NRSTS2021, A Risk Adapted Study Evaluating Maintenance Pazopanib, Limited Margin, Dose-Escalated Radiation Therapy and Selinexor in Non-Rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS)

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: Up to 30 years old
Healthy Volunteers: This study is NOT accepting healthy volunteers
Inclusion Criteria:

Inclusion Criteria - All Patients

- Patients must be 1-30 years at the time of the biopsy that established the diagnosis of NRSTS.
- Surgical Resection: Patients who had an upfront resection prior to enrollment will be eligible if they are able to begin therapy within 28 days of resection assuming other eligibility criteria are met. Delayed resection is preferred for all patients with intermediate and high-risk disease.
- Lansky performance status score ≥ 60 for patients ≤ 16 years of age. Karnofsky performance status score ≥ 60 for patients >16 years of age. Note patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

Diagnosis

• Patients with CIC-DUX 4 rearranged sarcomas will be enrolled on the high-risk stratum only, regardless of presence of metastasis, size, or resection status.

Patient has low-risk disease if the patient has a:

- Low-grade tumor of any size where R0 or R1 surgical margins are anticipated or achieved.
- High-grade tumors that are < 5 cm where R0 or R1 resection margins are anticipated or achieved.

Patient must have adequate organ function in the organs that will be within the radiotherapy field.

Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR > 70 mL/min/1.73 m2, or
- A normal serum creatinine based on age/gender as follows

Age Maximum Serum Creatinine (mg/dL) Male Female 2 to < 6 years 0.8 0.8 6 to < 10 years 1 1 10 to < 13 years 1.2 1.2 13 to < 16 years 1.5 1.4 > 16 years 1.5 1.4

Adequate liver function defined as:

- Total bilirubin < 1.5 x upper limit of normal (ULN) for age
- SGOT (AST) or SGPT (ALT) < 2.5 x ULN for age

Adequate cardiac function defined as:

- Ejection fraction of > 55% by echocardiogram or cardiac MRI
- QTc < 480 msec

Adequate pulmonary function defined as:

- No evidence of dyspnea at rest, no exercise intolerance, and a resting pulse oximetry reading > 94% on room air if there is clinical indication for determination.

Inclusion Criteria - Intermediate and High Risk Participants

Patient has intermediate-risk if the patient has a:

- Low-grade non-metastatic initially unresectable disease at study enrollment where delayed resection is planned.
- High-grade < 5 cm non-metastatic initially unresectable disease at study enrollment where delayed resection is planned. Of note, patients enrolled on the low-risk arm who were unable to achieve gross total resection where delayed re-resection is planned are eligible for this arm.
- High-grade tumor > 5 cm that is potentially resectable.

Patient high-risk if the patient has:

- Metastatic disease at presentation
- Unresectable disease at study enrollment where delayed resection is not anticipated. Of note, patients enrolled on the low-risk arm who were unable to achieve gross total resection where delayed re-resection is not-planned are eligible for this arm.
- CIC-DUX4 rearranged sarcoma

Organ Function

Adequate bone marrow function defined as:

- Absolute neutrophil count > 1000/µL
- Platelet count > 100,000/µL
- Hemoglobin > 8 g/dL for patients < 16 years of age
- Hemoglobin > 9 g/dL for patients > 16 years of age

Note: No transfusions are permitted 7 days prior to laboratory studies to determine eligibility.

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Adequate cardiac function defined as:

- Ejection fraction of > 55% by echocardiogram or cardiac MRI
- QTc < 480 msec

Adequate pulmonary function defined as:

- No evidence of dyspnea at rest, no exercise intolerance, and a resting pulse oximetry reading > 94% on room air if there is clinical indication for determination.

Anticoagulation

Patients on low molecular weight heparin, warfarin (with a stable INR), or direct oral anticoagulants (DOAC) who have been on a stable dose of are eligible. Patients being treated for a pulmonary embolism or deep venous thrombosis (DVT) must have been treated for a minimum of 6 weeks prior to starting therapy treatment.

Life Expectancy

Patient must have a life expectancy of at least 3 months with appropriate therapy.

Exclusion Criteria:

- Patients with known primary CNS sarcoma or CNS metastases are not eligible. Note: Brain imaging is not an eligibility requirement. Tumors with intracranial extension will be allowed.
- Patients with the following histologic diagnosis are not eligible: intermediate locally aggressive tumors as defined by WHO, malignant rhabdoid tumor, alveolar soft part sarcoma, infantile fibrosarcoma, unresectable/metastatic dermatofibrosarcoma protuberans, inflammatory myofibroblastic tumor, desmoid fibromatosis, rhabdomyosarcoma, desmoplastic small round cell tumor, BCOR-CCNB3 fusion positive sarcoma.
- Bleeding diathesis: Patients with evidence of active bleeding or bleeding diathesis will be excluded (Note: Patients aged > 17 years with excess of 2.5 mL of hemoptysis are not eligible).
- Uncontrolled hypertension: Patients with uncontrolled hypertension (CTCAE v5 Grade ≥ 2) are ineligible. Hypertension must be well controlled on stable doses of medication for at least two weeks.

