Title

Pathological response in children and adults with large unresected intermediate-grade or high-grade soft tissue sarcoma receiving preoperative chemoradiotherapy with or without pazopanib (ARST1321): a multicentre, randomised, open-label, phase 2 tria...

Journal

The Lancet Oncology, 21(8)

ISSN

1470-2045

Authors

Weiss, Aaron R
Chen, Yen-Lin
Scharschmidt, Thomas J
et al.

Publication Date

2020-08-01

DOI

10.1016/s1470-2045(20)30325-9

Peer reviewed

HHS Public Access

Author manuscript

Lancet Oncol. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Lancet Oncol. 2020 August ; 21(8): 1110–1122. doi:10.1016/S1470-2045(20)30325-9.

Pathologic response in children and adults with large unresected intermediate- or high-grade soft tissue sarcoma receiving preoperative chemoradiation with or without pazopanib (ARST1321; PAZNTIS): a multicentre, randomised, open-label, phase 2 trial

Aaron R. Weiss[1],
Maine Medical Center, Portland, ME, USA

Yen-Lin Chen[1],
Massachusetts General Hospital, Boston, MA, USA

Thomas J. Scharschmidt[1],
James Cancer Hospital and Nationwide Children's Hospital, Columbus, OH, USA

Yueh-Yun Chi,
Department of Biostatistics, University of Florida, Gainesville, FL, USA

Jing Tian,
Department of Biostatistics, University of Florida, Gainesville, FL, USA

Jennifer O. Black,
Children's Hospital Colorado, Aurora, CO, USA

Jessica L. Davis,
Department of Pathology, Oregon Health & Science University, Portland, OR, USA

Julie C. Fanburg-Smith,
Penn State Children's Hospital, Hershey, PA, USA

Corresponding author: Aaron R. Weiss, DO, Maine Children's Cancer Program, 100 Campus Drive, Suite 107, Scarborough, ME 04105, Phone: 207-396-7565, Fax: 207-396-7577, weissa2@mmc.org.

[1]study co-chair

[2]study co-senior leadership

Contributors

ARW, YLC, TS, YYC, JA, EC, SHO, DSH, SLS, and DW participated in study conception and design. ARW, YLC and TS were responsible for overall study conduct. DSH, SLS and DW participated in study conduct oversight. ARW, YLC, TS, YYC, JOB, JLD, JCF, EZ, RA, OB, EC, JWD, AHJ, SCK, MLK, SK, RL, WHM, LM, SHO, AO, MTP, DAP, RLR, MAR, MS, BLS, EAS, JIS, ST, DSH, SLS, and DW participated in study conduct. YYC and JA participated in statistical design and analysis. JT participated in statistical analysis. ARW, YLC, TS, YYC, JT, WHM, DSH, SLS, and DW participated in data interpretation. ARW drafted the manuscript. All authors participated in manuscript revision, reviewed and approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

Data Sharing

An individual-level de-identified dataset containing the variables analyzed in the primary results paper can be expected to be available upon request. Requests for access to COG protocol research data should be sent to: datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use. In addition to above, release of data collected in a clinical trial conducted under a binding collaborative agreement between COG or the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical/biotechnology company must comply with the data sharing terms of the binding collaborative/contractual agreement and must receive the proper approvals. The study protocol is provided in the appendix (pp 1-241).

Eduardo Zambrano,
Presbyterian St. Luke/Rocky Mountain Hospital for Children, Denver, CO, USA

James Anderson,
Merck and Co., North Wales, PA, USA

Robin Arens,
Connecticut Children's Medical Center, Hartford, CT, USA

Odion Binitie,
Moffitt Cancer Center, Tampa, FL, USA

Edwin Choy,
Massachusetts General Hospital, Boston, MA, USA

Justin W. Davis,
Children's Oncology Group, Monrovia, CA, USA

Andrea Hayes-Jordan,
Department of Surgery, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

Simon C. Kao,
Department of Radiology, University of Iowa Carver College of Medicine, Iowa City, IA, USA

Mark L. Kayton,
Palm Beach Children's Hospital, St. Mary's Medical Center/Florida Atlantic University, West Palm Beach, FL, USA

Sandy Kessel,
Imaging and Radiation Oncology Core Rhode Island, Lincoln, RI, USA

Ruth Lim,
Massachusetts General Hospital, Boston, MA, USA

William H. Meyer,
Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Lynn Million,
Department of Radiation Oncology, Stanford University School of Medicine, Palo Alto, CA, USA

Scott H. Okuno,
Mayo Clinic, Rochester, MN, USA

Andrew Ostrenga,
Department of Pharmacy, University of Mississippi Medical Center, Jackson, MS, USA

Marguerite T. Parisi,
Seattle Children's Hospital, Seattle, WA, USA

Daniel A. Pryma,
Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA

R. Lor Randall,
Department of Orthopaedic Surgery, University of California Davis, Sacramento, CA, USA

Mark A. Rosen,
Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA

Mary Schlapkohl,
Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Barry L. Shulkin,
St. Jude Children's Research Hospital, Memphis, TN, USA

Ethan A. Smith,
Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Joel I. Sorger,
Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Stephanie Terezakis,
Department of Radiation Oncology, University of Minnesota/Masonic Cancer Center, Minneapolis, MN, USA

Douglas S. Hawkins[2],
Seattle Children's Hospital, Seattle, WA, USA

Sheri L. Spunt[2],
Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA

Dian Wang[2]
Department of Radiation Oncology, Rush University Medical Center, Chicago, IL, USA

Abstract

Background—Outcomes for children and adults with advanced soft tissue sarcoma (STS) remain poor with traditional therapy. We investigated whether the addition of pazopanib to preoperative chemoradiation would improve pathological near complete response rate compared to chemoradiation alone.

Methods—In this jointly conducted Children's Oncology Group and NRG Oncology multicentre, randomised, phase 2 trial, we enrolled eligible adults (≥18 years) and children (<18 years) from 57 hospitals within the United States and Canada with unresected, newly diagnosed trunk/extremity STS (> 5 cm, intermediate- or high-grade) of chemotherapy-sensitive histology (synovial sarcoma, angiosarcoma, adult fibrosarcoma, mesenchymal chondrosarcoma, leiomyosarcoma, liposarcoma (excluding myxoid liposarcoma), undifferentiated pleomorphic sarcoma, undifferentiated embryonal sarcoma of the liver, and unclassified STS too undifferentiated to be placed in a specific pathologic category ("soft tissue sarcoma NOS") using WHO 2013 criteria) and Lansky (patients ≤16 years) or Karnofsky (patients >16 years) performance status score of at least 70. Patients received ifosfamide (2.5 g/m^2 per dose intravenously on days 1-3 with MESNA) and doxorubicin (37.5 mg/m^2 per dose intravenously on days 1-2) + 45 Gy preoperative radiotherapy, followed by surgical resection at Week 13. Allocation concealment was achieved using a web-based system with patients randomly assigned

(1:1) in an unblinded fashion to receive or not receive oral pazopanib (< 18 years: 350 mg/m^2 once daily; ≥ 18 years: 600 mg once daily) with pazopanib held around delayed surgery. The study projected 100 randomized patients to show an improvement in the rate of ≥ 90% pathologic response by central pathology review at week 13 from 40% to 60%, the primary endpoint. Analysis was done per protocol. This study has completed accrual and is registered with ClinicalTrials.gov, NCT02180867.

Findings—Eighty-one eligible patients were randomized from July 7, 2014 to June 30, 2018. At the planned second interim analysis with 42 evaluable patients and a median (IQR) follow-up of 0.8 years (0.3, 1.6), the rate of ≥ 90% pathologic response was 58.3% (14 of 24) with and 22.2% (4 of 18) without pazopanib. Based on an interim analysis significance level of 0.081 (overall one-sided significance level of 0.20, power of 0.80, and O'Brien-Fleming-type cumulative error spending function), the 83.8% confidence interval for response difference was between 16.5% and 55.8%. The improvement in pathologic response rate with the addition of pazopanib crossed the predetermined boundary and enrollment was stopped. The most common grade 3–4 adverse events in Regimen A were leukopenia (16 (43%) of 37), neutropenia (15 (41%)), and febrile neutropenia (15 (41%)). The most common grade 3–4 adverse events in Regimen B were neutropenia (3 (9%) of 35) and febrile neutropenia (3 (9%)). Twenty-two (60%) of 37 Regimen A patients experienced a pazopanib-related serious adverse event. Pediatric and adult patients experienced similar rates of grade 3/4 toxicity. There were 7 deaths (3 Regimen A; 4 Regimen B), none were treatment-related.

Interpretation—In this presumed first prospective STS trial spanning the entire age spectrum, adding pazopanib to neoadjuvant chemoradiation improved the rate of pathologic near complete response suggesting this is a highly active and feasible combination in children and adults with advanced STS. The comparison of survival outcomes requires longer follow-up.

