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REVIEW
Children's Oncology Group's 2013 Blueprint for Research: Soft Tissue Sarcomas

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on behalf of the COG Soft Tissue Sarcoma Committee

In the US, approximately 850–900 children are diagnosed each year with soft tissue sarcomas (STS). Key findings from recent Children's Oncology Group (COG) clinical trials include safe reduction in therapy for low risk rhabdomyosarcoma (RMS), validation of *FOXO1* fusion as a prognostic factor, a modest improvement in outcome for high-risk RMS, and a biologically designed non-cytotoxic therapy for pediatric desmoid tumor. Planned Phase 2 trials include targeted agents for VEGF/PDGF, mTOR, and IGF-1R for children with RMS and VEGF for children with non-RMS STS (NRSTS). For RMS, COG Phase 3 trials potentially will explore VEGF/mTOR inhibition or chemotherapy interval compression. For NRSTS, a COG Phase 3 trial will explore VEGF inhibition.
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INTRODUCTION

Every year in the United States, approximately 850–900 children are diagnosed with soft tissue sarcomas (STS), with 5-year survival ranging from 15% for children with metastatic disease to 90% for children with favorable features. For children with rhabdomyosarcoma (RMS), the most common type of STS, the estimated 5-year event-free survival (EFS) rate for patients with low, intermediate and high disease is 95%, 65%, and 15%, respectively. In this manuscript, we outline the Children's Oncology Group (COG) STS Committee's recent and planned clinical trials and biologic correlative studies.

STATE OF THE DISEASE—CLINICAL

Rhabdomyosarcoma (RMS)

Overview and incidence. STS comprise 7.4% of all pediatric cancers, collectively the most common extra-cranial solid tumor type in children [1,2]. The most common soft-tissue sarcomas diagnosed in children is RMS. The incidence of RMS in children less than 20 years old is 4.3 per million per year [2]. In the United States approximately 350 children and adolescents are diagnosed with RMS per year [2]. Although it occurs less commonly after age 20 years, the incidence of RMS in adults is 70% that of children and adolescents [3].

Staging/stratification. Risk stratification for RMS is based on pre-treatment (TNM) staging, surgical/pathologic clinical group, and tumor histology, each of which is independently associated with outcome [4,5]. The TNM staging system for RMS is based on tumor size, invasiveness, nodal status, primary site of primary tumor (which is either favorable or unfavorable), and distant metastases [6]. Clinical group is based on the extent of residual tumor after surgery, regional lymph node involvement, and distant metastases [4]. Pediatric RMS has two biologically distinct histologic subtypes, embryonal (ERMS) and alveolar (ARMS) [7–11]. The combination of stage, group, and histology define three distinct RMS risk groups [5,12–14]: low-, intermediate-, and high-risk (Table I). The predominantly European Malignant Mesenchymal Tumor (MMT) committee of the International Society of Pediatric Oncology and European Paediatric Soft Tissue Sarcoma Group (EpSSG) have used similar but not identical clinically defined risk groups for treatment assignment with the addition of early response and delayed resection as factors for modification of treatment [15,16].

Current outcome. Vincristine and dactinomycin (VA) with cyclophosphamide (VAC) for patients with higher risk, are the standard chemotherapy regimens for RMS. The low-risk RMS category includes all non-metastatic ERMS at favorable primary sites and totally resected ERMS at unfavorable sites (Table I). The low-risk group can be further subdivided into two subsets. The most recent COG trial for low-risk RMS (ARST0331) showed that Subset 1 patients have an excellent outcome (2-year EFS, 88%; overall survival (OS), 98%) with short therapy duration (22 weeks) and a modest cumulative dose (4.8 g/m^2) of cyclophosphamide [17]. In contrast, Subset 2 had a lower than anticipated 3-year EFS, 66%, with a lower cumulative dose of cyclophosphamide [18], as compared to the previous COG low-risk RMS trial, D9602 (cyclophosphamide dose, 28.6 g/m^2, 3-year EFS, 83%, $P = 0.06$) [19].