Prior Therapy

- Patients must have had no prior systemic therapy for the treatment of the NRSTS
- Patients must have had no prior anthracycline or ifosfamide chemotherapy
- Patients must have had no prior use of pazopanib or similar multi-targeted TKI.

Patients must have had no prior radiotherapy to tumor-involved sites.

Note: Patients previously treated for a non-NRSTS cancer are eligible provided they meet the prior therapy requirements. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier are excluded.

- CYP3A4 Substrates WITH Narrow Therapeutic Indices: Patients chronically receiving medications known to be metabolized by CYP3A4 and with narrow therapeutic indices within 7 days prior to study enrollment, including but not limited to pimozide, aripiprazole, triazolam, ergotamine and halofantrine are not eligible. Note: the use of fentanyl is permitted.
- CYP3A4 Inhibitors: Patients chronically receiving drugs that are known potent CYP3A4 inhibitors within 7 days prior to study enrollment, including but not limited to itraconazole, clarithromycin, erythromycin, many NNRTIs, diltiazem, verapamil, and grapefruit juice are not eligible.
- CYP3A4 Inducers: Patients chronically receiving drugs that are known potent CYP3A4 inducers within 14 days prior to study enrollment, including but not limited to carbamazepine, phenobarbital, phenytoin, rifampin, and St. John's wort are not eligible (with the exception of glucocorticoids).
- Certain medications that are associated with a risk for QTc prolongation and/or Torsade's de Pointes, although not prohibited, should be avoided or replaced with medications that do not carry these risks, if possible.
- Subjects with any condition that may impair the ability to absorb oral medications/investigational product including:

- Subjects with any condition that may impair the ability to absorb oral medications/investigational product including:
    - prior surgical procedures affecting absorption including, but not limited to major resection of stomach or small bowel
    - active peptic ulcer disease
    - malabsorption syndrome

3.4.12 Thyroid Replacement Therapy: Patients who require thyroid replacement therapy are not eligible if they have not been receiving a stable replacement dose for at least 4 weeks prior to study enrollment.

3.4.13 Subjects with any condition that may increase the risk of gastrointestinal bleeding or gastrointestinal perforation, including:

- active peptic ulcer disease
- known intraluminal metastatic lesions
- inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease) or other gastrointestinal conditions which increase the risk of perforation
- history of abdominal fistula, gastrointestinal perforation or intra- abdominal abscess within 28 days prior to beginning study treatment.

3.4.14 Pulmonary embolism or DVT. Patients must not have experienced:

- An untreated pulmonary embolism or DVT in last 6 months or
- treated pulmonary embolism or DVT which has been treated with therapeutic anticoagulation for less than 6 weeks
- arterial thrombosis in last 12 months

History of serious or non-healing wound, ulcer, or bone fracture.

Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with pazopanib. In addition, these subjects are at increased risk of lethal infections when treated with marrow-suppressive therapy.

Patients who are receiving any other investigational agent(s).

Pregnancy and Breast Feeding

- Pregnancy and Breast Feeding Female patients who are pregnant are ineligible due to risks of fetal and teratogenic adverse events as seen in animal/human studies.
- Lactating females are not eligible unless they have agreed not to breastfeed their infants during treatment and for a period of 1 month following completion of treatment.
- Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.
- Unwillingness to use an effective contraceptive method for the duration of their study participation and for at least 1 month after treatment is completed if sexually active with reproductive potential.

Conditions & Interventions

Interventions:
PROCEDURE: Surgical resection, RADIATION: Proton beam radiation therapy, DRUG: Pazopanib, DRUG: Ifosfamide, DRUG: Doxorubicin, DRUG: Selinexor
Conditions:
Adipocytic Neoplasm, Liposarcoma, Atypical Fibroxanthoma, Angiomatoid Fibrous Histiocytoma, Fibrosarcoma NOS, Myxofibrosarcoma, Angiosarcoma, Osteosarcoma, Extraskeletal, Dedifferentiated Liposarcoma, Myxoid Liposarcoma, Pleomorphic Liposarcoma, Myxoid Pleomorphic Liposarcoma, Low Grade Fibromyxoid Sarcoma, Sclerosing Epithelioid Fibrosarcoma, Malignant Tenosynovial Giant Cell Tumor of Soft Tissue, Epithelioid Hemangioendothelioma, Glomus Tumor, Inflammatory Leiomyosarcoma, Leiomyosarcoma, Ossifying Fibromyxoid Tumor, Malignant, Myoepithelioma, Synovial Sarcoma, Epithelioid Sarcoma, Perineurioma, Malignant, Clear Cell Sarcoma, Extraskeletal Myxoid Chondrosarcoma, Granular Cell Tumor, Malignant, Melanotic Malignant Nerve Sheath Tumor, Malignant Peripheral Nerve Sheath Tumor, Perivascular Epithelioid Tumor, Malignant, Intimal Sarcoma, Myoepithelial Carcinoma, Undifferentiated Sarcoma, Pleomorphic Sarcoma, Undifferentiated, Round Cell Sarcoma, Undifferentiated, NTRK-Rearranged Spindle Cell Neoplasm, Phosphaturic Mesenchymal Tumor, Malignant, Round Cell Sarcoma, Well Differentiated Liposarcoma, Giant Cell Tumor of Soft Parts NOS, Low Grade Myofibroblastic Sarcoma, Dermatofibrosarcoma Protuberans, Fibrosarcomatous
Keywords:
Proton therapy