Funding—National Institutes of Health, St Baldrick's Foundation, Seattle Children's Foundation

Introduction

Soft tissue sarcomas (STS) comprise a heterogeneous group of histologic entities that represent 7% of childhood and 2% of adult cancers.[1] Excluding rhabdomyosarcoma, gastrointestinal stromal tumor, and Ewing sarcoma that receive disease-defined treatment, the divergent STS subtypes have often been treated in a similar manner. Surgical resection, with or without radiation, is the mainstay of treatment for the 60% of STS patients with small and superficial tumors. With this therapy, over 80% of patients can expect to achieve long-term survival.[2] However, outcomes for patients with more advanced (large and deep, metastatic) disease are significantly inferior, with survival in the 15-50% range despite both local and systemic therapy.[3, 4]

Neoadjuvant chemotherapy and/or radiation has been widely adopted for patients presenting with advanced STS.[5] This approach facilitates more conservative surgery and increases the likelihood of negative surgical margins, often allowing a lower dose of radiotherapy while accelerating the delivery of systemic therapy to treat metastatic disease.[6] Other potential advantages of preoperative radiotherapy include improved treatment efficacy by avoiding postoperative tumor bed hypoxia and, with resection of irradiated tissues, decreased risk of secondary neoplasia. However, improvements in outcome from neoadjuvant trials remain

modest and interpretation of results are confounded by numerous limitations including inadequate study design and heterogeneous patient and tumor characteristics. Combination ifosfamide plus doxorubicin is one of the most active and commonly used chemotherapy regimens.[7, 8] Overall, radiographic response rates following neoadjuvant chemotherapy are relatively low (20-40%)[3, 9] and meta-analyses of adjuvant chemotherapy trials demonstrate a marginal impact of chemotherapy on survival.[10, 11] This reflects in part that few STS histologies are chemotherapy-sensitive and often patients at lower risk for recurrence based upon tumor size and grade are included in these analyses.[12] However, outcomes for advanced STS remain suboptimal and more effective therapies are needed.

Agents that target the multiple signaling pathways involved in tumorigenesis across STS subtypes may contribute to the benefits of cytotoxic chemotherapy. The VEGFR, PDGFR and c-Kit pathways are among the most commonly dysregulated in STS.[13] The multi-targeted tyrosine kinase inhibitor, pazopanib, a potent inhibitor of these pathways, improved outcomes in adults with advanced STS and is FDA-approved for single-agent use in adults with advanced soft tissue sarcomas at a dose of 800 mg once daily based on results from the Phase III randomized PALETTE study.[14] A COG Phase I study of pazopanib in children with relapsed or refractory solid tumors (ADVL0815) established an MTD of 450 mg/m^2.[15] Preclinical studies have demonstrated a potential synergistic interaction between pazopanib and conventional cytotoxic chemotherapy, suggesting that these drug combinations may overcome chemoresistance.[16, 17] Few clinical trials combining pazopanib and cytotoxic chemotherapy have been conducted with only two focused on STS.[18, 19] No studies in adults or children have combined pazopanib with chemoradiation.

Traditionally, a significant change in the size of the tumor mass as determined by RECIST has been used as a surrogate of treatment efficacy in STS. However, correlation of imaging response with survival is inconsistent.[20] Treatment-induced pathologic response following neoadjuvant therapy may be a more reliable predictor of outcome in STS.[21] This is particularly the case with the incorporation of tyrosine kinase inhibitors such as pazopanib that induce cystic changes with minimal variations in tumor size despite a positive impact on outcome.[22, 23]

We conducted the presumed first collaborative prospective study by pediatric (Children's Oncology Group [COG]) and adult (NRG Oncology) cancer consortia in STS to evaluate a novel therapeutic approach in patients across the entire age spectrum. The study included two cohorts designed to test the randomized addition of pazopanib to neoadjuvant chemoradiotherapy (chemotherapy cohort) or radiotherapy (radiotherapy cohort). We report here the results of the phase II efficacy phase of the chemotherapy cohort whose primary aim was to compare the rates of pathologic near complete (≥ 90%) response of preoperative chemoradiation with or without pazopanib for potentially resectable advanced chemotherapy-sensitive STS.

Methods

Study design and participants

ARST1321 was a National Clinical Trials Network (NCTN) multicentre, randomised, open-label, phase II trial conducted by COG and NRG Oncology (NSC# 737754, IND# 118613). The NCTN's broad reach facilitated patient accrual from all National Cancer Institute supported cooperative groups. Patients were enrolled at 57 hospitals in the United States and Canada (appendix, table S1, p 1). Eligibility criteria included age ≥ 2 years, no prior chemotherapy or radiotherapy, initially unresected (but with delayed resectable intent) STS of the extremity and trunk with or without metastasis, tumor size > 5 cm, and grade 2 or 3 by the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system.[24] Only patients with protocol-defined chemotherapy-sensitive histologies as defined in the 2013 World Health Organization Classification of Soft Tissue Tumours were eligible including: synovial sarcoma, angiosarcoma, adult fibrosarcoma, mesenchymal chondrosarcoma, leiomyosarcoma, liposarcoma (excluding myxoid liposarcoma), undifferentiated pleomorphic sarcoma, undifferentiated embryonal sarcoma of the liver, and unclassified STS too undifferentiated to be placed in a specific pathologic category (often called "soft tissue sarcoma NOS").[25] Histopathologic diagnosis was confirmed by the enrolling institution following incisional or core biopsy. Fine needle aspiration biopsy was not acceptable to establish the diagnosis. Participants were required to have measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. If a subtotal resection of the primary tumor was performed prior to enrollment, the baseline study was to be done after this operation. In these instances, study eligibility depended on the pre-subtotal resection tumor size.

Additional eligibility criteria included life expectancy of at least 3 months with appropriate therapy, Lansky (age ≤ 16 years)/Karnofsky (age > 16 years) performance status ≥ 70 and adequate organ function: bone marrow (absolute neutrophil count ≥ 1500/μL, platelet count ≥ 100,000/μL, hemoglobin ≥ 8 g/dL for patients ≤ 16 years of age and ≥ 9 g/dL for patients > 16 years of age), pulmonary (no evidence of dyspnea at rest, no exercise intolerance, and a resting pulse oximetry reading > 94% on room air), renal (creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or a normal serum creatinine based on age/gender), hepatic (total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age and AST or ALT < 2.5 x ULN for age) and cardiac (shortening fraction ≥ 27% or ejection fraction ≥ 50%, QTc < 480 msec). Exclusion criteria included: known central nervous system metastases, bleeding diathesis, recent thrombosis treated with therapeutic anticoagulation for less than 6 weeks, uncontrolled hypertension, chronic CYP3A4 substrate medication use, medications associated with risk for QTc prolongation, inability to swallow whole tablets, and body surface area < 0.5 m^2.

The trial was approved by the Pediatric Central Institutional Review Board of the National Cancer Institute and by the institutional review boards of each participating institution, as required. Informed consent from the patient or parent/guardian and patient assent as appropriate was obtained before enrollment.

Randomization and masking

Patients were randomly assigned (1:1) with permuted blocks of size 4, to receive chemoradiation or chemoradiation plus pazopanib. Randomisation was controlled centrally via an interactive web response system to prevent knowledge of the next assignment in the sequence. Enrollment was done by the study site investigator. Participants were assigned six-digit trial numbers and treatment groups and a confirmatory email including the participant's trial number, treatment assignment, and credited NCTN trial group was sent to the investigator. The treatment arm assignment was not masked to patients, physicians, outcome assessors, and data analysts. Patients were enrolled on the study based on local pathologic assessment and the FNCLCC system was used for histologic grading.[24] In circumstances where more than one histology was present (e.g. dediffentiated liposarcoma arising in the background of well-differentiated liposarcoma) , the component with the highest grade determined the classification.

Procedures

We determined the feasibility of adding pazopanib to chemoradiation during an initial dose-finding phase.[26] Subsequently, patients were randomized to receive (Regimen A) or not receive (Regimen B) oral pazopanib (< 18 years: 350 mg/m^2 once daily; ≥18 years: 600 mg once daily). Chemotherapy comprised ifosfamide (2.5 g/m^2 per dose intravenously on days 1-3) with MESNA and doxorubicin (37.5 mg/m^2 per dose intravenously on days 1-2) at 3 week intervals with 45 Gy radiotherapy (25 fractions of 1.8 Gy) beginning with the start of cycle 2 chemotherapy (week 4 of protocol therapy). Radiotherapy was started at least 24 hours after completion of the Week 4 (cycle 2) doxorubicin. Three-dimensional target volumes were used including a clinical target volume of 1.5 cm margin for children and 3 cm longitudinal and 1.5 cm radial margin for adults for highly conformal therapy. Doxorubicin was omitted during cycles 3 and 4 due to concurrent radiotherapy. Dexrazoxane was administered with all doxorubicin-containing cycles. Patients assigned to Regimen A started pazopanib concurrently with the first cycle of chemotherapy (figure 1) and continued throughout treatment excluding the pre- (7 days) and post- (minimum 14 days) surgery phase. The administration of hematopoietic growth factor (filgrastim or pegfilgrastim) was required after all chemotherapy cycles except when doxorubicin was administered alone. Definitive surgery was performed at Week 13, if feasible. Three weeks after surgery, patients received two cycles of doxorubicin/ifosfamide and one of doxorubicin only at 3 week intervals, with or without pazopanib, completing all therapy at week 25 (cumulative doses: ifosfamide 45 g/m^2, doxorubicin 375 mg/m^2). Surgical margins were assessed using the R classification system (with R0 being the goal). In the event of an R2 resection (macroscopic residual disease), re-resection or postoperative boost radiotherapy to 21.6 Gy at 1.8 Gy per fraction was required at Week 16.[4, 27] In the event of an R1 resection (microscopic residual disease), a postoperative boost with a dose of 16.2 Gy in 1.8 Gy per fraction was highly recommended but optional at Week 16 based on the discretion of the treating physician. No boost was to be given after R0 resection (defined as the microscopic absence of tumor on the inked margins following resection regardless of the proximity of tumor cells to the margin). Patients with metastatic disease were eligible to undergo surgical resection of metastases at the completion of therapy, with radiotherapy (dose/fractionation per treating physician

discretion) for incompletely resected lesions. Involved lymph node dissection was recommended at the time of the Week 13 definitive surgery or at completion of therapy when metastatic disease was resected.