The intermediate-risk RMS category includes non-metastatic ARMS and unresected ERMS at unfavorable primary sites. The most recent COG intermediate-risk RMS trial, D9803, showed no difference in 4-year EFS between VAC and VAC plus topotecan (73% and 68%, respectively) [20]. These results were similar to the prior IRS-IV trial [21], which found no benefit to adding ifosfamide ± etoposide. The most recent MMT study for localized RMS randomly compared the European standard RMS therapy ifosfamide, vincristine, and dactinomycin (IVA) to the more complex IVA plus carboplatin, epirubicin, and etoposide with a similar (but not identical) risk-stratification for intermediate-risk RMS; no difference in outcome was seen [15]. In contrast to the COG local control strategy, local treatments in MMT studies were tailored to radiographic response and the ability to perform a delayed resection, with the goal of minimizing the use of radiotherapy (RT) and potentially reduce the total burden of local therapy [15,16]. Compared to similar patients treated with the

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TABLE I. Children's Oncology Group Rhabdomyosarcoma Prognostic Groups [5,12]

Risk group	Stage	Group	Histology	Approximate % of RMS	Long-term EFS %
Low, subset 1	1	I–II	ERMS	27%	85–95%
	1	III (orbit)	ERMS		
	2	I–II	ERMS		
Low, subset 2	1	III (non-orbit)	ERMS	5%	70–85%
	3	I–II	ERMS		
Intermediate	2–3	III	ERMS	27%	73%
	1–3	I–III	ARMS	25%	65%
High	4	IV	ERMS	8%	35%
	4	IV	ARMS	8%	15%

RMS, rhabdomyosarcoma; ERMS, embryonal RMS; ARMS, alveolar RMS; EFS, event-free survival.

COG local control strategy (which emphasizes the routine use of RT), EFS and OS were lower, particularly for ARMS [22].

The presence of distant metastases defines high-risk RMS. The most recent COG high-risk RMS study (ARST0431) included interval-compressed chemotherapy (VDC/IE) and vincristine/irinotecan (VI) [23]. Compared to prior COG high-risk studies and an international dataset of metastatic RMS [13], there was a modest improvement in 3-year EFS (38% and 29%, respectively), with a greater effect among ERMS (60% and 37%, respectively).

Non-Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS)

Overview and incidence. NRSTS comprise various mesenchymal malignancies that together represent 4.5% of all pediatric cancers, with an incidence of 6.7 per million per year in children less than 20 years old [2,24,25]. In the United States approximately 500–550 children and adolescents are diagnosed with NRSTS annually [2]. Its incidence has a bimodal distribution, with peaks in infancy and a rising incidence throughout adolescence [24]. Children and adults share a similar distribution of NRSTS tumor stage, but survival is superior for patients less than 50 years old [25]. Pediatric NRSTS differ from those of adults by inclusion of unique types (such as infantile fibrosarcoma) and distribution of histologies (synovial sarcoma and malignant peripheral nerve sheath tumor (MPNST) more common; liposarcoma, angiosarcoma, and leiomyosarcoma less common) [24–26].

Staging/stratification. Based upon extrapolation from soft tissue sarcoma trials in adults and single institution data, histologic grade, tumor size, extent of resection, and extent of metastasis have been reported to be the major NRSTS prognostic factors [27,28]. An international metaanalysis of unresected pediatric NRSTS confirmed these prognostic factors, adding age, completeness of delayed resection, histologic subtype, chemotherapy response, anatomic primary site, and use of RT [29]. The most frequently used pediatric NRSTS pathologic grading systems (Fédération Nationale des Centers de Lutte Contre le Cancer (FNCLCC) and Pediatric Oncology Group (POG)) are both associated with outcome but have a 34% discordance rate [30].

