-escalation steps, the dose of AR-42 will be increased in 10-mg increments until the maximum AR-42 dose of 40 mg is reached.
- If the number of DLTs indicates that the MTD has been exceeded with a pazopanib dose of 800 mg, the pazopanib dose will be decreased to 600 mg and the AR-42 dose will continue to increase in 10-mg increments regardless of relationship of the DLT to one or both study medications.

Table 1. AR-42 and Pazopanib Dose Levels

AR-42 Dose	Pazopanib Dose: 600 mg	Pazopanib Dose: 800 mg
40 mg	4B	4A
30 mg	3B	3A
20 mg	1 *(Starting Dose Level)*	2
10 mg	-1	N/A

Table 2. AR-42 and Pazopanib Dose-Escalation Guidelines

Dose Level	AR-42 Dose (Taken orally)	Pazopanib Dose (Taken orally)
	Once per day on 3 non-consecutive days/week during the first 3 weeks of each 4-week cycle	*Once per day continuously during each 4-week cycle*
-1	10 mg	600 mg
– If 0 or 1 DLT is observed with Dose Level -1, the MTD will be Dose Level -1. – If ≥ 2 DLTs are observed at Dose Level -1, the lowest possible dose level was not tolerated.		
1 ***(Starting Dose Level)***	20 mg	600 mg
– If 0 or 1 DLT is observed with Dose Level 1, the next cohort will receive Dose Level 2. – If ≥ 2 DLTs are observed at Dose Level 1, the next cohort will receive Dose Level -1.		
2	20 mg	800 mg
– If 0 or 1 DLT is observed with Dose Level 2, the next cohort will receive Dose Level 3A. – If ≥ 2 DLTs are observed at Dose Level 2, the next cohort will receive Dose Level 3B.		
3A	30 mg	800 mg
3B	30 mg	600 mg
– If 0 or 1 DLT is observed with Dose Level 3A, the next cohort will receive Dose Level 4A. – If ≥ 2 DLTs are observed at Dose Level 3A, the next cohort will receive Dose Level 3B. – If 0 or 1 DLT is observed with Dose Level 3B, the next cohort will receive Dose Level 4B. – If ≥ 2 DLTs are observed at Dose Level 3B, the highest dose level without ≥ 2 DLTs will be the MTD.		
4A	40 mg	800 mg
4B	40 mg	600 mg
– If 0 or 1 DLT is observed with Dose Level 4A, the MTD will be Dose Level 4A. – If ≥ 2 DLTs are observed at Dose Level 4A, the next cohort will receive Dose Level 4B. – If 0 or 1 DLT is observed with Dose Level 4B, the MTD will be Dose Level 4B. – If ≥ 2 DLTs are observed at Dose Level 4B, the MTD will be the highest dose level without ≥ 2 DLTs.		

6.7 Definitions of Dose-Limiting Toxicity, Maximum Tolerated Dose, and Recommended Phase 2 Dose

6.7.1 DLT-Evaluable Criteria

The DLT evaluation period will be the first treatment cycle. Patients must have taken a minimum of 6 AR-42 doses **and** a minimum of 21 pazopanib doses during cycle 1 to be considered evaluable for DLT, if DLT has not been observed at the delivered dose.

6.7.2 DLT Definition

DLT is defined as **any ≥ grade 3** toxicity occurring during the DLT evaluation period and attributed to one or both of the study medications **EXCEPT the following:**

- The first incidence of grade 3 PPE at any dose level (subsequent incidences of grade 3 PPE will be considered DLT)
- Grade 3 nausea and vomiting in the absence of adequate prophylaxis and/or responsive to medical management within 48 hours
- Grade 3 diarrhea in the absence of adequate prophylaxis and/or responsive to medical management within 48 hours
- Grade 3 fatigue responsive to medical management
- Grade 3 asymptomatic hypertension lasting ≤ 7 days
- Grade 3 electrolyte abnormalities that are corrected within 48 hours and, when corrected, can be maintained
- Grade 3 asymptomatic lipase elevation lasting ≤ 7 days
- Grade 3 decrease in platelet count if no clinically significant hemorrhage has occurred
- Grades 3 and 4 decrease in white blood cell count
- Grade 3 decrease in neutrophil count
- Grade 4 decrease in neutrophil count lasting ≤ 7 days
- Grades 3 and 4 decrease in lymphocyte count

6.7.3 MTD

Dose escalation will follow a modified 3+3 plan (Table 3) using the dose levels listed in Table 1 and the guidelines in Table 2 to determine the MTDs and the RP2Ds for AR-42 and pazopanib. DLT is defined in Section 6.7.2. Patients will be enrolled in cohorts of 3 beginning at dose level 1.

Table 3. Modified 3+3 Dose Escalation

Number of Patients with DLT at a Given Dose Level *(Refer to Section 6.7.2 for DLT definition)*	**Escalation Decision Rule** *(Refer to Table 1 in Section 6.6 for dose levels and Table 2 for dose-escalation guidelines)*
0 out of 3	Enroll 3 patients at the next dose level.
≥ 2[A]	MTD has been exceeded. No further treatment at this dose is allowed. Three (3) additional patients will be enrolled per dose levels as noted on Table 2.
1 out of 3[A]	Enroll at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, escalate doses to the next dose level (unless MTD has already been exceeded at that dose level, in which case, the current dose level is the MTD).[B] • If 1 or more of this group experience DLT (total of 2), then the MTD has been exceeded. Three (3) additional patients will be enrolled at the next lower dose level if only 3 patients were treated previously at that dose.[B]
Patients enrolled to complete a total enrollment of 12 at the MTD	
≤ 3	The MTD has been confirmed.[B]
≥ 4	The MTD has been exceeded; 3 additional patients will be enrolled at the next lower dose level (if available).[B]

A. The first incidence of grade 3 PPE at any dose level will NOT be considered a DLT. (Subsequent incidences of grade 3 PPE will be considered DLT.)

B. Confirmation that a dose level does not exceed the MTD requires evaluation of a minimum of 6 DLT-evaluable patients. **To confirm the RP2Ds, additional patients will be enrolled at the MTDs until a total of 12 patients have been treated at the MTDs.**

6.7.4 RP2D

The RP2D may be equal to, but may not exceed, the MTD. A RP2D below the MTD may be considered given the overall tolerability of the treatment regimen including the frequency of AEs that are not DLTs and the frequency of dose modifications.

6.8 Required QT Monitoring and QT Interval Prolongation Instructions

6.8.1 Monitoring

- A 12-lead ECG and evaluation of QTc interval will be performed weekly in cycle 1, on day 1 of cycle 2, and then on day 1 of every other cycle.
- If the QTc is ≥ grade 2, follow instructions in Table 7 for additional observation and/or ECG requirements.
- If medically indicated, ECGs may be performed any time during treatment and follow-up.

6.8.2 Requirements for Manual Read of QTc Interval

Any time QTc is evaluated:

- If the HR is < 60 bpm or >100 bpm, manual read of the QT interval by a cardiologist is required; also the Fridericia formula for QT interval correction should be used (ie, QTcF).
- If HR is between 60-100 bpm, a manual read of QTc is NOT required.

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

6.8.3 Concurrent Use of Drugs Known to Cause Clinically Significant QT Prolongation

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

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

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

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

6.8.5 Follow instructions in Table 7 for any episode of syncope (grade 3) or near-syncope (pre-syncope grade 2) or QTc grade 3 (≥ 501 ms on 2 or more ECGs), or grade 4 (≥ 501 ms or > 60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia).

6.9 General Concomitant Medication and Supportive Care Guidelines

6.9.1 Nausea/Vomiting

Anti-emetics should be prescribed as clinically indicated.

6.9.2 Diarrhea

Diarrhea, a common side effect of pazopanib and AR-42, can be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours. Clinically significant diarrhea should be managed aggressively to prevent electrolyte abnormalities and dehydration. Anti-diarrheal prophylaxis should be considered in subsequent cycles.