All patients underwent baseline MRI of the primary site or CT if the patient had a contraindication to MRI followed by repeat imaging using the same modality prior to Week 13 surgery. Lymph node sampling was recommended in patients with enlarged regional lymph nodes detected by physical exam or diagnostic imaging. Metastatic sites were determined by the institution and biopsy was recommended for uncertainty. Imaging response was assessed using volumetric measurements of the primary tumor using an elliptical model (0.5 times the product of the three largest perpendicular diameters) to assess the diagnostic imaging response to neoadjuvant therapy. [18F]–Fluorodeoxyglucose Positron Emission Tomography (FDG PET) imaging was recommended but optional. Results of FDG PET will be reported separately.

Tumor response was assessed by imaging prior to Week 13 using RECIST criteria (version 1.1).[28] Complete Response (CR) was defined as the disappearance of all target lesions and any pathological lymph nodes were reduced in short axis to < 10 mm. Partial Response (PR) was defined as at least 64% decrease in volume compared to the measurement obtained at study enrollment. Progressive Disease (PD) was defined as at least 40% increase in tumor volume compared to the smallest volume obtained since the beginning of therapy or the appearance of one or more new lesions. Stable Disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Maximum tumor diameter and tumor location were determined by central imaging review.

We evaluated the definitive resection specimen obtained at Week 13, after 4 cycles of Induction, for pathologic response (percentage of non-viable tumor), the primary endpoint for this study, via central pathology review.[29] Submission of formalin-fixed paraffin blocks was preferred; if blocks were unavailable, hematoxylin and eosin stained sections of all blocks plus 10 plus-charged unstained slides were requested. Submission of a cross section of the tumor with specimen map was strongly encouraged. Four experienced adult and pediatric soft tissue sarcoma pathologists, who were unaware of the treatment assignments, assessed pathologic response, reviewing the material together in-person to achieve consensus.

A complete blood count with differential, electrolytes, and liver function studies were monitored prior to each cycle and then weekly. Amylase, lipase, and urinalysis was monitored prior to each cycle. Initiation of each chemotherapy cycle required an absolute neutrophil count of at least 750 cells per μL and platelet count at least 75 000 per μL. The adverse event profile of the treatments delivered (chemoradiation) was evaluated using the CTCAE versions 4.0 and 5.0 (amendment in 7/2018) and reported by participating sites. In addition to standard adverse event reporting practice, the following gradable protocol-defined targeted toxicities were explicitly monitored: wound complications, hypertension, cardiotoxicity, dermatitis, gastrointestinal toxicity, and nephrotoxicity. Incidence of wound complication was tallied and calculated from the standard adverse event reporting and may not reflect the events reported explicitly for wound complication. Late wound events may

not be fully captured by the data cutoff for this manuscript, but will be reported in a separate manuscript. A serious adverse event was any adverse drug event (experience) occurring at any dose that resulted in any of the following outcomes: (1) death, (2) a life-threatening adverse drug experience, (3) an adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations which are part of routine medical practice, (4) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, (5) a congenital anomaly/birth defect, or (6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. All serious adverse events required expedited reporting via the NCI's CTEP Adverse Event Reporting System (CTEP-AERS). All serious adverse events that resulted in hospitalization for greater than 24 hours, required reporting of grade 1-3 events within 7 calendar days and grade 4-5 events within 5 calendar days. All serious adverse events that resulted in hospitalization for less than 24 hours, required reporting of grade 3 events within 7 calendar days and grade 4-5 events within 5 calendar days.

Protocol-defined dose reductions and interruptions were ascribed to the following adverse effects when specific parameters were met: hematologic toxicity (neutropenia, thrombocytopenia), mucositis, nephrotoxicity (Fanconi's Syndrome, proteinuria, hematuria), cardiotoxicity (left ventricular systolic dysfunction, QTc prolongation, hypertension), gastrointestinal toxicity (hyperbilirubinemia, hypertransaminasemia, hyperamylasemia and/or hyperlipasemia), radiation toxicity (radiation dermatitis, radiation recall), impaired wound healing and wound complications, neurotoxicity, rash (palmar-plantar erythrodysesthesia), and electrolyte abnormalities (see protocol for full dose reduction/ interruption details [appendix pp 63-80]).

Patients who met the following criteria were removed from protocol therapy (a) progressive disease, (b) unacceptable toxicity due to protocol therapy, (c) refusal of further protocol therapy by patient/parent/guardian, (d) completion of planned therapy, (e) physician determined it was in patient's best interest, (f) development of a second malignancy, or (g) repeat eligibility studies (if required) were outside the parameters required for eligibility. Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data is required unless consent was withdrawn. Off Study criteria consisted of (a) death, (b) lost to follow-up, (c) patient enrollment onto another study with tumor therapeutic intent (eg, at recurrence), (d) withdrawal of consent for any further data submission, or (e) the fifth anniversary of the date the patient was enrolled on this study.

Outcomes

The primary endpoint for this report was the protocol Week 13, after 4 cycles of Induction, pathologic response (defined as the percentage of non-viable tumor as assessed by the central pathology review) for patients with chemotherapy-sensitive STS. Pathologic near complete response was defined as ≥ 90% non-viable tumor. Additional primary objectives of this study were: (1) to identify the dose of pazopanib that is feasible (as measured by the

incidence of protocol-defined dose-limiting toxicities and percentage of full-dose pazopanib taken over the first 6 weeks of therapy) when given in combination with radiation or chemoradiation; (2) to compare the rates of protocol Week 10 pathologic near complete (≥ 90%) response with the addition of pazopanib to preoperative radiotherapy versus preoperative radiotherapy alone for patients with chemotherapy-resistant STS in the phase 2 portion of the study for this cohort; and (3) to compare the rates of event-free survival (EFS; defined by the time from study enrollment to the first occurrence of progression, , a secondary cancer or death from any cause) with the addition of pazopanib to preoperative radiotherapy versus preoperative radiotherapy alone in the phase 3 portion of the study for this cohort. The first and second primary objectives will be addressed in a separate report. The third primary objective will not be reported since that cohort did not advance beyond the phase 2 portion of the study. Secondary endpoints were: (1) to estimate the local failure (defined as disease recurrence only at the primary site of disease at diagnosis), regional failure (defined as disease recurrence at lymph nodes regional to the primary disease site), distant failure (defined as disease recurrence at sites other than the primary site at diagnosis and nodes regional to that site (metastatic disease, whether or not present at diagnosis)) free survival, disease free survival (defined by the time from study enrollment to relapse or progression), and overall survival (defined by the time from study enrollment to death from any cause) with the addition of pazopanib to preoperative chemoradiation or preoperative radiation; (2) to compare the of pattern of local, regional, and distant recurrence (confirmed by pathology and imaging) between preoperative chemoradiation or radiation with the addition of pazopanib; and (3) to define the toxicities of ifosfamide and doxorubicin chemotherapy and radiation when combined with pazopanib and radiation alone when combined with pazopanib (as characterized using the current CTCAE version). Exploratory endpoints were: (1) to gain insight into the disease biology of childhood and adult STS through analysis of actionable mutations and whole genome sequencing; (2) to determine if microvessel density and circulating tumor DNA predict response to pazopanib and outcome; (3) to determine the effect of pazopanib on doxorubicin exposure; (4) to evaluate change in FDG PET maximum standard uptake value from baseline to Week 10 or 13 in patients with unresected tumors and to correlate this change with pathologic response and EFS; and (5) to compare the rate of response by standard imaging and pathologic assessment to determine which correlates better with disease control and outcome.

It is important to note that we report here the primary results from an interim monitoring that led to the closure of the chemoradiotherapy portion of the study and further study accrual. As a result, analyses of the additional above mentioned primary, secondary, and exploratory aims will be forthcoming in separate reports when data are sufficiently mature.

Statistical analysis

This randomized phase II screening study used a primary endpoint of Week 13 pathologic near complete (≥ 90%) response rate for chemoradiotherapy plus pazopanib, compared to chemoradiotherapy alone. The expected null (chemoradiotherapy alone) pathologic response rate (≥ 90% at Week 13) was 40%. The one-sided significance level was set at 20%. Seventy eligible patients with Week 13 pathologic response information were anticipated to provide 80% power to detect a true response rate of 60% with pazopanib. The power calculations

were performed assuming that the comparison of pathologic response rates would not be performed using a continuity correction. Based upon the experience from the prior COG STS study (ARST0332), up to 20% of patients were expected to be lost due to ineligibility or off protocol therapy prior to the Week 13 surgical evaluation for reasons other than disease progression (patients off protocol therapy prior to protocol Week 13 for disease progression or non-response were considered Week 13 non-responders). We expected to randomize up to 100 patients total (50 per treatment, 31 annually) before we reached the required 70 eligible patients evaluable for response. Interim monitoring for efficacy and futility was performed, starting at about 43% of the expected information (Week 13 response known for 30 eligible patients) and again yearly. Interim monitoring for efficacy used an O'Brien-Fleming boundary (truncated at 3 standard deviations). For futility monitoring, we repeatedly tested the hypothesis that Prob[Response (chemotherapy + pazopanib)] – Prob[Response (chemotherapy alone)] = 0.20 versus the alternative if the difference was less than 0.20 at a p-value of 0.05.