Current outcome. COG ARST0332 assigned NRSTS patients to one of three risk groups based upon extent of resection, POG tumor grade, tumor size, and distant metastases (Table II). COG ARST0332 attempted to confirm prospectively the predictive value of this risk stratification system within the context of protocol-directed therapy. Low-risk NRSTS were managed with surgery only, but with adjuvant RT for high-grade, marginally excised tumors. Intermediate-risk NRSTS were treated with ifosfamide/doxorubicin (ID) chemotherapy and RT. High-risk NRSTS were managed with ID chemotherapy and RT, with the exception of completely resected low-grade metastatic tumors, which were treated with surgery alone. Based upon single institutional reports of outcome [24,25], the anticipated 5-year survivals for low-, intermediate-, and high-risk NRSTS are 90%, 50%, and 15%, respectively.

Desmoid Tumor (DT)

Overview and incidence. DT, also known as aggressive or desmoid-type fibromatosis, has an overall annual incidence of 2–4 per 1 million people [31]. DT has two incidence peaks: between 6 and 15 years and between puberty and 40 years of age in women [32] with a female predominance during adolescence [33]. Mortality from desmoid tumor is rare, but substantial morbidity is common due to disease progression and therapy (historically surgical resection ± RT). A small minority of DTs occur in children with a germline *adenomatous polyposis coli* (*APC*) gene mutation [34].

TABLE II. Children's Oncology Group Non-Rhabdomyosarcoma Soft Tissue Sarcoma Prognostic Groups [27,28]

Risk group	Grossly resected	Tumor grade	Tumor size	Distant metastases	Approximate % of NRSTS	5-year survival
Low	Yes	Low	Any	No	60%	90%
	Yes	High	<5 cm	No		
Intermediate	Yes	High	>5 cm	No	30%	50%
	No	Any	Any	No		
High	Any	Any	Any	Yes	10%	15%

NRSTS, non-rhabdomyosarcoma soft tissue sarcoma.

Staging/stratification. DT may be multifocal, but because distant metastases do not occur, traditional staging systems do not apply. Risk factors for local recurrence/progression include inadequate surgical resection [35], β-catenin mutation [36], and age <18 years [37].

Current outcome. Two sequential pediatric DT trials conducted by POG and COG used vinblastine/methotrexate (POG 9650) [38] and sulindac/tamoxifen (ARST0321) [39], respectively, and enrolled pediatric patients with unresectable or recurrent DT. The 1-year EFS for these two studies was 58% and 44%, respectively.

STATE OF THE DISEASE—BIOLOGICAL

Molecular Targets: RMS

Xenograft models identified topoisomerase I as a key target in RMS [40,41]. The addition of a topoisomerase I inhibitor, topotecan, did not improve the outcome for intermediate- [20] or high-risk RMS [42]. However, pre-clinical models predicted that another topoisomerase I inhibitor, irinotecan, would be more effective than topotecan [40,41,43]. The clinical activity of irinotecan, particularly when combined with vincristine (as predicted by xenograft models [44]) was confirmed in ARST0121 (phase II study of recurrent RMS) [45] and in D9802 and ARST0431, both phase II window studies of metastatic RMS [23,46]. The 70% response rate on D9802 was the highest ever seen in a phase II window including other drug pairs [46,47], supporting the current intermediate-risk RMS study, ARST0531 (VAC ± irinotecan). Xenograft modeling also supported the combination of topoisomerase I inhibition with temozolomide [48], which is being tested clinically in ARST08P1, and to which clinical activity was seen in Ewing sarcoma [49].