6.9.3 Fluid and Electrolyte Replacement

- Patients who develop nausea, vomiting, diarrhea, mucositis, anorexia, or other toxicity that can contribute to fluid loss or inadequate fluid intake should be carefully monitored. Fluids should be administered, as indicated, to prevent and/or treat dehydration and to minimize the risk of postural hypotension and renal failure.
- To reduce the risk for prolongation of the QT interval, electrolyte levels (ie, potassium, magnesium, and calcium) should be checked according to the requirements on the study calendar (Table 19 and Table 20). Replacement of electrolytes, if needed, is at the investigator's discretion. Recheck serum potassium, magnesium, and calcium levels after replacement and consider chronic supplementation of potassium, magnesium, and/or calcium.

6.9.4 Palmar-plantar Erythrodysesthesia

PPE, also known as hand-foot skin reaction, has been reported in patients taking pazopanib. Biopsy specimens of patients with PPE secondary to tyrosine kinase inhibition show hyperkeratosis, keratinocyte necrosis, and dermal inflammation. In 240 patients with STS, about 11% of patients who received pazopanib experienced PPE compared to 1% taking placebo.

PPE, associated with pain and limitations in activities of daily living (ADL), may require treatment interruption and/or dose modification. Pazopanib dose modification instructions for PPE are provided in Table 9.

6.9.4.1 PPE Prevention

- Before initiating pazopanib treatment, check the condition of the patient's hands and feet. Suggest a manicure/pedicure, when indicated. Recommend use of a pumice stone for callus or rough spot removal. During pazopanib treatment, instruct patients to avoid pressure points and items that rub, pinch, or create friction.
- Instruct the patient to apply moisturizing lotions to their hands and feet twice each day throughout treatment.

6.9.4.2 PPE Treatment

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

- Instruct the patient to protect tender areas as follows:
  - Use socks/gloves to cover moisturizing creams
  - Wear well-padded footwear; use insole cushions or inserts.
  - Soak feet in tepid water and Epson salts.
- Creams may be used as follows:
  - Non-urea-based creams may be applied liberally.
  - Keratolytic creams (eg, urea-based creams, salicylic acid 6%) may be used sparingly and only to affected (hyperkeratotic) areas.
  - Alpha hydroxyl acids (AHA)-based creams may be applied liberally twice each day. Approximately 5% to 8% strength provides gentle chemical exfoliation.
  - Topical analgesics (eg, lidocaine 2%) may be used for pain control.
  - Topical corticosteroids (eg, clobetasol 0.05%) should be considered for patients with grade 2 or grade 3 PPE. Systemic steroids should be avoided.
- Use of Celecoxib

  A meta-analysis of PPE prevention strategies concluded, with statistically significant results, that celecoxib was the most promising agent (26). Therefore, to reduce the severity of pazopanib-related PPE, celecoxib is recommended as follows:
  - Celecoxib 200 mg once daily may begin at the first clinical signs or symptoms of grade 2 PPE.
  - When PPE resolves, celecoxib 200 mg once daily throughout each treatment cycle, even in the absence of signs or symptoms of PPE, is recommended.

6.9.5 Hypertension

Hypertension, including hypertensive crisis, has been observed during pazopanib therapy. Hypertension should be managed aggressively to prevent complications. Management of hypertension is at the investigator's discretion.

- BP will be monitored weekly during the first 6 weeks of study treatment, at the beginning of every cycle beginning with cycle 3, and as clinically indicated throughout study treatment.
- Refer to Table 7 for grading definitions to be used for pazopanib dose modifications related to hypertension and for treatment instructions. CTCAE v4.0 will be used to grade hypertension for AE reporting purposes.

  Note: Grade 3 hypertension will not be considered a DLT unless the patient is experiencing symptoms of hypertension and/or grade 3 hypertension persisted longer than 7 days. This guideline also applies to hypertension requiring an additional antihypertensive agent(s).

6.9.6 Anemia

Tranfusions, if necessary per the investigator, are permitted.

6.10 Prohibited/Discouraged Medications

- Cancer treatment, other than the treatment specified in the protocol, is not permitted.
- Non-prescription nutritional and dietary supplements are discouraged but not prohibited unless the supplement is known to interact with or modulate drug metabolism pathways, eg, St. John's wort. **Supplements known to have adverse effects on the liver are prohibited.** If nutritional and/or dietary supplements are used, the dose and schedule of the supplements should be documented.
- Hepatotoxicity is a known toxicity of pazopanib. Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations and should be avoided. Also, acetaminophen may confound interpretation of hepatotoxicity and should, therefore, be avoided when possible.
- Drugs and other substances that inhibit or induce cytochrome P450 3A enzymes.

  Refer to Section 4.2.19 for additional information regarding prohibited or discouraged medications. If such medications have been used, the patient must have discontinued these agents ≥ 1 week before starting/resuming pazopanib.
  - Coadministration of pazopanib with strong inhibitors of CYP3A4 (eg, ketoconazole, ritonavir, clarithromycin) should be avoided.
  - Coadministration of CYP3A4 inducers (eg, rifampin) may decrease plasma pazopanib concentrations and should be avoided.
  - Grapefruit and grapefruit juice should be avoided.
- Concomitant treatment with strong inhibitors of P-gp or BCRP should be avoided due to risk of increased exposure to pazopanib.

- Concomitant use of pazopanib with drugs that raise gastric pH should be avoided. If such drugs are needed, short-acting antacids should be considered in place of proton pump inhibitors and H2-receptor antagonists. The antacid and pazopanib dosing should be separated by several hours to avoid a reduction in pazopanib exposure.

6.11 Study Pocket Card for Patients

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

6.12 Elective Surgery During Study Participation

Both study medications should be held at least 2 weeks prior to scheduled surgery. Any plans for elective surgery should be discussed with the Sponsor-Investigator.

6.13 Follow-Up Period

Patients who discontinue treatment **for any reason other than consent withdrawal** remain on study in follow-up status for a 30-day evaluation period following the last dose of both study medications. During this 30-day post-treatment period, resolution or stabilization of ongoing treatment-related AEs and evolution of new treatment-related AEs will be reported. Additionally, if the patient has not had tumor progression, tumor response assessments performed during this 30-day follow-up period will also be reported.

Patients are off the study at the end of the 30-day follow-up period or when subsequent anticancer therapy begins, whichever occurs first. The primary reason(s) for a patient's discontinuation of study treatment and the patient's follow-up status will be recorded in the source documents and the CRFs.

7 DOSING DELAYS/DOSING MODIFICATIONS

7.1 Recording Dose Modifications

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

7.2 Toxicity Assessment

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

If a patient experiences more than one toxicity:

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

7.3 Toxicity Grading

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

7.4 General Instructions and Guidelines

- If treatment delays are required, the cycle may be extended to 5 weeks; however, all AR-42 doses must be taken during the first 4 weeks of the 5-week cycle. Any doses not given within the first 4 weeks of the extended cycle will be omitted.
- If one or both of the study medications are held due to toxicity, a **maximum of 3 consecutive weeks is permitted for recovery**. If recovery has not been sufficient to resume treatment 3 consecutive weeks after the decision to hold either or both of the study medications, both study medications must be discontinued.
- If AR-42 treatment must be interrupted for an AR-42-related toxicity, the patient should continue taking pazopanib unless dose modification instructions specifically indicate that pazopanib should be held or omitted.
- If pazopanib treatment must be interrupted due to a pazopanib-related toxicity, the patient should continue taking AR-42 unless dose modification instructions specifically indicate that AR-42 should be held or omitted..

7.5 AR-42 Dose Reduction Guidelines

7.5.1 Dose Reduction Steps for AR-42

AR-42 dose modifications, when required, will follow the predefined dose reduction steps outlined in Table 4.

Table 4. AR-42 Dose Reduction Steps for Toxicity Management

Dose Reduction Step	Reduced AR-42 Dose*			
	When Starting Dose is 10 mg	**When Starting Dose is 20 mg**	**When Starting Dose is 30 mg**	**When Starting Dose is 40 mg**
- 1	Discontinue AR-42	10 mg	20 mg	30 mg
- 2	Not Applicable	Discontinue AR-42	10 mg	20 mg
- 3		Not Applicable	Discontinue AR-42	10 mg
- 4			Not Applicable	Discontinue AR-42
*The AR-42 dose indicated on this table should be taken according to the same instructions and schedule outlined in Section 6.2.1.				