The analytical cohort was the 81 eligible patients randomized to either Regimen A or Regimen B. Patient characteristics, radiographic responses, and toxicities were summarized and compared for the entire analytical cohort. The Week 13 pathologic responses were compared only for patients whose Week 13 post-surgery tumor tissues were reviewed centrally by pathologists, i.e., excluding patients who went off therapy before Week 13 due to reasons other than progressive disease and patients whose specimens have not been reviewed. The per protocol analysis was performed to compare the Week 13 pathologic responses using the one-sided Fisher's Exact test at the significance level of 0.2. The software SAS (version 9.4) was used for the analysis. The data were current as of June 30, 2018. This study is registered with ClinicalTrials.gov, NCT02180867.

Three protocol amendments were approved that affected trial recruitment or conduct: (1) the dose level of pazopanib for the efficacy phase of the chemotherapy cohort was added following completion of the dose-finding phase (January 25, 2016); (2) expansion of eligibility for the chemotherapy cohort to patients with FNCLCC Grade 2 disease and the incorporation of more detailed guidance for impaired wound healing and wound complications (November 21, 2016); and (3) timeframe for diagnostic imaging for eligibility was extended from 3 weeks prior to enrollment to 4 weeks prior to enrollment (August 27, 2018).

Role of the funding source

The funders of the study were not involved in study design, data collection, data interpretation, writing or review of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

ARST1321 was opened for patient enrollment on July 07, 2014. During the scheduled COG Fall 2018 Data Safety Monitoring Committee (DSMC) review, based on the planned second interim analysis, the DSMC recommended halting further accrual because the pathologic response boundary was crossed; accrual was stopped on October 1, 2018. We report the data

from this trial based on the June 30, 2018 interim analysis that led to study suspension and conclusion that Regimen A, with the addition of pazopanib, improved the pathologic response rate (the primary objective).

Figure 2 shows the CONSORT diagram for this study. Eighty-nine patients were enrolled as of June 30, 2018, of whom 81 were eligible: 42 (52%) randomized to Regimen A (with pazopanib) and 39 (48%) randomized to Regimen B (without pazopanib). Eight patients were ruled ineligible for the following reasons: incorrect disease type or histology (1), organ function requirements (1), organ function requirements and prior therapy (1), stage/extent of disease (1), timing of start of protocol therapy (1), inadequate tissue (1), and primary site imaging performed outside the required 3 week from enrollment eligibility window (2). The annual accrual rate of 28 patients approximated the expected accrual of 31 patients. Patient characteristics are summarized in Table 1. The most common histologies were synovial sarcoma and undifferentiated pleomorphic sarcoma. Although the majority of patients were ≥ 18 years (n=49; 60%), the entire age spectrum was well represented and all NCTN cooperative groups contributed to enrollment (appendix, figure S1, p 3). Median (IQR) years in follow-up was 0.8 (0.3, 1.6) for Regimen A and 1 (0.3, 1.6) for Regimen B.

Week 13 response was available for 42 patients (60% of expected information). The rate of ≥ 90% pathologic response was 58.3% (14 of 24) for Regimen A and 22.2% (4 of 18) for Regimen B (table 2), with the difference in the rate of ≥ 90% pathologic response between the two groups 36.1% (83.8% CI: 16.5%-55.8%). One patient (4%) on Regimen A and 4 (22%) patients on Regimen B developed progressive disease prior to Week 13 surgery and were deemed “non-responders”. With a significance level of 0.081 (for the second efficacy analysis with overall one-sided significance level of 0.20, power of 0.80, and O’Brien-Fleming-type cumulative error spending function), the 83.8% confidence interval for the difference excluded 0. At this predetermined interim analysis timepoint, the efficacy boundary was crossed indicating that Regimen A was more efficacious than Regimen B. Of the 37 patients whose Week 13 specimens were centrally reviewed (excluding 5 patients not reviewed but being categorized as “non-responders” for developing progressive disease prior to Week 13 surgery), the median pathologic response (percentage of non-viable tumor) was 95% (n=23, IQR: 40.0 - 95.0) for Regimen A and 50% (n=14, IQR: 25.0 - 90.0) for Regimen B.

Interim monitoring was based on the data available at the time of the analysis. The reduction from 81 patients to 42 patients available for pathologic response assessment was due to the fact that some of the patients went off therapy before the surgery and thus did not have the post-surgery specimens for pathology review. The timing of the interim monitoring was determined in accordance with the protocol, by the number patients with Week 13 response evaluated (expected information) and yearly afterwards. Patients in Regimen B had a higher rate of pathologic response inevaluability due to more ineligible patients and patients who went off therapy before Week 13 for reasons other than progressive disease (figure 2). The median time from start of therapy to surgery was 88 days (n=23, range: 78-125 days) for Regimen A and 92 days (n=14, range: 84-115 days) for Regimen B. In addition, the median time from start of radiation to surgery was 64 days (n=22, range: 51-102 days) for Regimen

A and 68 days (n=14, range: 57-94 days) for Regimen B. One patient on Regimen A did not receive radiation.

Radiographic response at the Week 13 timepoint following Induction, before surgery, revealed 52% (14 of 27) partial response or greater for Regimen A and 58% (14 of 24) for Regimen B. Progressive disease by Week 13 was 4% (1 of 27) for Regimen A and 8% (2 of 24) for Regimen B. There was no statistically significant difference in radiographic response by treatment arm (p= 0.45; table 2).

Nine (11%) of 81 patients (5 (12%) of 42 from Regimen A and 4 (10%) of 39 from Regimen B) were excluded from the analysis of treatment-related data, including toxicities, because of the delay in data submission or the patients had not completed the Induction by the time of the data cutoff. No unexpected toxicities were reported among the 72 eligible patients whose treatment related data were submitted by the time of data cutoff. One (1%) CTCAE gradable protocol-defined targeted toxicity occurred on the chemotherapy arm (grade 3 radiation dermatitis). One eligible patient (1%) was removed from Induction protocol therapy due to "unacceptable toxicity" (from Regimen A). Eighteen (25%) of 72 patients were removed from protocol therapy before the Week 13 surgery time point (6 (16%) of 37 from Regimen A; 12 (34%) of 35 from Regimen B). Most frequent reasons for removal included physician determining it was in patient's best interest (1 (3%) of 37 from Regimen A; 7 (20%) of 35 from Regimen B) and refusal of further protocol therapy by patient/parent/guardian (4 (11%) of 37 from Regimen A; 3 (9%) of 35 from Regimen B). Thirty-two of the 37 Regimen A patients (87%) had planned (n=15; 41%) and/or unplanned (n=24; 65%) dose modifications for pazopanib administration, and 5 (14%) had no modification throughout the protocol therapy. Five (14%) of 37 patients from Regimen A (1 during Induction, 1 during Surgery, 3 during Continuation; reason: unacceptable toxicity due to protocol therapy) and no patients from Regimen B discontinued therapy for drug-related toxicity.

Table 3 details the grade 3, 4, and 5 toxicities during protocol treatment for each regimen. There were no grade 1-2 adverse events with incidence of ≥10% for any of the treatment groups. The most common grade 3–4 adverse events in Regimen A were leukopenia (16 (43%) of 37), neutropenia (15 (41%)), and febrile neutropenia (15 (41%)). The most common grade 3–4 adverse events in Regimen B were neutropenia (3 (9%) of 35) and febrile neutropenia (3 (9%)). Only pazopanib-related serious adverse event data were collected (appendix, table S2, p 4). Twenty-two (60%) of 37 Regimen A patients experienced a pazopanib-related serious adverse event. The most frequent serious adverse event was febrile neutropenia reported in 10 (27%) of 37. Three (8%) of 37 patients from Regimen A and 4 (11%) of 35 patients from Regimen B died, including one during protocol treatment. All were caused by the disease and none were related to treatment.

Table 4 details reported toxicities by treatment phase (Induction, Surgery, Continuation), regimen, and age (< 18 years, ≥ 18 years). Grade ≥ 3 adverse events, the worst event for each patient in each treatment phase, with >10% overall incidence during each treatment phase were included. The most common toxicities during the Induction and Continuation phases of therapy were febrile neutropenia and myelotoxicity. There was a greater frequency of toxicity on Regimen A. The type and incidence of toxicities were similar in pediatric and

adult patients. There was an increased incidence of wound complications during the Continuation phase. In total, 8 patients (11%; 7 (19%) of 37 on Regimen A) had ≥ Grade 3 wound complications during protocol therapy, of which 4 (50%) were ≥ 18 years of age. Additional wound complication data has been reported separately.[30]

Discussion

This prospective phase II randomized study showed that the addition of pazopanib to combination chemoradiation improved pathologic response in children and adults with large, unresected, intermediate- or high-grade chemosensitive STS, the primary endpoint of this study and a predictor of improved outcome in STS. In addition, to our knowledge, this is the first prospective STS study to treat patients of all ages under the same protocol that was co-developed by both pediatric (COG) and adult (NRG Oncology) cancer consortia, successfully reaching the anticipated accrual target.