The insulin-like growth factor 1 receptor (IGF-1R), mammalian target of rapamycin (mTOR), and angiogenesis pathways have been identified as potential targets by pre-clinical RMS models. The IGF-1R pathway is particularly active in RMS, both due to autocrine IGF-I and IGF-II secretion [50] and transcriptional control of IGF-1R expression by PAX-FOXO1 in ARMS [51]. IGF-1R is a receptor tyrosine kinase that promotes cell growth and inhibits apoptosis, and thus represents a potential target of interest in various sarcomas [52]. IMC-A12 is a specific IGF-1R monoclonal antibody with anti-tumor activity in RMS [53], is well tolerated as a single agent in children with refractory solid tumors [54], and is being tested in the high-risk RMS study ARST08P1. Activation of the mTOR-signaling pathway is common in RMS [55,56], and mTOR inhibitors are active against RMS cell lines and xenografts [57–59]. The mTOR inhibitor temsirolimus had only a 6% response rate in recurrent RMS [60]. Inhibition of angiogenesis, through vascular endothelial growth factor (VEGF) blockade, represents another attractive RMS target based upon xenograft models [61]. Bevacizumab, a monoclonal antibody against all five VEGF isoforms, was tested in children with advanced solid tumors [62]. Temsirolimus and bevacizumab are being evaluated in combination with chemotherapy in a randomized phase II study of recurrent RMS, ARST0921. A multi-targeted tyrosine kinase inhibitor, such as sorafenib, could alternatively be used as an anti-angiogenic agent by inhibition of VEGF receptors 1 and 2 (VEGFR-1, -2) [63]. Sorafenib inhibits platelet-derived growth factor receptors α and β (PDGFRα and PDGFRβ) [64], whose expression is associated with inferior outcome in RMS [65,66]. Sorafenib also inhibits RAF, a downstream target of RAS [67]. RAS activating mutations are present in 35–50% of ERMS [68], and RAS-transformed cell lines [69] and zebrafish [70] offer pre-clinical models for this pathway activation.

Molecular Targets: NRSTS

The wide range of histologic subtypes and primary driving molecular abnormalities complicates the development of broadly applicable targeted therapies in NRSTS. Rarely genetic alterations confer unique sensitivity to a molecularly targeted agent, such as the COL1A1-PDGFβ fusion in dermatofibrosarcoma protuberans leading to imatinib sensitivity [71] or activating ALK-related translocations in inflammatory myofibroblastic tumor leading to crizotinib sensitivity [72]. However, the more commonly described molecular events that define a NRSTS histologic subtype, including the SYT-SSX fusion in synovial sarcoma and NF1 mutations in MPNST, are not obvious targets for pharmacologic inhibition. Two of the most frequently observed pediatric NRSTS histologic subtypes, undifferentiated sarcoma and embryonal sarcoma of the liver, have no defining molecular abnormality. Tyrosine kinases expressed in a range of NRSTS subtypes include VEGFR, PDGFR, c-Kit, and epidermal growth factor receptor (EGFR) [73–76]. Elevated expression of VEGF and PDGFR correlates with higher malignancy grade and worse outcome [77,78]. Pazopanib, a potent inhibitor of VEGFR, PDGFR, and PDGF [79] prolonged time to progression in advanced adult STS and is FDA approved for this indication [80].

Molecular Targets: DT

Several potential biologic targets exist for DT. DT is associated with germ-line APC mutations [81,82], and frequent somatic mutations in APC or β-catenin (CTNNB1), which encodes a downstream effector of APC [83,84]; either alteration leads increased β-catenin protein activity. APC mutation enhances the activity of the peroxisome proliferator-activated receptor δ, which is blocked by non-steroidal anti-inflammatory agents [85]. Pharmacological or genetic cyclooxygenase-2 inhibition suppressed intestinal polyp formation in patients with germ-line APC mutations [86] and in mice with mutations in the orthologous mouse *Apc* gene [87]. The association between DT growth and incidence during pregnancy also implicated estrogen signaling in DT biology [32], along with the frequent expression of the estrogen receptor β in spontaneous DT [88].