7.5.2 Dose Modification Instructions for AR-42

In addition to the general dose modification instructions provided in Section 7.4, and the dose reduction steps listed on the table above, dose modification instructions for specific toxicities related to AR-42 are listed in Table 5.

Note: Some pazopanib-related toxicities may result in medical reasons to also hold, omit, or discontinue AR-42. When AR-42 modification/discontinuation is also required, the pazopanib dose modification tables (Table 7, Table 8, Table 9, and Table 10) will also specify the required AR-42 modification.

Table 5. AR-42 Dose Modification Instructions

Grade (CTCAE v4.0)	AR-42 Modification *(Refer to Table 4 for AR-42 dose reduction steps)*
Blood and Lymphatic System Disorders	
Grade 3 or 4 anemia	Hold/omit[A] AR-42 until resolution to ≤ grade 2; transfusions are permitted.
Grade 3 or 4 febrile neutropenia	Hold/omit[A] until resolved; reduce dose by one dose reduction step when resuming treatment.[B]
Infections and Infestations	
Grade 3 infection	Hold/omit[A] until recovered to ≤ grade 2; at the investigator's discretion, the dose may be reduced by one dose reduction step when resuming treatment.[B]
Grade 4 infection	Hold/omit[A] until recovered to ≤ grade 2; reduce dose by one dose reduction step when resuming treatment. At the investigator's discretion, study treatment may be discontinued.
Investigations	
Grade 3 or 4 ECG QTc interval prolonged	Refer to Table 7 for instructions.
Grade 3 neutrophil count decreased; required ≤ 7 days for recovery to ≤ grade 2	Hold/omit[A] until ≤ grade 2. Dose reduction is **not** required when resuming treatment.
Grade 3 neutrophil count decreased; > 7 days required for recovery to ≤ grade 2	Hold/omit[A] until ≤ grade 2; reduce dose by one dose reduction step when resuming treatment.
Grade 4 neutrophil count decreased	
Grade 3 platelet count decreased; ≤ 7 days required for recovery to ≤ grade 2	Hold/omit[A] until ≤ grade 2. Dose reduction is **not** required when resuming treatment.
Grade 3 platelet count decreased; > 7 days required for recovery to ≤ grade 2	Hold/omit[A] until ≤ grade 2; reduce dose by one dose reduction step when resuming treatment.
Grade 4 platelet count decreased	
Nervous System Disorders	
Grade 2 pre-syncope or grade 3 syncope *(potentially reflecting cardiotoxicity)*	Refer to Table 7 for instructions.
Other Toxicities Possibly Related to AR-42 *(see footnote c)*	
Grade 2 toxicity that is persistent, intolerable, or unresponsive to optimal management	At the investigator's discretion, reduce AR-42 by one dose reduction step.[B]
Grade 3 toxicity	Hold/omit[A] until resolution to ≤ grade 1, baseline, or tolerable grade 2; reduce dose by one dose reduction step when resuming treatment.[B]
Grade 4 toxicity	Discontinue study treatment.

A. If recovery takes longer than the first 4 weeks of the cycle, any remaining doses are omitted.
B. At the investigator's discretion (after the DLT evaluation period [Section 6.7.1]), the dose may be escalated to the most recent dose taken by the patient when treatment resumes.
C. Excludes alopecia, nausea and vomiting that improve with antiemetic therapy, lymphopenia, and other lab abnormalities that are asymptomatic and/or not clinically significant per investigator.

7.6 Pazopanib Dose Reduction Guidelines

Treatment with pazopanib will be interrupted and/or the dose reduced for clinically significant toxicities that are related to pazopanib therapy. Dose modifications will follow predefined dose reduction steps according to the guidelines shown on the table below.

Table 6. Pazopanib Dose Reduction Steps for Toxicity Management

Dose Reduction Step	Reduced Pazopanib Dose	
	When Starting Dose is 600 mg	**When Starting Dose is 800 mg**
- 1	400 mg	600 mg
- 2	200 mg	400 mg
- 3	Discontinue pazopanib	200 mg
- 4	Not Applicable	Discontinue pazopanib
*The pazopanib dose indicated on this table should be taken according to the same instructions and schedule outlined in Section 6.2.2.		

7.7 Pazopanib Dose Modification Instructions

In addition to the general dose modification instructions provided in Section 7.4, dose modification instructions for pazopanib-related toxicities are listed in Table 7, Table 8 (liver function abnormalities), Table 9 (PPE), and Table 10 (Other).

Note: For some toxicities, AR-42 instructions are also included on the tables listed above.

Table 7. Pazopanib Dose Modification Instructions

Toxicity	Pazopanib Modification *(Refer to Table 6 for pazopanib dose reduction steps)*
Cardiac	
Grade 2 heart failure	Hold/omit[A] pazopanib and determine LVEF. • *If < 15% absolute decline in LVEF compared with baseline **or** a decline in LVEF of < 10% compared with baseline **and** ≥ 50%:* - When symptoms of heart failure show clinical improvement, resume pazopanib with reduction in dose of one dose reduction step.[B] • *If ≥ 15% absolute decline in LVEF compared with baseline **or** a decline in LVEF of ≥ 10% compared with baseline **and** < 50%:* - Continue holding until clinical improvement in symptoms and until LVEF improves to within 10% of baseline. - Refer patient for cardiology consult. - Reduce pazopanib dose by one dose reduction step when resuming treatment.[B] - At investigator's discretion, pazopanib may be discontinued.
Grade 3 or 4 heart failure	Discontinue pazopanib (also discontinue AR-42).
Grade 3 or 4 MI	Discontinue pazopanib (also discontinue AR-42).
Endocrine Disorders	
Grade 2 hypothyroidism	Continue pazopanib (dose reduction not required); initiate hypothyroidism management.
Grade 3 or 4 hypothyroidism	Discontinue pazopanib; initiate/continue hypothyroidism management.
Gastrointestinal Disorders	
≥ Grade 1 fistula ≥ Grade 2 perforation	Discontinue pazopanib (also discontinue AR-42).
Investigations	
Grade 3 ECG QTc interval prolonged *See Section 6.8 for additional instructions regarding QT monitoring.*	Hold/omit[A] pazopanib and AR-42. • Check potassium, magnesium, and calcium levels; immediately administer potassium, magnesium, and/or calcium to achieve potassium level of ≥ 4 mEq, magnesium level of ≥ 2 mEq, and calcium WNL. • Consider chronic supplementation for maintenance of electrolytes. • Review with investigator prior to patient's next scheduled treatment, considering the following: - Hold pazopanib and AR-42 until QTc recovers to pre-study treatment baseline (≤ grade 1 [≤ 480ms]). - When QTc returns to baseline, resume pazopanib and AR-42 with additional QTc monitoring at earliest opportunity within 8 days after resuming study treatment. - If QTc prolongation is thought to be related to pazopanib, decrease pazopanib and AR-42 doses by one dose reduction step when resuming study treatment. • For recurrent grade 3 QTc thought to be related to pazopanib and/or AR-42 despite dose reduction, discontinue pazopanib and AR-42.
Grade 4 ECG QTc interval prolonged	Discontinue pazopanib (also discontinue AR-42).
Elevation in AST, ALT, and/or bilirubin	Refer to Table 8.