Treatment-induced tissue necrosis following neoadjuvant therapy has been established as a reliable predictor of outcome in bone sarcomas. Similar correlations have been reported in STS, although the data are less robust. In the largest study evaluating this association, 496 patients with intermediate to high-grade extremity STS underwent surgical resection following protocol neoadjuvant chemoradiotherapy.[21] The 5- and 10-year local recurrence rates for patients with ≥ 95% pathologic necrosis were significantly lower (6% and 11%, respectively) compared to those patients with < 95% pathologic necrosis (17% and 23%, respectively, p=0.002). The 5- and 10-year survival rates were also significantly higher for patients with ≥ 95% pathologic necrosis (80% and 71%, respectively) than those with < 95% pathologic necrosis (62% and 55%, respectively, p=0.0001). When analyzed in a multivariate manner, pathologic necrosis was an independent predictor of survival. In a recent large meta-analysis reviewing 1663 STS patients from 21 studies, patients with <90% necrosis had significantly higher risk for recurrence (hazard ratio [HR] 1.47; 95% CI: 1.06–2.04; p=0.02) and death (HR 1.86; 95% CI: 1.41–2.46; p < 0.001).[31]

NRG Oncology (formally RTOG) completed two phase II trials (RTOG 9514 and RTOG 0630) for patients with localized, high-grade STS of the extremity or body wall receiving neoadjuvant chemoradiotherapy (RTOG 9514) or preoperative radiation alone (RTOG 0630).[32] On RTOG 9514, 27.5% had a pathologic complete response (pCR) and on RTOG 0630 19.4% had pCR. With a median follow-up of greater than 5 years, overall survival was 100% for patients with pCR versus 76.5% (RTOG 9514, 95% confidence interval (CI) 62.3-90.8) and 56.4% (RTOG 0630, 95% CI 43.3-69.5) for patients with < pCR. pCR was associated with improved overall (p=0.01) and disease-free [HR 4.91 (1.51-15.93); p=0.008] survival relative to < pCR. Local failure rate was 0% in patients with pCR versus 11.7% (RTOG 9514, 95% CI 3.6-25.1) and 9.1% (RTOG 0630, 95% CI 3.3-18.5) for patients with < pCR.

The pathologic response rates in advanced STS appear to be consistent across multiple studies at 30-50%.[21, 32] The marked difference in pathologic response rates on the two arms of ARST1321, supports that pazopanib added to chemoradiation induces tumor response to a much greater degree than chemoradiation alone. It will be important to determine whether

greater pathologic response rate will translate into improved patient local control and survival. We plan to analyze these survival outcomes when the study follow-up is sufficiently mature. Because our study was terminated early when an interim boundary was crossed, the eventual outcome analysis may be compromised by the study's relatively small sample size.

Recognizing that the majority of STS histologies are chemotherapy-resistant, our study was restricted to the STS histologies that are considered sensitive to chemotherapy. We based our eligibility on published reports for chemotherapy-sensitive STS tumor types including synovial sarcoma, angiosarcoma, undifferentiated sarcoma, pleomorphic sarcoma, leiomyosarcoma, liposarcoma, mesenchymal chondrosarcoma, and embryonal sarcoma of the liver.[12] Our predecessor study ARST0332 collected data on pathologic response in a similar subset of patients treated. Histologies with an overall good pathologic response (≥ 90%) at Week 13 included synovial sarcoma, unclassified sarcoma, and embryonal sarcoma of the liver, which were among the most common histologies seen on ARST0332. Good pathologic response was seen in a smaller number of other histologies, including fibrosarcoma, mesenchymal chondrosarcoma and angiosarcoma.

Neoadjuvant chemotherapy and/or radiation is commonly incorporated into frontline therapy for patients with advanced STS when treating for curative intent. While a standard systemic therapy is not currently established, ifosfamide and doxorubicin is considered the most active combination and most commonly used chemotherapy regimen.[7, 8] Despite this approach, only marginal benefit is demonstrated in multiple meta-analyses and overall outcomes remain poor.[10, 11] This may be due to the heterogenous nature of STS and reliance on a "one-size-fits all" approach to treatment. ARST1321 was designed to improve upon current neoadjuvant chemoradiotherapy with the addition of a more biologically-targeted therapy. To our knowledge, this is the first study prospectively evaluating pazopanib in combination with chemoradiation in STS.

Pazopanib as monotherapy has modest toxicities, including a low incidence of myelosuppression, hepatic and pancreatic enzyme elevation, electrolyte abnormalities, proteinuria, hypertension, left ventricular dysfunction, fatigue, hypopigmentation, hand-foot syndrome, rash, anorexia, diarrhea and nausea.[14, 15, 23] The majority of drug-related adverse events have been Grade 1 or 2 and reversible on treatment dose reduction or discontinuation.

Anticipating a combination of overlapping and drug-specific toxicities with pazopanib added to our backbone therapy, adverse events on this study were carefully monitored. In fact, following an initial dose-finding phase, the pazopanib dose chosen for the efficacy phase was lower than the recommended monotherapy MTDs for children and adults.[26] At this dose level, reported grade ≥ 3 adverse events for the efficacy phase were greater on the pazopanib arm. Not unexpectedly, myelotoxicity and febrile neutropenia encompassed a significant portion of those event differences. We observed relatively few reported drug-specific adverse events. Of interest, the type and frequency of toxicities were generally similar for pediatric and adult patients. Wound complications were of particular concern in the pazopanib arm given pazopanib's known toxicity. Although our reported rate in this manuscript is 9.9%, due to late reports of wound toxicity and different reporting mechanisms, we expect the final

rate of wound complications to be higher. This will be the subject of a more comprehensive evaluation and publication focusing on wound effects among patients on this study. However, it should be noted that our wound complication rate is expected to remain well within the accepted historical rate (up to 30%) for patients receiving neoadjuvant chemoradiation without the use of a tyrosine kinase inhibitor.[33] One of the advantages of performing a study that incorporates the entire age spectrum is a unique opportunity to compare toxicities directly among children and adults with uniformly delivered therapy. Our finding that toxicities were similar across the age spectrum suggests that age should not be an absolute determinant for consideration of this therapy approach.

We acknowledge that patients who enrolled but were not included in this analysis would be informative. However, we report here the results from an interim monitoring that led to the closure of the chemoradiotherapy portion of the study. The findings of this analysis not only led to the cessation of study accrual, but also indicates that statistical testing for the primary outcome is complete. We have focused this paper on what was known at the time the study was suspended, and have not provided data on patients enrolled between the data cutoff date for the interim analysis and the date that accrual was halted due to the findings of the interim analysis simply for descriptive purposes. These data will be used in the planned outcome analysis when mature, since these additional patients will contribute information on local control and survival outcome comparisons.

One of the limitations of our study is the limited chemotherapy response data available to define which “chemosensitive” tumors would be eligible for this study. However, we were careful to only include those subtypes with strong supportive evidence-based data in combination with high pathologic response rates of similarly treated patients on predecessor COG and NRG Oncology STS studies. Of the over 45 high grade STS histologies, only 9 were eligible for enrollment onto this chemotherapy study. We also acknowledge, with such inter- and intratumoral heterogeneity, it is possible one single pathologic response system is inadequate to accurately and consistently grade pathologic response across all subtypes.

Another potential limitation of our study is that a number of patients were removed from study prior to Week 13 surgery. As a result, although there were 81 eligible patients at the time of the second interim analysis, only 42 patients had the post-surgery specimens for pathology review and were evaluable for pathologic response. However, contrary to what may have been predicted, more patients were inevaluable on Regimen B in part because a higher number of patients went off therapy before Week 13. The most common reason was the physician determining it was in patient's best interest (8 total; 7 from Regimen B). This finding suggests pazopanib did not contribute an undue toxicity burden to patients.

Further, it is important to note that the primary outcome of this phase II study was pathologic response, evaluated on the tumor tissues obtained during the surgery at Week 13, after 4 cycles of Induction. Thus, patients who went off therapy before Week 13 did not continue the protocol therapy and therefore did not have surgery and tumor tissues post-surgery for pathology review. Reponses from these patients, except if the reason for off therapy was progressive disease, were excluded because pathologic data were not available. Assessment of histologic response is variable and dependent on the length of neoadjuvant

therapy in osteosarcoma. Thus, it was critical to have pathologic assessment at the time required by study, and unfortunately, with this study design, patients who did not have a pathologic response assessment at the protocol mandated time cannot add any additional information.

Lastly, the study was designed and monitored with an overall one-sided level of significance of 0.2. The inflated level of significance was justified for the study of the small patient population and lends a limitation of extraneous false positive discovery. Nevertheless, it is important to interpret these results within the context of the intended design of the study. This was a randomized phase II screening study and was not intended to be a definitive phase III trial. As such, the results presented cannot be viewed as conclusive evidence. Further maturation of this data and additional studies are needed to demonstrate the superiority of this approach, particularly as it relates to its impact on outcome.

The success of co-developing, conducting, and completing a clinical trial for STS patients of all ages is meaningful. Adolescent and young-adult oncology (AYAO) patients often experience inferior outcomes across multiple cancer types compared to their pediatric and older adult counterparts.[34] This is, in part, due their underrepresentation in clinical trials. While STS affects the entire age spectrum, it is currently unknown whether age influences disease behavior. STS affords us a unique opportunity to develop clinical trials with expanded and more inclusive eligibility criteria that enhance AYAO patient enrollment and may ultimately improve outcomes within this vulnerable population. Thus, collaborative studies such as this are important for the AYAO community. While the majority of ARST1321 patients were enrolled at COG and NRG Oncology sites, most encouragingly we met our anticipated accrual target with all NCTN cooperative groups participating and the AYAO population well-represented (appendix, figure S1, p 3). The success of our study will likely encourage additional joint pediatric-adult studies in STS and diseases that extend across age boundaries in the future.