MAJOR RECENT FINDINGS

Rhabdomyosarcoma

Low-risk RMS. ARST0331 enrolled 342 eligible low-risk RMS patients over 7 years and closed ahead of schedule. For Subset 1 (comprising a quarter of all RMS patients), shorter duration therapy with a modest cyclophosphamide dose likely to preserve male fertility had excellent outcome and represents a new standard of care in North America [17]. For Subset 2, the reduction in cumulative cyclophosphamide dose from 26.4 g/m^2, as used on IRS-IV/D9602, to 4.8 g/m^2 resulted in a significantly lower EFS [18]. Vaginal/uterine primary site ERMS was eligible

for a unique local control strategy designed to avoid definitive RT or surgery and was associated with a high local failure rate [89]. However, even after excluding female GU primary site ERMS, the EFS for Subset 2 was significantly inferior to IRS-IV and D9602. Based upon these results, a cyclophosphamide dose >4.8 g/m^2 is recommended by COG and inclusion in a future intermediate-risk RMS is considered.

High-risk RMS. ARST0431 combined the most active chemotherapy drug pairs from prior COG RMS phase II window studies [46,47] and enrolled 109 high-risk RMS patients over 23 months. It also incorporated interval-compressed VDC/IE, which COG AEWS0031 showed improved outcome for localized Ewing sarcoma [90]. Even after adjusting for prognostic groups within patients with metastatic disease, the EFS on ARST0431 was superior to prior COG and international studies [13], particularly for patients with more "favorable" metastatic disease, including ERMS and those with lower metastatic risk scores as defined by Oberlin [23]. ARST0431 provided a backbone onto which temozolomide and IMC-A12 are being added in ARST08P1. ARST0431 also suggested that interval-compressed VDC/IE could improve the outcome for RMS, although this will require confirmation in a future randomized trial.

FOXO1 fusion status and outcome. Tumor samples prospectively collected from the most recently completed intermediate-risk RMS trial, COG D9803 [20], demonstrated the prognostic significance of *PAX/FOXO1* for RMS. First, 255 of 278 (92%) cases previously classified as ARMS were re-reviewed for pathology, resulting in 33% of cases being re-classified as ERMS instead of ARMS, using more stringent pathologic criteria for the diagnosis of ARMS. Restricting the analysis to confirmed ARMS cases, FISH or RT-PCR for PAX-*FOXO1* fusion was performed on 130 ARMS cases (representing 84% of ARMS cases confirmed with pathology re-review). Cases with *PAX3-FOXO1* and *PAX7-FOXO1* translocations had an inferior 5-year FFS (54% and 65%, respectively) compared to ERMS and ARMS translocation negative (ARMSn; 76% and 89%, respectively), $P < 0.001$ [91]. This large, and homogeneously treated population of patients with ARMS confirms previous analyses with more selected cohorts [11]. The more favorable outcome for ARMSn and ERMS supports future classification and risk assignment by fusion status rather than histology. Beyond studying the prognostic impact of the *PAX-FOXO1* translocation, on-going work will confirm the prognostic significance of gene expression profiles, initially described using frozen tumor tissue and the Affymetrix GeneChip human U133A expression array with mostly IRS IV cases [10][92], and extend the analysis by using the more modern Nanostring nCounter assay with formalin-fixed paraffin embedded (FFPE) tumor tissue from D9803 study cases only.

NRSTS

ARST0332 used a novel risk-based strategy for NRSTS, with dual goals of limiting the toxicity of therapy for low-risk NRSTS and maximizing the efficacy of therapy for intermediate- and high-risk NRSTS. Patients with low-risk NRSTS had surgery $\pm$ adjuvant RT, depending on the histologic grade of tumor and surgical margin status. Intermediate- and high-risk NRSTS that were not excised were treated with neoadjuvant doxorubicin/ifosfamide and RT prior to definitive tumor resection; NRSTS with prior resection were treated with adjuvant doxorubicin/ifosfamide and RT. ARST0332 enrolled 588 patients, which was three times the accrual of all prior prospective trials combined in the U.S. for pediatric NRSTS and among the largest contemporary STS study including trials for adults. Uniform central pathology review confirmed the histologic sub-types, and central imaging review documented tumor features, response to therapy, and the pattern of treatment failure. Over 30 distinct pathologic sub-types were included. The outcome results from this trial are anticipated by early 2014.