Table 7. Pazopanib Dose Modification Instructions *(continued)*

Nervous System Disorders	
≥ Grade 2 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	• An evaluation for RPLS should be performed if the patient presents with seizures, headache (in conjunction with other RPLS symptoms), visual disturbances, confusion, or altered mental function. • If RPLS is diagnosed, discontinue pazopanib (also discontinue AR-42).
Grade 2 pre-syncope or grade 3 syncope *(potentially reflecting cardiotoxicity)*	Hold/omit[A] pazopanib and AR-42. • Obtain 12-lead ECG for cardiology review/consultation. • Check potassium, magnesium, and calcium levels; immediately administer potassium, magnesium, and/or calcium to achieve potassium level of ≥ 4 mEq, magnesium level of ≥ 2 mEq, and calcium WNL. If ECG shows new dysrhythmia or QTc ≥ grade 2 (> 480ms), hospitalize for monitoring with cardiology consultation. • Hold pazopanib and AR-42 until any potassium, magnesium, and calcium abnormalities are corrected, symptoms resolved, and QTc improved to ≤ grade 1 (≤ 480ms). • Reintroduce pazopanib and AR-42 with input from cardiology and with additional QTc evaluation, either concurrent with reintroduction or at earliest possible opportunity within 8 days from reintroduction. • If event is thought to be related to study treatment, reduce the dose of pazopanib and AR-42 by one dose reduction step when resuming study treatment.[B] • Consider chronic supplementation for maintenance of electrolytes. • For recurrent syncope or near-syncope thought to be related to study treatment, consider discontinuation of both pazopanib and AR-42.
Renal and Urinary Disorders	
≥ Grade 2 proteinuria	Hold/omit[A] pazopanib. If assessment of proteinuria was based on a urine dipstick reading, a 24-hour urine collection is required. Based on the 24-hour urine specimen: • If grade 2 proteinuria, consult nephrology. - If urine protein is < 3.0 gm/24 hours, study treatment may be continued without dose modification pending nephrology consult. - If ≥ 3.0 gm/24 hours, hold study treatment until improvement to < 3.0 gm/24 hours or additional nephrology recommendations. • If grade 3 proteinuria, consult nephrology and discontinue pazopanib.
Respiratory, Thoracic, and Mediastinal Disorders	
≥ Grade 2 pneumonitis	Discontinue pazopanib (also discontinue AR-42).
Skin and Subcutaneous Disorders	
PPE (hand-foot syndrome)	See Table 9 for instructions related to PPE

Table 7. Pazopanib Dose Modification Instructions *(continued)*

Vascular Disorders	
Grade 3 hypertension defined as systolic BP >160 mmHg **and** diastolic BP >100 mm/Hg	• Hold/omit[A] pazopanib until resolution to ≤ grade 2. • Administer standard antihypertensive therapy. • When resuming pazopanib, decrease pazopanib dose by one dose reduction step; **monitor BP weekly for 4 weeks.** • If BP remains controlled for at least one cycle, the pazopanib dose may be escalated by one dose step at the investigator's discretion.
Grade 4 hypertension	Discontinue pazopanib (also discontinue AR-42)

A. If recovery takes longer than the first 4 weeks of the cycle, any remaining doses for that cycle are omitted. Refer to Section 7.4 for additional information.

B. At the investigator's discretion (after the DLT evaluation period [Section 6.7.1]), the dose may be escalated by one dose step when the toxicity has resolved and treatment can be resumed.

7.7.1 Liver Function Abnormalities

For patients with observed worsening of serum liver tests considered to be related to pazopanib (ie, where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring instructions in the table below will be followed.

Table 8. Dose Modification/Interruption for Pazopanib-Related Increase in ALT and/or AST

Increase in AST/ALT (per NCI CTCAE v4.0)	First Occurrence	Restart	Recurrence
Grade 2 ALT and/or AST > 3-5 x ULN	Continue study treatment **with weekly monitoring** of liver function until transaminases return to grade 1 or baseline.		
Grade 3 ALT and/or AST > 5-20 x ULN	Hold/omit pazopanib and AR-42; **weekly monitoring** until transaminases return to grade 1 or baseline.[A]	If the potential benefit of reinitiating study treatment is considered to outweigh the risk of hepatotoxicity, reduce pazopanib and AR-42 by one dose reduction step.[B] **Measure serum transaminases weekly for at least 4 weeks**.	Discontinue pazopanib and AR-42
Grade 2 or 3 with Concurrent Bilirubin Elevation ALT and/or AST > 3-20 x ULN ***and*** Bilirubin > 2 x ULN	Hold/omit pazopanib and AR-42; **weekly monitoring** until transaminases return to grade 1 or baseline.[A]	If the potential benefit of reinitiating study treatment is considered to outweigh the risk of hepatotoxicity, reduce pazopanib and AR-42 by one dose reduction step.[B] **Measure serum transaminases and bilirubin weekly for at least 4 weeks**.	Discontinue pazopanib and AR-42
Grade 4 ALT and/or AST > 20 x ULN	Discontinue pazopanib and AR-42.		

A. If more than a 3-week delay is required, discontinue pazopanib.

B. Refer to Table 6 for pazopanib dose reduction steps.

7.7.2 PPE

Refer to Section 6.9.4 for supportive care instructions and recommendations for the prevention and treatment of PPE. Refer to the table below for study treatment instructions.

Table 9. Pazopanib Dose Modification Instructions for PPE

Grade of event (NCI CTCAE v4.0)	**Occurrence**	**Pazopanib Dose Modification[A]** *(Refer to Table 6 for pazopanib dose reduction steps.)*
Grade 1 • Minimal skin changes or dermatitis (eg, erythema, edema, hyperkeratosis) without pain • Numbness, dysesthesia, paresthesia, tingling, painless swelling, or erythema of hands and/or feet • Does not disrupt normal activities	Any	Continue study treatment; maintain dose level.
Grade 2 • Skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain • Painful erythema and swelling of hands and/or feet • Limiting instrumental ADL[B]	Any	• If PPE is NOT interfering with instrumental ADL, maintain pazopanib (and AR-42) dose. • If PPE is interfering with instrumental ADL, reduce pazopanib by one dose reduction step for the remainder of the treatment cycle.[C] • If no improvement in spite of supportive care and pazopanib dose reduction, omit pazopanib for the remainder of the cycle. When resuming treatment, decrease pazopanib dose by one dose reduction step.[C,D]
Grade 3 • Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain • Moist desquamation, ulceration, blistering, or severe pain of the hands and/or feet • Limiting self-care ADL[E]	1st Occurrence	• Omit pazopanib and AR-42 for a minimum of 7 days and until toxicity resolves to ≤ grade 1.[D] • When resuming treatment, decrease pazopanib dose by one dose reduction step.[C]
	2nd Occurrence	• Omit pazopanib and AR-42 for a minimum of 7 days and until toxicity resolves to ≤ grade 1.[D] • When resuming treatment, decrease pazopanib dose by one dose reduction step.[C]
	3rd Occurrence	Discontinue pazopanib and AR-42.

A. More conservative management is permitted per investigator discretion.
B. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone managing money, etc.
C. If toxicity returns to ≤ grade 1 after dose reduction, pazopanib escalation is permitted, **up to the enrolled dose level,** at the discretion of the investigator if the patient has completed 1 cycle at a reduced dose without recurrence of the event.
D. If > 3 consecutive weeks of delay are required for recovery, discontinue pazopanib and AR-42.
E. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications; the patient is not bedridden.

7.7.3 Other Toxicity

The instructions on the table below should be followed for toxicities not addressed on the previous dose modification tables.

Table 10. Pazopanib Dose Modification for Other Toxicity

NCI CTCAE v4.0	Initiation of Treatment Cycle	Dosing Interruption During the Cycle[A]	Dose Modification If Treatment Resumed During the Same Cycle[A]	Dose for Subsequent Cycles[A]
Grade 1	Start cycle on time	Continue treatment (no interruption)	Not Applicable	No change
Grade 2	Start cycle on time ***or*** delay start of the cycle until ≤ grade 1 or baseline grade per investigator discretion[B]	Continue treatment ***or*** interrupt dosing (pazopanib and AR-42) until resolution to ≤ grade 1 or baseline grade per investigator discretion[B]	No change ***or*** reduce pazopanib dose by one dose reduction step per investigator discretion[C]	No change ***or*** reduce pazopanib dose by one dose reduction step per investigator discretion[C]
Grade 3	Delay start of the cycle until ≤ grade 1 or baseline grade[B]	Interrupt dosing until resolution to ≤ grade 1 or baseline grade[B]	Reduce pazopanib dose by one dose reduction step[C]	Reduce pazopanib dose by one dose reduction step[C]
Grade 4	Delay start of the cycle until ≤ grade 1 or baseline grade[B]	Omit dosing for the remainder of the treatment cycle	Reduce pazopanib dose by one dose reduction step ***or*** discontinue both pazopanib and AR-42 per investigator's discretion[C]	If grade 4 toxicity recurs at reduced pazopanib dose, discontinue both pazopanib and AR-42

A. Excludes alopecia, nausea and vomiting that improve with antiemetic therapy, hypersensitivity that improves with medical management, and laboratory abnormalities that are asymptomatic and/or not clinically significant in the opinion of the investigator.