In conclusion, the addition of pazopanib to neoadjuvant chemoradiation results in increased rates of pathologic near complete response suggesting this is a highly active combination in children and adults with advanced STS. Toxicity rates were similar across the age spectrum. This study represents a successful collaboration between adult and pediatric cooperative groups and a model for future AYAO-inspired trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was funded by National Clinical Trials Network Operations Center Grant U10CA180886, National Clinical Trials Network Statistics & Data Center Grant U10CA180899, National Cancer Institute IROC Operations Grant CA180803, St. Baldrick’s Foundation and Seattle Children’s Foundation, from Kat’s Crew Guild through the Sarcoma Research Fund. We gratefully acknowledge all of the patients and their families, care providers, and research personnel who participated in this study and a special thank you to the staff at the Operations Center of the Children’s Oncology Group for all of their assistance in shepherding this study through from inception to completion.

Declaration of interests

ARW reports grants from the National Cancer Institute/Children's Oncology Group, during the conduct of the study and non-financial support from SpringWorks Therapeutics, outside the submitted work. TS reports personal fees from Stryker Orthopedics and Daiichi-Sanko, outside the submitted work. JA reports salary support from Merck and Co during the conduct of the study and outside the submitted work. EC reports a grant from Novartis during the conduct of the study. JLD reports personal fees from Bayer, Loxo Oncology, and Lilly, outside the submitted work. MLK is a co-inventor on U.S. patents 5641867, 6228837, 6734168, 9125959, 9339574, 9839709, none of which are directly related to this work and none of which are currently under licensure. DAP reports grants and personal fees from Siemens, Progenics, and 511 Pharma, personal fees from Actinium Pharmaceuticals and Bayer, and grants from Nordic Nanovector, outside the submitted work. ST reports a grant from NIH NCTN Grant (2U01CA180886) for Radiation Oncology Review, during the conduct of the study. DSH reports grants and non-financial support from Loxo Oncology, Bayer, and Bristol Myers Squibb, non-financial support from AstraZeneca and Celgene, grants from Merck Sharpe Dohme, Lilly, Eisai, Glaxo Smith Kline, Novartis, Sanofi, Amgen, Seattle Genetics, Jazz Pharmaceuticals, and Incyte, outside the submitted work. SAS reports grants from National Cancer Institute/ Children's Oncology Group, during the conduct of the study and grants from F. Hoffman-LaRoche Ltd, Novartis, Alex's Lemonade Stand Foundation, Cookies for Kids' Cancer, Bayer Healthcare Phramaceuticals, Inc., Sanofi US Services, Inc., Loxo Oncology, Incyte Corporation, Bristol Myers Squibb , St. Baldrick's Foundation, Pfizer, Inc., and University of California, Santa Cruz, outside the submitted work. All other co-authors declare no competing interests.

References

1. Ferrari A, Sultan I, Huang TT, et al. Soft tissue sarcoma across the age spectrum: a population-based study from the Surveillance Epidemiology and End Results database. Pediatric blood & cancer 2011; 57(6): 943–9. [PubMed: 21793180]
2. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1996; 14(5): 1679–89. [PubMed: 8622088]
3. Pappo AS, Devidas M, Jenkins J, et al. Phase II trial of neoadjuvant vincristine, ifosfamide, and doxorubicin with granulocyte colony-stimulating factor support in children and adolescents with advanced-stage nonrhabdomyosarcomatous soft tissue sarcomas: a Pediatric Oncology Group Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005; 23(18): 4031–8. [PubMed: 15767644]
4. Spunt SL, Million L, Chi YY, et al. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. The Lancet Oncology 2020; 21(1): 145–61. [PubMed: 31786124]
5. Pasquali S, Palassini E, Stacchiotti S, Casali PG, Gronchi A. Neoadjuvant treatment: a novel standard? Current opinion in oncology 2017; 29(4): 253–9. [PubMed: 28426465]
6. Pasquali S, Gronchi A. Neoadjuvant chemotherapy in soft tissue sarcomas: latest evidence and clinical implications. Therapeutic advances in medical oncology 2017; 9(6): 415–29. [PubMed: 28607580]
7. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology 2014; 25 Suppl 3: iii102–12. [PubMed: 25210080]
8. von Mehren M, Randall RL, Benjamin RS, et al. Soft Tissue Sarcoma, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network : JNCCN 2018; 16(5): 536–63. [PubMed: 29752328]
9. Le Cesne A, Judson I, Crowther D, et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: A trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2000; 18(14): 2676–84. [PubMed: 10894866]
10. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008; 113(3): 573–81. [PubMed: 18521899]

11. Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M. Meta-analysis of ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma. Cancer treatment reviews 2008; 34(4): 339–47. [PubMed: 18313854]
12. Eriksson M Histology-driven chemotherapy of soft-tissue sarcoma. Annals of oncology : official journal of the European Society for Medical Oncology 2010; 21 Suppl 7: vii270–6. [PubMed: 20943627]
13. Le Tourneau C, Faivre S, Raymond E. New developments in multitargeted therapy for patients with solid tumours. Cancer treatment reviews 2008; 34(1): 37–48. [PubMed: 17983706]
14. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet (London, England) 2012; 379(9829): 1879–86.
15. Glade Bender JL, Lee A, Reid JM, et al. Phase I pharmacokinetic and pharmacodynamic study of pazopanib in children with soft tissue sarcoma and other refractory solid tumors: a children's oncology group phase I consortium report. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013; 31(24): 3034–43. [PubMed: 23857966]
16. Li Y, Yang X, Su LJ, Flaig TW. Pazopanib synergizes with docetaxel in the treatment of bladder cancer cells. Urology 2011; 78(1): 233 e7–13.
17. Hashimoto K, Man S, Xu P, et al. Potent preclinical impact of metronomic low-dose oral topotecan combined with the antiangiogenic drug pazopanib for the treatment of ovarian cancer. Molecular cancer therapeutics 2010; 9(4): 996–1006. [PubMed: 20371722]
18. Munhoz RR, D'Angelo SP, Gounder MM, et al. A Phase Ib/II Study of Gemcitabine and Docetaxel in Combination With Pazopanib for the Neoadjuvant Treatment of Soft Tissue Sarcomas. The oncologist 2015; 20(11): 1245–6. [PubMed: 26449382]
19. Hamberg P, Boers-Sonderen MJ, van der Graaf WT, et al. Pazopanib exposure decreases as a result of an ifosfamide-dependent drug-drug interaction: results of a phase I study. British journal of cancer 2014; 110(4): 888–93. [PubMed: 24366297]
20. Schuetze SM. Imaging and response in soft tissue sarcomas. Hematology/oncology clinics of North America 2005; 19(3): 471–87, vi. [PubMed: 15939192]
21. Eilber FC, Rosen G, Eckardt J, et al. Treatment-induced pathologic necrosis: a predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2001; 19(13): 3203–9. [PubMed: 11432887]
22. Yoon SS, Duda DG, Karl DL, et al. Phase II study of neoadjuvant bevacizumab and radiotherapy for resectable soft tissue sarcomas. International journal of radiation oncology, biology, physics 2011; 81(4): 1081–90.
23. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009; 27(19): 3126–32. [PubMed: 19451427]
24. Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1997; 15(1): 350–62. [PubMed: 8996162]
25. Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F, editors. WHO Classification of Tumours of Soft Tissue and Bone Pathology and Genetics of Tumours of Soft Tissue and Bone. 4th ed. Lyon: IARC Press; 2013.
26. Chen JL, Weiss AR, Scharschmidt T, et al. Results of the dose-finding phase of ARST 1321 from the Children's Oncology Group and NRG Oncology: Neoadjuvant chemoradiation or radiation therapy +/− pazopanib in non-rhabdomyosarcoma soft tissue sarcomas. American Society of Clinical Oncology Annual Meeting; 2019; Chicago, IL; 11070.
27. Wang D, Zhang Q, Eisenberg BL, et al. Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. Journal of clinical oncology :

official journal of the American Society of Clinical Oncology 2015; 33(20): 2231–8. [PubMed: 25667281]

28. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England : 1990) 2009; 45(2): 228–47.
29. Schaefer IM, Hornick JL, Barysauskas CM, et al. Histologic Appearance After Preoperative Radiation Therapy for Soft Tissue Sarcoma: Assessment of the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group Response Score. International journal of radiation oncology, biology, physics 2017; 98(2): 375–83.
30. Scharschmidt T, Chen JL, Wang D, et al. ARST1321: Pazopanib neoadjuvant trial in non-rhabdomysarcoma soft tissue sarcomas: A report of major wound complications. American Society of Clinical Oncology Annual Meeting; 2019; Chicago, IL; 11059.
31. Salah S, Lewin J, Amir E, Abdul Razak A. Tumor necrosis and clinical outcomes following neoadjuvant therapy in soft tissue sarcoma: A systematic review and meta-analysis. Cancer treatment reviews 2018; 69: 1–10. [PubMed: 29843049]
32. Wang D, Harris J, Kraybill WG, et al. Pathologic complete response and survival outcomes in patients with localized soft tissue sarcoma treated with neoadjuvant chemoradiotherapy or radiotherapy: Long-term update of NRG Oncology RTOG 9514 and 0630. American Society of Clinical Oncology Annual Meeting; 2017; Chicago, IL; 11012.
33. DeLaney TF, Spiro IJ, Suit HD, et al. Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. International journal of radiation oncology, biology, physics 2003; 56(4): 1117–27.
34. Bleyer A, Barr R. Cancer in young adults 20 to 39 years of age: overview. Seminars in oncology 2009; 36(3): 194–206. [PubMed: 19460577]