DT

ARST0321 was a phase II study to determine the EFS and safety of sulindac and tamoxifen for children with recurrent DT or DT not amenable to surgery or radiation therapy [39]. ARST0321 was open for 5 years, enrolled 59 eligible patients, and completed on schedule. It was the largest prospective study of pediatric DT and of non-cytotoxic chemotherapy in DT ever. In contrast to the prior vinblastine/methotrexate treatment on POG 9650 [38], sulindac and tamoxifen was an oral regimen and had modest toxicity, including ovarian cysts in 40% of females. The 2-year EFS was 36%, lower than the 2-year EFS of 46% seen on POG 9650. The lack of similar prospective studies with uniform therapy and entry criteria preclude further comparisons to other treatment approaches.

STRATEGIC APPROACH: TARGETED THERAPY

RMS

Newly diagnosed population. Because of the excellent overall outcome in low-risk RMS, further attempts to improve outcome in RMS will be restricted to intermediate- and high-risk RMS. ARST0531 (randomized comparison of VAC vs. VAC/VI) will reach its accrual around December 2012. However, mature results from ARST0531 will not be available until approximately December 2014. Rather than delay a successor study while awaiting the ARST0531, several potential investigative approaches could be considered, using either the VAC or VAC/VI backbone. If either bevacizumab to temsirolimus proves superior in ARST0921, it could be tested in new diagnosed intermediate-risk RMS. ARST08P1 is a pilot study for high-risk RMS, including sequential cohorts with the addition of either IMC-A12 or temozolomide to intensive chemotherapy. If either cohort results in an improved EFS compared to historic controls, it could similarly be tested in intermediate-risk RMS. Finally, a randomized phase II screening study of VAC $\pm$ a targeted biologic agent (such as sorafenib) using early FDG PET response as the primary end point could identify a promising novel agent to study in a future phase III intermediate-risk study.

ARST08P1 will complete accrual around February 2014. Potential agents that could be tested in high-risk RMS include crizotinib, a dual ALK and c-met inhibitor. ALK amplification is common in RMS, particularly in ARMS and metastatic ERMS [93]. C-met expression is also common in RMS and associated with inferior outcome [94]. A recent STS Committee collaboration with Javed Khan at the National Cancer Institute to perform whole genome and exome sequencing of 44 and 147 RMS cases, respectively, yielded several novel recurrent mutations and amplifications. With further analysis, particularly of pathway interactions, we anticipate novel targets will be revealed, although

they may be low enough in frequency to challenge classical clinical trial designs.

Relapsed RMS. The outcome of relapsed RMS is particularly poor [95] and was not improved by protocol-directed multi-agent therapy as investigated on ARST0121 [45]. Although it did not improve post-relapse survival, ARST0121 demonstrated the feasibility of enrolling patients with RMS at first recurrence. Based upon this prior success, ARST0921 is evaluating a similar population with relapsed/refractory RMS, using a backbone similar to the vinorelbine and oral cyclophosphamide regimen piloted in Italy [96] and currently under investigation as a maintenance regimen in RMS in the EpSSG. Intravenous cyclophosphamide at 1.2 g/m^2 was selected to match the dose used in all front-line RMS trials. Potential candidate agents for incorporation into a successor relapsed/refractory RMS trial may become available from various preclinical models, including the Pediatric Preclinical Testing Program (PPTP), zebrafish [70], or transgenic mouse models [97].