B. If treatment cannot resume after a 3-week delay, pazopanib and AR-42 must be discontinued.

C. Refer to Table 6 for pazopanib dose reduction steps.

8 ADVERSE EVENT DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

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

8.1.2 Suspected Adverse Reaction (SAR)

A SAR is any AE for which there is a reasonable possibility that the drug caused the AE. “Reasonable possibility” means that there is evidence to suggest a causal relationship between the drug and the AE.

An AE with an attribution of possible, probable, or definite (see Section 8.1.8) is a SAR.

8.1.3 Serious AE (SAE) or Serious SAR (SSAR)

An AE or SAR is considered “serious” if, in the view of the investigator, it results in any of the following outcomes:

- death,
- a life-threatening AE,

  An AE or SAR is considered “life-threatening” if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- inpatient hospitalization or prolongation of existing hospitalization,

  Note: Planned inpatient hospitalizations (eg, for planned surgery or for logistical reasons such as completion of a therapy that cannot be completed due to outpatient clinic business hours) are exempt from SAE reporting. Events that prolong such hospitalizations should be considered “serious” and are still subject to SAE reporting requirements.
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

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

8.1.4 AE Expectedness

AEs can be 'Unexpected' or 'Expected'. Expected AEs are those AEs, the specificity and severity of which are consistent with the listings for AR-42 and pazopanib found in protocol Sections 9.1 and 9.2, respectively, or in the most current version of the AR-42 Investigator's Brochure or the most current FDA-approved prescribing information for pazopanib.

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

- The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) protocol-related documents, such as the research protocol approved by the institutional review board (IRB), any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease, disorder, or condition of the patient(s) experiencing the AE and the patient's predisposing risk factor profile for the AE.

8.1.5 Unexpected SAR

A SAR is considered "unexpected" if

- it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed;
- or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.
- "Unexpected" as used in this definition, also refers to SARs that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.6 Unanticipated Problem (UP)

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

- unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the research protocol and informed consent document approved by the IRB; and (b) the characteristics of the patient population being studied;
- related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.7 AE Description and Grade

The descriptions and grading scales found in the revised CTCAE version 4.0 will be utilized for AE reporting.

8.1.8 AE Attribution

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

8.2 Known AEs

Known AEs for AR-42 are described in protocol Section 9.1 and in the AR-42 Investigator Brochure. Known AEs for pazopanib are described in protocol Section 9.2 and in the current pazopanib (Votrient) prescribing information.

8.3 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy. A secondary malignancy is not metastasis from the previous cancer. Any secondary malignancy should be reported via expedited reporting processes outlined on Table 11.

8.4 Time Period and Grade of AE Capture

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

8.5 Procedures for Recording AEs, SARs, SAEs, SSARs, DLTs, and UPs

All AEs (including SAEs, SARs, and SSARs), DLTs, and UPs will be recorded in MCC's OnCore Clinical Trials Management System. In most cases, it is acceptable to record in OnCore only the highest grade of a toxicity occurring during a particular study segment when an event has serial fluctuations in grade over time.

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

8.6 Expedited Reporting Procedures for SAEs, SSARs, UPs, and DLTs

Refer to Table 11 for expedited reporting by investigators to the Sponsor-Investigator and reporting by the Sponsor-Investigator to the Data Safety and Monitoring Committee (DSMC), IRB, FDA, and Arno Therapeutics, Inc.

Table 11. Expedited Reporting Requirements

SAEs	UPs	SSARs	DLTs
Sponsor-Investigator[A] Andrew Poklepovic	**Sponsor-Investigator**[A] Andrew Poklepovic		**Sponsor-Investigator**[B] Andrew Poklepovic
[redacted]			
Study Team[A]	**Study Team**[A]		**Study Team**[B]
[redacted]			
Arno Therapeutics[C]	**DSMC**[D] [redacted]	**FDA**[E]	
	IRB[F]	**Arno Therapeutics**[C]	
	Arno Therapeutics[C]		

A. Investigators will report event to the Sponsor-Investigator/Study Team within 1 business day of becoming aware of the occurrence. A PDF of a de-identified OnCore SAE or Deviation record may be used for expedited event reporting purposes.

B. Investigators will report event to the Sponsor-Investigator/Study Team within 1 business day of becoming aware of the occurrence. Receipt of reports is confirmed. If confirmation is not received within 1 business day, contact the research nurse by telephone [redacted].

C. The Sponsor-Investigator/Study Team will provide the de-identified OnCore SAE Record within 24 hours of becoming aware of the occurrence to Arno Therapeutics, Inc. A de-identified OnCore Deviation Record will be provided to Arno Therapeutics within 2 business days of becoming aware of the occurrence. If FDA reporting is required (see footnote E below), a copy of the completed MedWatch Form 3500A will be provided by the Sponsor-Investigator/Study Team to Arno Therapeutics at the time of FDA submission.

D. The Sponsor-Investigator/Study Team will report event within 1 business day of becoming aware of the occurrence. A PDF of a de-identified OnCore SAE or Deviation record may be used for expedited event reporting purposes.

E. Using MedWatch Form 3500A, the Sponsor-Investigator will report to the FDA any:

- AE that is **all of the following**: 1) possibly, probably, or definitely related to study drug (ie, the event is a SAR); 2) serious (ie, a SSAR); and 3) unexpected. Events meeting these criteria will be reported to the FDA **within 15 days of determining that the event is reportable.**
- clinically important increase in the rate of SSARs **within 15 days of determining that the event is reportable**
- unexpected fatal or life-threatening SSARs **within 7 days of initial receipt of the information regarding the event.**

F. The Sponsor-Investigator/Study Team will report each UP to the VCU IRB within 5 business days of becoming aware of the occurrence.

9 PHARMACEUTICAL INFORMATION

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

9.2 Pazopanib

The following information is based on the prescribing information for Votrient (pazopanib) with a revision date of September 2015.

9.2.1 Product Description

Chemical Name: 5-[[4-[)2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohycrochloride

Molecular Formula: $C_{21}H_{23}N_7O_2S\bullet HCl$

Molecular Weight: 473.99

Mechanism of Action: Pazopanib is a tyrosine knase inhibitor

How Supplied:

Pazopanib hydrochloride is a white to slightly yellow solid. It is very slightly soluble at pH of 1 and practically insoluble above pH of 4 in aqueous media. Pazopanib tablets are modified capsule-shaped, gray, film-coated tablets with GS JT debossed on one side. Each pazopanib 200-mg tablet contains 216.7 mg of pazopanib hydrochloride. The inactive ingredients in the pazopanib tablet core are magnesium stearate, micro crystalline cellulose, povidone sodium, and starch glycolate. In the coating, the inactive ingredients are hypromellose, iron oxide black, macrogol/polyethylene glycol 400 (PEG 400), polysorbate 80, and titanium dioxide.

9.2.2 Route of Administration

Pazopanib tablets are to be taken by mouth on an empty stomach, at least 1 hour before or 2 hours after food. Pazopanib tablets should not be crushed.

9.2.3 Storage

Pazopanib tablets should be stored at room temperature between 20° and 25°C (68° and 77°F); excursions permitted to 15-30°C (59-86°F).

9.2.4 Stability

When stored as directed, tablets are stable until the date indicated on the package.

9.2.5 Availability and Ordering

Pazopanib is commercially available. Patients or their third party payor (ie, health care insurance) will be responsible for the cost of pazopanib treatment.