Research in Context

Evidence before this study

Outcomes for patients with advanced soft tissue sarcoma remain poor despite both local and systemic therapy. Neoadjuvant combined chemotherapy and radiotherapy followed by definitive tumor resection produced a high rate of local tumor control with a tolerable risk of wound complications in previous adult studies. With promising results from the use of single agent pazopanib in adult soft tissue sarcomas, we initiated a prospective, randomized study combining preoperative chemoradiation +/− pazopanib in pediatric and adult patients with advanced and metastatic soft tissue sarcomas utilizing pathologic response as a primary endpoint. In designing this clinical trial, we considered both retrospective and prospective published data from pediatric and adult soft tissue sarcoma studies, excluding those focusing on rhabdomysosarcoma. We searched PubMed for articles published in English up to December 31, 2013, using the search terms: “soft tissue sarcoma”, “pediatric”, “adult”, “neoadjuvant”, “chemotherapy”, “ifosfamide”, “doxorubicin”, “tyrosine kinase inhibitor”, “pazopanib”, “radiotherapy”, “chemoradiation”, “chemoradiotherapy”, “pathologic response”, and “pathologic necrosis”. We did not find any studies reporting on the use of pazopanib with neoadjuvant chemoradiotherapy in soft tissue sarcoma.

Added value of this study

Our study demonstrated that the addition of pazopanib to combination chemoradiation improved pathologic response in children and adults with advanced soft tissue sarcoma. Additionally, to our knowledge, this is the first collaborative prospective study by pediatric and adult cancer consortia in soft tissue sarcoma to evaluate a novel therapeutic approach in patients across the entire age spectrum.

Implications of all the available evidence

We anticipate that the findings of this study may change the approach to advanced, unresected soft tissue sarcomas in children and adults and encourage additional joint pediatric-adult studies in soft tissue sarcoma and diseases that extend across age boundaries in the future. It will be important to determine whether greater pathologic response rate will translate into improved patient local control and survival.

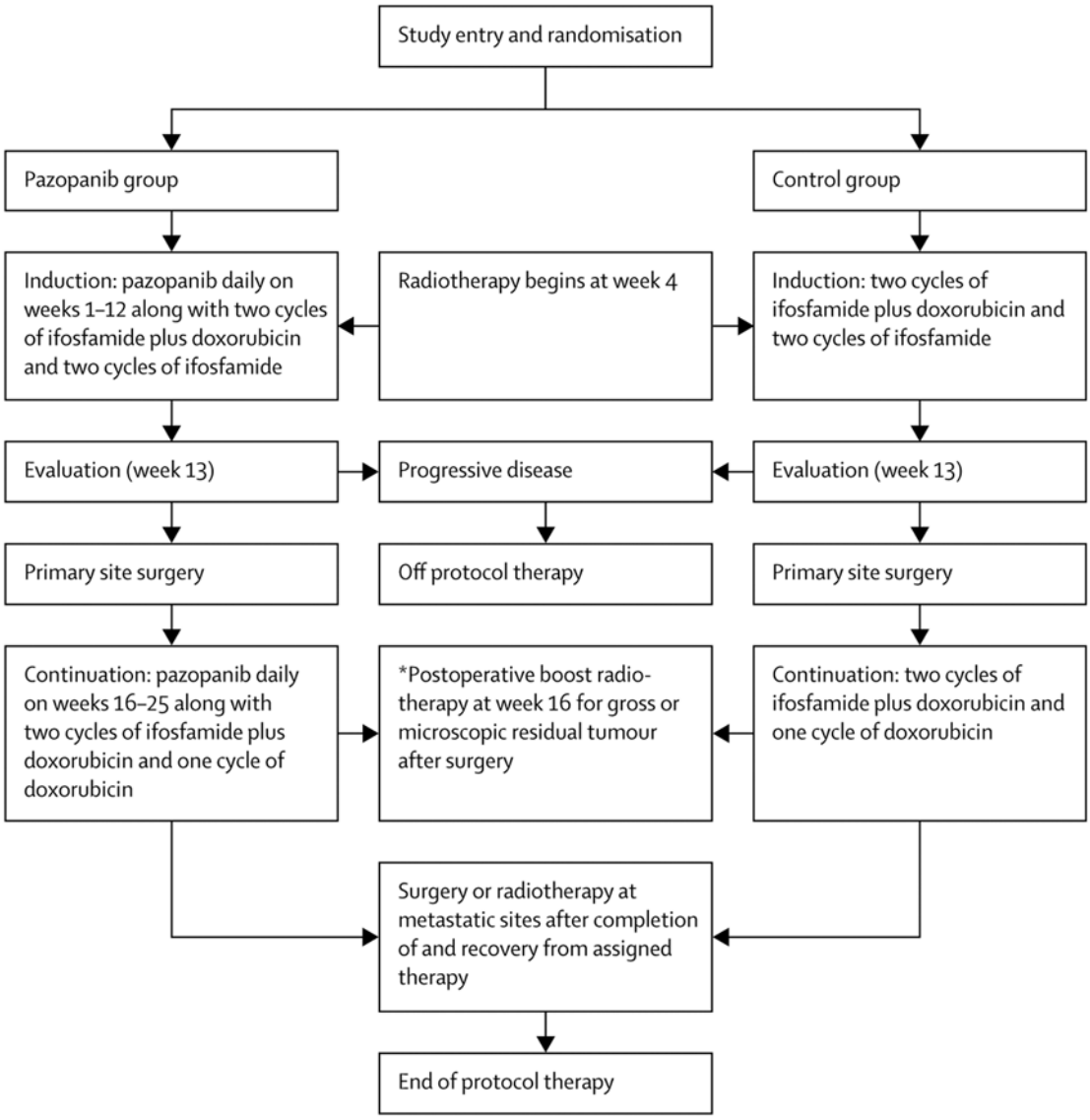

Figure 1: Study design

Pazopanib dose was 350 mg/m2 per day if the patient was younger than 18 years, and 600 mg per day if the patient was 18 years or older. Pazopanib dose was held before and after surgery. Ifosfamide dose was 7·5 g/m2 per cycle. Doxorubicin dose was 75 mg/m2 per cycle. Each cycle lasted 21 days. *Postoperative boost radiotherapy was required for gross residual disease and was optional for positive margins.

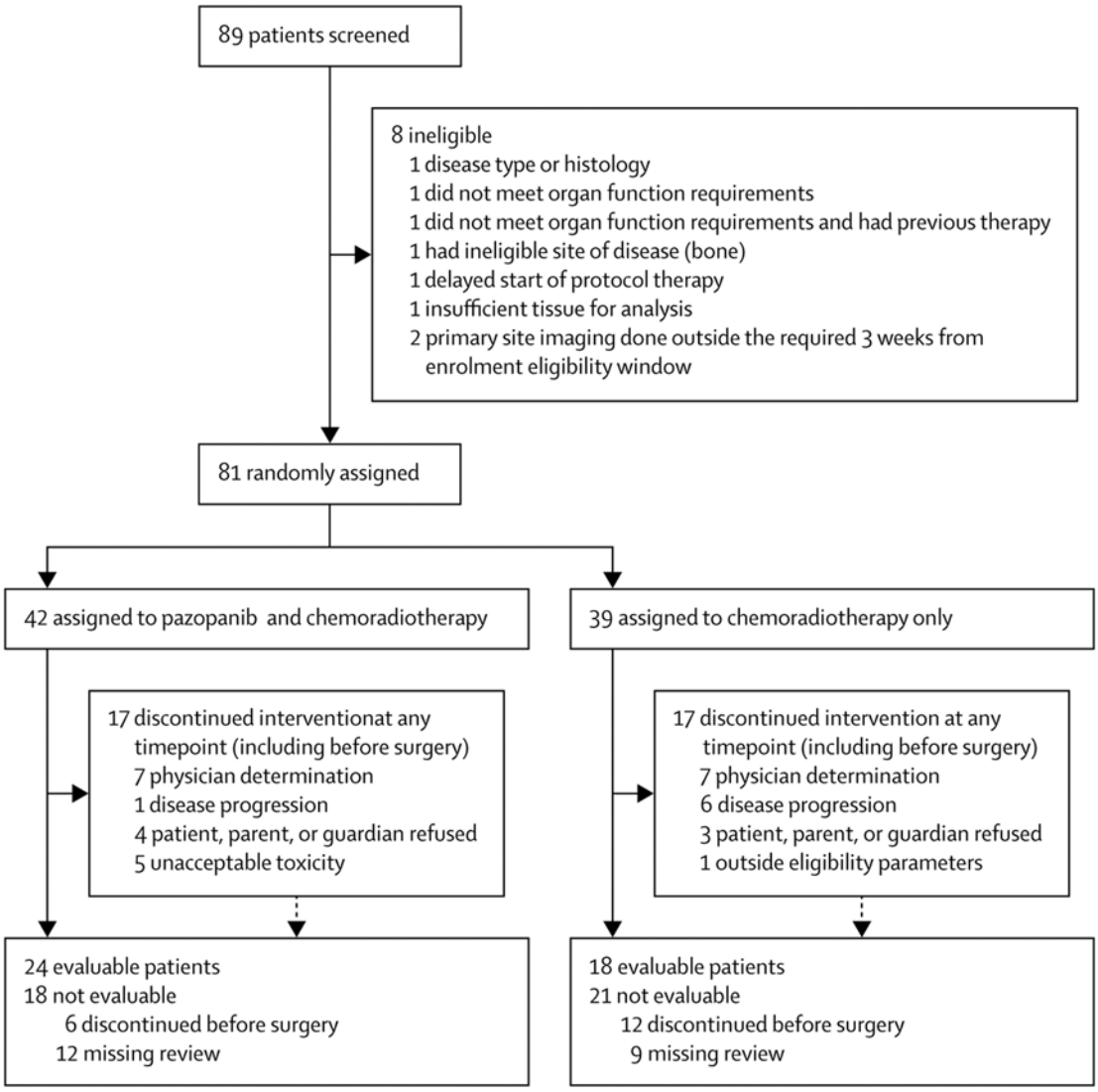

Figure 2:
Trial Profile

Table 1:

Patient characteristics

	Regimen A[1] (n=42)	Regimen B[2] (n=39)
Age		
Median (range)	25.1 (5.7–71.3)	18.7 (5.8–73.5)
< 18 years	14 (33%)	18 (46%)
≥ 18 years	28 (67%)	21 (54%)
Sex		
Male	17 (40%)	24 (62%)
Female	25 (60%)	15 (38%)
Tumor size (cm)		
Median (range)	10.6 (4.2, 26.0)	9.6 (4.6, 32.6)
Primary site		
Extremity	38 (90%)	33 (85%)
Trunk	4 (10%)	6 (15%)
T Stage		
T2a	4 (10%)	8 (21%)
T2b	30 (71%)	28 (74%)
Tx	8 (19%)	2 (5%)
Unknown	0	1
N Stage		
N1	8 (19%)	3 (8%)
N0	26 (62%)	26 (68%)
Nx	8 (19%)	9 (24%)
Unknown	0	1
Metastases		
None	31 (74%)	28 (72%)
Lung only	7 (17%)	7 (18%)
Other	4 (9%)	4 (10%)
Histology		
Synovial sarcoma	22 (52%)	20 (51%)
Undifferentiated pleomorphic sarcoma	8 (19%)	10 (26%)
Embryonal sarcoma of the liver	1 (2%)	2 (5%)
Leiomyosarcoma	3 (7%)	1 (3%)
Other	8 (19%)	6 (15%)

[1]Regimen A = Chemoradiation + Pazopanib

[2]Regimen B = Chemoradiation

Table 2:

Disease response

	Regimen A (n, %)	Regimen B (n, %)	p value
Pathologic response	n=24 evaluable	n=18 evaluable	
≥ 90%	14 (58.3%)	4 (22.2%)	0.02[1]
< 90 %	10 (41.7%)	14 (77.8%)	
Institutional radiographic response following Induction	n=27 evaluable	n=24 evaluable	
Complete response	0 (0%)	2 (8%)	0.45
Partial Response	14 (52%)	12 (50%)	
Stable Disease	12 (44%)	8 (33%)	
Progressive Disease	1 (4%)	2 (8%)	
Not evaluated	15	15	

[1] One-sided with a 0.081 level of significance for the second interim monitoring.

Table 3:

Regimen A (chemoradiation plus pazopanib) versus Regimen B (chemoradiation alone) Grade 3, 4, and 5 toxicities during protocol treatment. No grade 1-2 adverse event with incidence of ≥10% for any of the treatment group, and no grade 5 adverse event for Regimen A. The top row provides the number (N) of patients whose treatment-related data have been reported as of the data cut-off (5 Regimen A and 4 Regimen B patients were excluded because of delay in reporting or the patients had not completed the Induction by the time of the data cutoff).

	REGIMEN A (*N* = 37)		REGIMEN B (*N* = 35)		
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 5
Anemia	2 (5%)	0	1 (3%)	0	0
Anorexia	3 (8%)	0	0	0	0
Atrial fibrillation	1 (3%)	1 (3%)	0	0	0
Atrial flutter	1 (3%)	1 (3%)	0	0	0
Blood and lymphatic system disorders	1 (3%)	0	0	0	0
Cognitive disturbance	1 (3%)	0	0	0	0
Death NOS	0	0	0	0	1 (3%)
Dehydration	2 (5%)	0	0	0	0
Delirium	3 (8%)	0	0	0	0
Depression	1 (3%)	0	0	0	0
Dermatitis radiation	1 (3%)	0	0	0	0
Device related infection	1 (3%)	0	1 (3%)	0	0
Encephalopathy	1 (3%)	0	0	0	0
Esophagitis	1 (3%)	0	0	0	0
Fatigue	2 (5%)	0	0	0	0
Febrile neutropenia	13 (35%)	2 (5%)	1 (3%)	2 (6%)	0
Hallucinations	1 (3%)	0	0	0	0
Hyperglycemia	0	0	1 (3%)	0	0
Hypokalemia	1 (3%)	1 (3%)	0	0	0
Hyponatremia	2 (5%)	0	1 (3%)	0	0
Hypophosphatemia	2 (5%)	0	0	0	0
Hypotension	1 (3%)	0	0	0	0
Hypoxia	1 (3%)	0	0	0	0
Ileus	0	1 (3%)	0	0	0
Laryngospasm	0	1 (3%)	0	0	0
Lymphocyte count decreased	0	7 (19%)	0	2 (6%)	0
Mucositis oral	2 (5%)	0	0	0	0
Nausea	1 (3%)	0	0	0	0
Neutrophil count decreased	0	15 (41%)	0	3 (9%)	0
Non-cardiac chest pain	1 (3%)	0	0	0	0
Pain	1 (3%)	0	0	0	0

	REGIMEN A (*N* = 37)		REGIMEN B (*N* = 35)		
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 5
Pain in extremity	1 (3%)	0	0	0	0
Perforation bile duct	0	1 (3%)	0	0	0
Platelet count decreased	2 (5%)	8 (22%)	0	1 (3%)	0
Pleural effusion	0	0	1 (3%)	0	0
Pneumothorax	1 (3%)	0	0	0	0
Pulmonary edema	1 (3%)	0	0	0	0
Sepsis	0	4 (11%)	0	0	0
Skin infection	2 (5%)	0	1 (3%)	0	0
Stroke	0	1 (3%)	0	0	0
Thromboembolic event	2 (5%)	1 (3%)	0	0	0
Upper respiratory infection	0	0	1 (3%)	0	0
Urinary tract infection	2 (5%)	0	0	0	0
Uterine hemorrhage	1 (3%)	0	0	0	0
Vomiting	4 (11%)	0	0	0	0
White blood cell decreased	2 (5%)	14 (38%)	0	2 (6%)	0
Wound complication	0	2 (5%)	0	0	0
Wound dehiscence	4 (11%)	0	1 (3%)	0	0
Wound infection	3 (8%)	0	0	0	0

Table 4:

Regimen A (chemoradiation plus pazopanib) versus Regimen B (chemoradiation alone) toxicity by treatment phase.* The top row provides the number (N) of patients whose treatment-related data have been reported as of the data cut-off (5 Regimen A and 4 Regimen B patients were excluded because of delay in reporting or the patients had not completed the Induction by the time of the data cutoff.)

Adverse Event	Induction						Surgery					Continuation					
	REGIMEN A			REGIMEN B			REGIMEN A			REGIMEN B		REGIMEN A			REGIMEN B		
	< 18	≥ 18	Overall	< 18	≥ 18	Overall	< 18	≥ 18	Overall	< 18	Overall	< 18	≥ 18	Overall	< 18	≥ 18	Overall
	N = 11	*N* = 26	*N* = 37	*N* = 17	*N* = 18	*N* = 35	*N* = 8	*N* = 20	*N* = 28	*N* = 10	*N* = 19	*N* = 8	*N* = 12	*N* = 20	*N* = 9	*N* = 7	*N* = 16
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	N (%)	n (%)	n (%)	N (%)	n (%)
Febrile neutropenia	4 (36)	5 (19)	9 (24)	0 (0)	1 (6)	1 (3)	0 (0)	1 (5)	1 (4)	0 (0)	0 (0)	1 (13)	4 (33)	5 (25)	0 (0)	2 (29)	2 (13)
Lymphocyte count decreased	3 (27)	4 (15)	7 (19)	0 (0)	1 (6)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	1 (5)	1 (11)	0 (0)	1 (6)
Neutrophil count decreased	3 (27)	11 (42)	14 (38)	2 (12)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (25)	2 (17)	4 (20)	2 (22)	0 (0)	2 (13)
Platelet count decreased	3 (27)	6 (23)	9 (24)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (25)	1 (8)	3 (15)	1 (11)	0 (0)	1 (6)
White blood cell decreased	3 (27)	10 (39)	13 (35)	2 (12)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (38)	3 (25)	6 (30)	1 (11)	0 (0)	1 (6)
Wound complication†	1 (9)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (13)	1 (5)	2 (7)	1 (10)	1 (5)	1 (13)	3 (25)	4 (20)	0 (0)	0 (0)	0 (0)

*Grade 3 and above worst event for each patient in each combined treatment phase (only adverse events with >10% overall incidence during Induction, Surgery or Continuation were included).

†Percentages were calculated from standard adverse event reporting and may not reflect the events reported explicitly for wound complication; late wound events may not be fully captured by the data cutoff for this manuscript.