More Information

Description:
The study participant has been diagnosed with non-rhabdomyosarcoma (NRSTS). Primary Objectives Intermediate-Risk * To estimate the 3-year event-free survival for intermediate-risk patients treated with ifosfamide, doxorubicin, pazopanib, surgery, and maintenance pazopanib, with or without RT. * To characterize the pharmacokinetics of pazopanib and doxorubicin in combination with ifosfamide in intermediate-risk participants, to assess potential covariates to explain the inter- and intra-individual pharmacokinetic variability, and to explore associations between clinical effects and pazopanib and doxorubicin pharmacokinetics. High-Risk * To estimate the maximum tolerated dose (MTD) and/or the recommended phase 2 dosage (RP2D) of selinexor in combination with ifosfamide, doxorubicin, pazopanib, and maintenance pazopanib in high-risk participants. * To characterize the pharmacokinetics of selinexor, pazopanib and doxorubicin in combination with ifosfamide in high-risk participants, to assess potential covariates to explain the inter- and intra-individual pharmacokinetic variability, and to explore associations between clinical effects and selinexor, pazopanib and doxorubicin pharmacokinetics. Secondary Objectives * To estimate the cumulative incidence of primary site local failure and distant metastasis-free, disease-free, event-free, and overall survival in participants treated on the risk-based treatment strategy defined in this protocol. * To define and describe the CTCAE Grade 3 or higher toxicities, and specific grade 1-2 toxicities, in low- and intermediate-risk participants. * To study the association between radiation dosimetry in participants receiving radiation therapy and the incidence and type of dosimetric local failure, normal adjacent tissue exposure, and musculoskeletal toxicity. * To evaluate the objective response rate (complete and partial response) after 3 cycles for high-risk patients receiving the combination of selinexor with ifosfamide, doxorubicin, pazopanib, and maintenance pazopanib. * To assess the relationship between the pharmacogenetic variation in drug-metabolizing enzymes or drug transporters

maintenance pazopanib. * To assess the relationship between the pharmacogenetic variation in drug-metabolizing enzymes or drug transporters and the pharmacokinetics of selinexor, pazopanib, and doxorubicin in intermediate- or high-risk patients. Exploratory Objectives * To explore the correlation between radiographic response, pathologic response, survival, and toxicity, and tumor molecular characteristics, as assessed through next-generation sequencing (NGS), including whole genome sequencing (WGS), whole exome sequencing (WES), and RNA sequencing (RNAseq). * To explore the feasibility of determining DNA mutational signatures and homologous repair deficiency status in primary tumor samples and to explore the correlation between these molecular findings and the radiographic response, survival, and toxicity of patients treated on this protocol. * To explore the feasibility of obtaining DNA methylation profiling on pretreatment, post-induction chemotherapy, and recurrent (if possible) tumor material, and to assess the correlation with this and pathologic diagnosis, tumor control, and survival outcomes where feasible. * To explore the feasibility of obtaining high resolution single-cell RNA sequencing of pretreatment, post-induction chemotherapy, and recurrent (if possible) tumor material, and to characterize the longitudinal changes in tumor heterogeneity and tumor microenvironment. * To explore the feasibility of identifying characteristic alterations in non-rhabdomyosarcoma soft tissue sarcoma in cell-free DNA (cfDNA) in blood as a non-invasive method of detecting and tracking changes during therapy, and to assess the correlation of cfDNA and mutations in tumor samples. * To describe cardiovascular and musculoskeletal health, cardiopulmonary fitness among children and young adults with NRSTS treated on this protocol. * To investigate the potential prognostic value of serum cardiac biomarkers (high-sensitivity cardiac troponin I (hs-cTnI), N-terminal pro B-type natriuretic peptide (NT-Pro-BNP), serial electrocardiograms (EKGs), and serial echocardiograms in patients receiving ifosfamide, doxorubicin, and pazopanib, with or without selinexor. * To define the rates of near-complete pathologic response (\>90% necrosis) and change in FDG PET maximum standard uptake value (SUVmax) from baseline to week 13 in intermediate risk patients with initially unresectable tumors treated with induction pazopanib, ifosfamide, and doxorubicin, and to correlate this change with tumor control and survival outcomes. * To determine the number of high-risk patients initially judged unresectable at diagnosis that are able to undergo primary tumor resection after treatment with ifosfamide, doxorubicin, selinexor, and pazopanib. * To identify the frequency with which assessment of volumes of interest (VOIs) of target lesions would alter RECIST response assessment compared with standard linear measurements.

Contact(s): cancer@cchmc.org
Principal Investigator:
Principal Investigator ID:
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