9.2.6 Agent Accountability

Not applicable

9.2.7 Agent Destruction and Return

Not applicable

9.2.8 Contraindications

None

9.2.9 Drug Interactions

Refer to the current Votrient (pazopanib) prescribing information and to Section 6.10 for information and instructions regarding potential drug interactions.

9.2.10 Warnings and Precautions

Refer to the current Votrient (pazopanib) prescribing information for information regarding the following:

- Hepatic toxicity and hepatic impairment
- QT prolongation and Torsades de Pointes
- Cardiac dysfunction
- Hemorrhagic events
- Arterial thromboembolic events
- Venous thromboembolic events
- Thrombotic microangiopathy
- Gastrointestinal perforation and fistula
- Interstitial lung disease/pneumonitis
- RPLS
- Hypertension
- Wound healing
- Hypothyroidism
- Proteinuria
- Infection
- Increased toxicity with other cancer therapy
- Increased toxicity in developing organs
- Pregnancy

9.2.11 Adverse Events Occurring in Patients with RCC

The most common adverse reactions in patients with advanced RCC (≥ 20%) are diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting. Adverse reactions occurring in patients with RCC are summarized in the following 3 tables: ≥ 10% of patients in Table 13; < 10 in Table 14; and selected laboratory abnormalities in > 10% of patients in Table 15.

Table 13. Adverse Reactions Occurring in ≥ 10% of Patients with RCC

Adverse Reactions	Pazopanib (N = 290)			Placebo (N = 145)		
	All Grades* %	Grade 3 %	Grade 4 %	All Grades* %	Grade 3 %	Grade 4 %
Diarrhea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair color changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Anorexia	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0
*NCI CTCTAE v3.0						

Table 14. Adverse Reactions Occurring in < 10% of Patients with RCC

Adverse Reactions	Pazopanib (N = 290)	Placebo (N = 145)
	All Grades* (%)	All Grades* (%)
Alopecia	8	<1
Chest pain	5	1
Dysgeusia	8	<1
Dyspepsia	5	<1
Dysphonia	4	<1
Facial edema	1	0
PPE	6	<1
Proteinuria	9	0
Rash	8	3
Skin depigmentation	3	0
Weight loss	9	3
Arthralgia and muscle spasms were also reported in other clinical trials.		
*NCI CTCTAE v3.0		

Table 15. Selected Laboratory Abnormalities Occurring in > 10% of Patients with RCC and More Commonly (≥ 5%) in Patients Who Received Pazopanib versus Placebo

Parameters	Pazopanib (N = 290)			Placebo (N = 145)		
	All Grades* %	Grade 3 %	Grade 4 %	All Grades* %	Grade 3 %	Grade 4 %
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0
*NCI CTCTAE v3.0						

9.2.12 Adverse Events Occurring in Patients with STS

The most common adverse reactions in patients with advanced STS (≥ 20%) are fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, hair color changes (depigmentation), vomiting, tumor pain, dysgeusia, headache, musculoskeletal pain, myalgia, gastrointestinal pain, and dyspnea. Adverse reactions occurring in patients with STS are summarized in Table 16, Table 17, and Table 18.

Table 16. Adverse Reactions Occurring in ≥ 10% of Patients with STS

Adverse Reactions	Pazopanib (N = 240)			Placebo (N = 123)		
	All Grades[A] %	Grade 3 %	Grade 4 %	All Grades[A] %	Grade 3 %	Grade 4 %
Fatigue	65	13	1	48	4	1
Diarrhea	59	5	0	15	1	0
Nausea	56	3	0	22	2	0
Weight decreased	48	4	0	15	0	0
Hypertension	42	7	0	6	0	0
Appetite decreased	40	6	0	19	0	0
Hair color changes	39	0	0	2	0	0
Vomiting	33	3	0	11	1	0
Tumor pain	29	8	0	21	7	2
Dysgeusia	28	0	0	3	0	0
Headache	23	1	0	8	0	0
Musculoskeletal pain	23	2	0	20	2	0
Myalgia	23	2	0	9	0	0
Gastrointestinal pain	23	3	0	9	4	0
Dyspnea	20	5	<1	17	5	1
Exfoliative rash	18	<1	0	9	0	0
Cough	17	<1	0	12	<1	0
Peripheral edema	14	2	0	9	2	0
Mucositis	12	2	0	2	0	0
Alopecia	12	0	0	1	0	0
Dizziness	11	1	0	4	0	0
Skin disorder[B]	11	2	0	1	0	0
Skin hypopigmentation	11	0	0	0	0	0
Stomatitis	11	<1	0	3	0	0
Chest pain	10	2	0	6	0	0

A. NCI CTCTAE v3.0
B. 27 of 28 cases of skin disorder were PPE

Table 17. Other Adverse Reactions Occurring in ≥ 5% of Patients with STS and More Commonly (> 2%) in Patients Who Received Pazopanib versus Placebo

Adverse Reactions	Pazopanib (N = 240)	Placebo (N = 123)
	All Grades* (%)	All Grades* (%)
Insomnia	9	6
Hypothyroidism	8	0
Dysphonia	8	2
Epistaxis	8	2
Left ventricular dysfunction	8	4
Dyspepsia	7	2
Dry skin	6	<1
Chills	5	1
Vision blurred	5	2
Nail disorder	5	0
*NCI CTCTAE v3.0		

Table 18. Selected Laboratory Abnormalities Occurring in > 10% of Patients with STS and More Commonly (≥ 5%) in Patients Who Received Pazopanib versus Placebo

Parameters	Pazopanib (N = 240)			Placebo (N = 123)		
	All Grades* %	Grade 3 %	Grade 4 %	All Grades* %	Grade 3 %	Grade 4 %
Hematologic						
Leukopenia	44	1	0	15	0	0
Lymphocytopenia	43	10	0	36	9	2
Thrombocytopenia	36	3	1	6	0	0
Neutropenia	33	4	0	7	0	0
Chemistry						
AST increased	51	5	3	22	2	0
ALT increased	46	8	2	18	2	1
Glucose increased	45	<1	0	35	2	0
Albumin decreased	34	1	0	21	0	0
ALP increased	32	3	0	23	1	0
Sodium decreased	31	4	0	20	3	0
Total bilirubin increased	29	1	0	7	2	0
Potassium increased	16	1	0	11	0	0
*NCI CTCTAE v3.0						

10 MEASUREMENT OF EFFECT

10.1 Criteria for Tumor Response

Tumor response will be evaluated and recorded according to RECIST v1.1 (27)

10.2 Imaging

Only imaging of the initial sites of disease is required at subsequent time points to provide tumor measurements for assessment of antitumor effect. Brain imaging after initiation of study therapy is only required for patients who have a history of brain metastasis.

The same type of imaging used at baseline should be used at each scheduled assessment which will be performed at the end of every other 4-week cycle (ie, approximately every 8 weeks). At the investigator's discretion, additional imaging may be performed when clinically indicated.

10.3 Criteria for Tumor Response

In the event of a PR or CR, the imaging used when the response was first documented must be repeated at the time of the next scheduled imaging, ie, in about 8 weeks, to confirm tumor response. (At the investigator's discretion, confirmatory scans can be performed sooner, but no less than 4 weeks following the imaging indicating the PR or CR.)

10.4 Central Review for Imaging Interpretation

Centralized radiologic review for response evaluation will be conducted.

11 CORRELATIVE STUDIES

11.1 Participation in Correlative Studies

Tumor samples archived following the most recent biopsy or surgery will be used for the correlative studies. Participation in the correlative studies using archived tumor samples, **if available**, is mandatory.

11.2 Collection, Immunostaining, and Distribution of Samples

- The study team will coordinate collection of all correlative tumor samples. Additionally, the study team will ensure that samples are de-identified prior to distribution to the laboratories performing the correlative studies.

- Massey Cancer Center Clinical and Translational Research Lab (CTRL) will receive, process, store, and/or distribute tumor samples to the laboratories performing the correlative studies as needed based on the plans outlined in Section 11.3.
- Questions regarding study requirements should be directed to the study team. The principal investigator should be contacted in the event that a correlative sample must be missed or is found to be inadequate for submission.
- Collection and distribution of all tumor samples will be logged by the study team in OnCore.

11.3 Archived Tumor Samples

Expression of multiple cellular proteins will be analyzed by IHC methods using samples from tumor archived at the time of the most recent diagnostic biopsy or surgery.

11.3.1 Tumor Sample Requirement

When sufficient archived tumor tissue is available:

- Request a tumor block from archived samples from **the most recent diagnostic biopsy or surgical resection**.
- If an outside hospital does not transfer blocks of tissue, request 10 unstained slides, each with specimen 4 microns thick.
- To obtain an archived biopsy specimen from an outside hospital:
  - Request that a tissue block be sent to the study team; the study team will coordinate with VCU Anatomic Pathology for slide preparation.
  - If the outside hospital does not transfer blocks of tissue, request delivery of 10 unstained slides, each with specimen 4 microns thick.
- The study team should request tumor samples **by the end of cycle 2** (ie, within about 8 weeks after initiation of study treatment).

11.3.2 Tumor Sample Labeling

The tumor sample should be labeled with the following information:

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

11.3.3 Immunostaining of Unstained Slides

All unstained slides will be delivered to the CTRL where immunostains for total CD95 expression and the expression of other proteins of interest will be performed.

11.3.4 Interpretation of Immunostain Results

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

12 STUDY CALENDARS

The schedule of tests, exams, disease assessments, collection of samples for correlative studies, and study treatment are listed on 2 tables: requirements during screening through treatment cycle 1 on Table 19 and requirements during remaining treatment beginning with cycle 2 and continuing through study follow-up on Table 20.

Table 19. Study Calendar - Screening Through Treatment Cycle 1

Tests, Exams, and Other Requirements	Screening *(Days Prior to Cycle 1, Day 1)*			Study Treatment – Cycle 1				
	Within 28 Days	**Within 14 Days**	**Within 7 Days**	**Day 1[A]**	**Day 8[B]**	**Day 15[B]**	**Day 22[B]**	**Day 29[B]** *(If cycle was extended)[C]*
Informed Consent	X							
Demographics	X							
Medical/Surgical History	X							
Height	X							
Weight		X		X	X	X	X	X
Vital Signs		X		X	X	X	X	X
BP		X		X	X	X	X	X
Performance Status		X		X	X	X	X	X
Baseline Conditions/Symptoms		X						
AE Assessment					X	X	X	X
Concurrent Medications[D]		X			X	X	X	X
Physical Exam		X		X	X	X	X	X
CBC with Differential		X		X	X	X	X	X
Platelet Count		X		X	X	X	X	X
Serum Chemistry[E]		X		X	X[F]	X[F]	X[F]	X[F]
aPTT and INR		X						
Lipase		X						
TSH and T4		X						
Serum Pregnancy Test[G]			X					
Urinalysis for protein		X[H]						
12-Lead ECG[I]	X				X	X	X	X
LVEF Assessment[J]	X[K]							
Imaging/Disease Assessment	X[L]							
Correlative Tumor Sample Collection				X[M]				
AR-42 PO[N]				Once daily 3 days/week during 1st 3 weeks				X[O]
Pazopanib PO[N]				Once daily continuously				X[O]
Study Med Diary Review/Pill Count				X	X	X	X	X

Table 19 Footnotes:

A. Except for BP and vital signs, baseline evaluations performed within 1 week prior to initiation of study treatment do not need to be repeated on cycle 1, day 1.

B. Within +/- 24 hours.

C. Day 29 requirements only apply to patients who had a treatment interruption earlier in the cycle that required extending the cycle beyond 28 days (up to a maximum of 35 days).

D. Include over-the-counter medications.

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

F. Refer to Table 8 for instructions regarding increased frequency of liver function monitoring **(weekly for at least 4 weeks)** when pazopanib-related elevations (AST, ALT, bilirubin) occur.

G. Only required for WCBP; see Section 4.1.12 for the definition of WCBP.

H. If urinalysis reading for protein is ≥ 2+ (100 mg/dL), a 24-hour urine sample must be collected and tested (see Section 4.1.6 for related eligibility criterion).

I. Refer to Section 4.2.13, Section 6.8, and Table 7 for instructions related to QTc interval prolongation.

J. Assessment may be performed by echocardiogram or by a nuclear study (eg, MUGA scan; first-pass technique).

K. Determination of LVEF is required **within 3 months** prior to cycle 1, day 1 study treatment.

L. Baseline imaging **must be contrast-enhanced** and include the following:
   - Chest CT, CT or MRI of abdomen and pelvis, and all other suspected sites of disease **within 28 days** prior to initiation of study treatment; for patients with a CT contrast allergy, the chest CT may be performed without contrast or, if the chest is not a known site of disease, a chest x-ray may be used
   - Brain CT or MRI **within 8 weeks** prior to initiation of study treatment

M. Collection of tumor samples archived following the most recent biopsy or surgery; tumor samples must be requested by the end of cycle 2 (Section 11).

N. Refer to Sections 6.1 through 6.6 for treatment-related instructions including the AR-42 and pazopanib dose levels.

O. If cycle has been extended to 5 weeks, AR-42 doses must be given during the 1st 4 weeks of the cycle allowing a 1-week AR-42 rest period (Section 6.2.1); pazopanib continues daily.

Table 20. Study Calendar – Treatment Beginning with Cycle 2 Through Follow-Up

Tests, Exams, and Other Requirements	Cycle 2		Cycle 3	Cycle 4	End of Treatment[C]	End of 30-Day Follow-Up
	Day 1[A]	Day 15[B]	Day 1[A]	Day 1[A]		
Weight	X		X	X	X	
Vital Signs	X		X	X	X	
BP	X	X	X	X	X	
Performance Status	X		X	X	X	
Assessment of AEs	X		X	X	X	X[D]
Concurrent Medications[E]	X		X	X	X	
Physical Exam	X		X	X	X	
CBC with Differential	X	X	X	X	X	
Platelet Count	X	X	X	X	X	
Serum Chemistry[F]	X[F]	X[F]	X[F]	X[F]	X	
Lipase	X		X	X	X	
TSH and T4				X[G] *(Every 3 cycles)*		
Urinalysis for Protein			X[H] *(Every 2 cycles)*			
12-Lead ECG[I]	X			X[J] *(Every 2 cycles)*		
LVEF Assessment[K]				X[L] *(Every 3 cycles)*		
Tumor Imaging/Disease Assessment[M]			X[N] *(Every 2 cycles)*		X[O]	
Correlative Tumor Sample Collection	X[P]					
AR-42 PO[Q]	Once daily 3 days/week during 1st 3 weeks of each 4-week cycle[R]					
Pazopanib PO[Q]	Once daily continuously[R]					
Study Medication Diary Review & Pill Count	X		X	X	X	

Table 20 Footnotes:

A. Within 3 days prior to or on day 1 of each treatment cycle.
B. Within 3 days prior to or on day 15.
C. Within 2 weeks after the end of study treatment.
D. If the patient is unable to return for a study visit at this time, the study team may contact the patient, family member, and/or other care providers to get information needed to complete the AE assessment at this time point.
E. Include over-the-counter medications.
F. Serum chemistry includes the following panels and tests: basic metabolic panel (sodium, potassium, carbonate, chloride, glucose, calcium, BUN, and creatinine); hepatic panel (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, and total protein); and magnesium and phosphorous. (Refer to Table 8 for instructions regarding increased frequency of liver function monitoring **[weekly for at least 4 weeks]** when pazopanib-related elevations [AST, ALT, bilirubin] occur.)
G. Following completion of 3 cycles of study treatment beginning on day 1 of cycle 4, repeating on day 1 of cycle 7, and continuing after every 3 cycles of treatment (ie, about every 3 months).
H. Following completion of 2 cycles of study treatment beginning on day 1 of cycle 3, repeating on day 1 of cycle 5, and continuing after every 2 cycles of treatment (ie, about every 2 months). *If urine protein is 2+ (100 mg/dL), a 24-hour urine sample must be collected and tested*.
I. Refer to Section 6.8 and Table 7 for instructions related to QTc interval prolongation.
J. On day 1 (+/- 1 week) of cycles 4, 6, and continuing after every 2 cycles of treatment (ie, about every 2 months [+/- 1 week]).
K. LVEF assessment should be performed using the same method used at baseline to determine eligibility.
L. Following completion of 3 cycles of study treatment beginning on day 1 of cycle 4 (+/- 1 week), repeating on day 1 of cycle 7 (+/- 1 week), and continuing after every 3 cycles of treatment (ie, about every 3 months [+/- 1 week]).
M. Imaging may be limited to known sites of disease. Brain imaging required for patients with brain metastasis diagnosed and treated prior to initiation of study treatment. The imaging used at baseline should be used at each subsequent imaging time point.
N. Following completion of 2 cycles of study treatment beginning on day 1 of cycle 3 (+/- 1 week) and continuing after every 2 cycles of treatment (ie, about every 2 months [+/- 1 week]); see Section 10.
O. For patients who discontinued study treatment in the absence of disease progression: If it has been 8 or more weeks since the most recent disease assessment, a final on-study tumor response assessment should be performed, if possible.
P. If not already requested during cycle 1, archived tumor samples must be requested by the end of cycle 2; see Section 11.
Q. Refer to Section 6.2 through 6.6 for additional treatment-related instructions.
R. Continuing until treatment is discontinued (see Section 6.5); if the cycle has been extended to 5 weeks, AR-42 doses must be given during the 1st 4 weeks of the cycle allowing a 1-week AR-42 rest period (Section 6.2.1); pazopanib continues daily.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a phase 1 study of AR-42 in combination with pazopanib in patients with advanced RCC or STS. A modified 3+3 dose-escalation design will be conducted. Additional patients will be enrolled at the MTD until a total of 12 patients have been treated at the MTD.

13.2 Sample Size/Accrual Rates

With the 7 proposed dose levels (-1, 1, 2, 3A, 3B, 4A, and 4B) and starting at dose level 1 (as indicated in Table 1 in Section 6.6), the number of patients needed for evaluation of DLT ranges from 4 to 36. To take into account the up to 20% of patients subsequently found to be inevaluable for DLT, the maximum number of patients required to determine the MTD is 45. Per the dose-escalation plan, it is likely that 4-5 dose levels will be explored. With an average of 4.5 patients per cohort, the likely scenarios involve 18-23 patients and, therefore, it is expected that 23-29 patients evaluable for DLT will be enrolled in the study. With 6 additional patients who will be treated at the MTD, the maximum number of patients needed for the study is 51 with a likely sample size of 29-35 patients.

Based on past recruitments, the recruitment rate is expected to be about 1-2 per month. Therefore, the anticipated enrollment period is expected to be about 15-35 months.

13.3 Statistical Analysis for Primary Objective

Patients' treatment dose level, dose modification, evaluability for DLT, and DLTs will be listed and summarized by basic descriptive statistics such as frequency and proportion. The MTDs/RP2Ds will be found based on the criteria defined in Section 6.7

13.4 Statistical Analysis for Secondary Objectives

Patients' demographics, AEs and SAEs, treatment status, number of patients who had discontinuation of study therapy, and clinical response will be listed and summary descriptive statistics, including frequency/proportion for discrete variables and mean/median/standard deviation for continuous variables, will be calculated. The clinical response (CR + PR) rate will also be calculated along with its 95% confidence interval.

13.5 Statistical Analysis for Exploratory Objectives

The study is not sufficiently powered to establish definitive outcomes for the correlative exploratory endpoint. Any comparison with a significant alpha, 0.05, will be deemed of interest to warrant further evaluation. An ordinal regression and a logistic regression will be used to assess the association between expression of each biomarker and clinical response.

13.6 Evaluability for DLT, Toxicity, and Response

13.6.1 DLT-Evaluable Population

DLT-evaluable patients are those who have taken a minimum of 6 doses of AR-42 during the first treatment cycle and a minimum of 21 doses of pazopanib during the first treatment cycle, or those who have experienced a DLT with any study treatment during cycle 1 as described in Section 6.7.1.

Note: Patients who for any reason are not evaluable for DLT will be replaced.

13.6.2 Safety-Evaluable Population

Patients who have received any study treatment will be evaluable for safety and toxicity analyses.

13.6.3 Efficacy-Evaluable Population

Efficacy-evaluable patients are those who have received any doses of AR-42 and pazopanib in cycle 2 (regardless of the number of doses taken during cycle 1), and have had at least 1 imaging assessment of response after receiving study treatment.

For efficacy evaluation, patients are coded as having a response or not having a response as follows:

- Responders: Best response assessment is a PR or a CR (Section 10).
- Non-Responders: Best response assessment is stable disease or progressive disease; also included are patients who did not have assessment of tumor response at least once after initiation of study treatment or who were otherwise not evaluable for response.

The coding of patients as responders or non-responders will be made by the Sponsor-Investigator with the concurrence of the Biostatistician.

14 DATA AND SAFETY MONITORING PLAN

The data and safety monitoring plan for this study consists of 3 elements: the study team, the audit committee, and the DSMC.

14.1 Study Team

The study team minimally consists of the Sponsor-Investigator, the research nurse, the clinical research associate, and the study biostatistician. While patients are on treatment, the Sponsor-Investigator, the research nurse, and the clinical research associate will meet at least monthly, and will meet at least quarterly with the study biostatistician, to review study status. This review will include, but not be limited to, reportable AEs and UPs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further patient enrollment and the specific intervention for

a next patient enrollment are addressed. All meetings, including attendance, are documented.

14.2 Audit Committee

This study will be audited by the MCC Audit Committee.

14.3 DSMC

The MCC-14-10774 clinical trial will be monitored by the MCC DSMC according to the schedule identified by the MCC Protocol Review and Monitoring Committee.

15 REGULATORY COMPLIANCE AND ETHICS

15.1 Ethical Standard

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

15.2 Regulatory Compliance

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

15.3 Institutional Review Board

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

15.4 Informed Consent Process

Informed consent is a process that is initiated prior to the patient's agreeing to participate in the study and continues throughout the patient's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to patients and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the patient and written documentation of informed consent is required prior to starting the study intervention/administering study product.

Consent forms will be IRB-approved and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. Patients should have the opportunity

to discuss the study with their surrogates and to think about it prior to agreeing to participate. The patient will sign the informed consent document prior to any procedures being done specifically for the study. Patients may withdraw consent at any time throughout the course of the trial. A copy of the consent form will be given to the patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.5 Patient Confidentiality

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

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

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

16 DATA COLLECTION AND MANAGEMENT

16.1 Data Management Responsibilities

The Sponsor-Investigator is responsible for: (i) reviewing SAE reports; (ii) determining if SSARs need to be reported to the FDA, and if so, filing the report; (iii) filing annual IND reports; and (iv) filing IND amendments.

The Sponsor-Investigator is responsible for: (i) the overall conduct of the investigation; (ii) ongoing review of trial data including all safety reports; and (iii) apprising participating investigators of any UPs.

The Sponsor-Investigator is responsible for: (i) the data management; and (ii) reporting SAEs, SSARs, UPs, and DLTs as required in Section 8.

Any laboratory conducting correlative studies must maintain the laboratory records and documentation.

16.2 CRFs and Data Collection

MCC OnCore data management will provide standard electronic CRFs (eCRFs) and create study-specific eCRFs to be able to capture all information required by the protocol. The eCRFs will be approved by the study team to ensure the most effective data acquisition.

The Sponsor-Investigator and other investigators and study coordinators must maintain source documents for each patient in the study. All information on eCRFs will be traceable to these source documents, which are generally maintained in the patient's file.

All DLT events are reported to the Sponsor-Investigator within 1 business day by email as indicated on Table 11.

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

16.3 Study Record Retention

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

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APPENDIX 1. PERFORMANCE STATUS CRITERIA

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

APPENDIX 2. COCKCROFT-GAULT FORMULA

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