Trial design strategies. With approximately 100 intermediate-risk and 40 high-risk RMS available annually, randomized phase III trials are only feasible for intermediate-risk RMS without international collaboration beyond COG. The prior COG trial design strategy incorporating cytoxic chemotherapy agents with activity in single arm phase II studies in patients with recurrent or metastatic disease has failed to generate a positive phase III trial [20,21] or to improve survival over the past 20 years in RMS [98]. Instead, the STS Committee will conduct randomized phase II trials to identify agents with more compelling evidence of activity as a requirement for committing to a larger phase III trial. Early response to chemotherapy is more efficient than EFS as a primary end point for randomized phase II studies. However, one particular challenge in RMS is the lack of correlation between initial response (as determined by anatomic imaging) and outcome [99], and delayed resection after chemotherapy is rarely performed to determine pathologic response. Instead, the STS Committee plans to use FDG PET imaging as measure of early response. FDG PET response is predictive of outcome in extremity STS [100], Ewing sarcoma [101], osteosarcoma [102], and a preclinical RMS model [103]. Both ARST0531 and ARST08P1 include FDG PET imaging to confirm its predictive value in RMS and validate its use as the primary end point in future randomized phase II RMS trials, since anatomic imaging of early response does not predict outcome [95]. High-risk and recurrent RMS trials will include agents with compelling preclinical but more limited clinical evidence of activity and could include novel agents with a moderate to high risk of increased toxicity.

NRSTS

Newly diagnosed NRSTS. The successful completion of ARST0332 on time demonstrated the feasibility of conducting a NRSTS therapeutic trial in a pediatric population. Although no randomized question was addressed, the early results from ARST0332 yielded critical data necessary for planning a successor study. Since no novel therapy was included in ARST0332, it is likely that the outcome for intermediate- and high-risk NRSTS treated with protocol-directed chemo-RT will be similar to historic results [26,27], confirming the need for novel treatment strategies. An initial analysis of pathologic response following ID and RT identified chemotherapy-sensitive histologies (including synovial sarcoma, undifferentiated/unclassifiable sarcoma, embryonal sarcoma of the liver), defined as 40% or greater favorable pathologic response rate (>90% necrosis) after neoadjuvant chemo-RT. Similar results have been seen in NRSTS in adults [104–106]. Eighty percent of ARST0332 patients treated with neoadjuvant chemo-RT had chemotherapy-sensitive histologies. For this population, further modification of the ID and RT backbone is both rational and feasible. An alternative strategy is needed for chemotherapy resistant histologies, including alveolar soft part sarcoma, MPNST, and clear cell sarcoma. Collectively, this population had a 15% favorable pathologic response rate after neoadjuvant chemo-RT. The most compelling new agent to add to ID/RT for chemotherapy-sensitive histologies and RT for chemotherapy-resistant histologies is pazopanib, given its broad tyrosine kinase inhibition (including VEGFR) and its single agent activity in adults with NRSTS [79,80]. To try to improve accrual and to allow biologic analysis of both pediatric and adult NRSTS, COG will collaborate with the Radiation Therapy Oncology Group (RTOG).

Relapsed NRSTS. The COG STS Committee has not conducted NRSTS trials for relapsed NRSTS, instead relying on the COG Developmental Therapeutics Committee for single agent phase II studies. COG phase II studies of trabectedin (ADVL0221), ixabepilone (ADVL0524), IMC-A12 (ADVL0821), and MLN8237 (ADVL0921), have included NRSTS cohorts, and the planned phase II study of pazopanib will also include a NRSTS stratum.

Trial design strategies. Similar to the strategy in RMS, NRSTS trial designs will depend upon randomized phase II screening studies to identify promising agents, with the built-in potential to expand to a randomized phase III study if the phase II goal is achieved. Similar to RMS, response as assessed by anatomic criteria is not associated with outcome [107–109]. In contrast, pathologic response is associated with outcome in NRSTS treated with neoadjuvant therapy [110,111]. FDG PET metabolic response is also associated with outcome in NRSTS [100]. Both pathologic and metabolic response can be assessed early in treatment, making them ideal primary or secondary end points for a phase II screening study. ARST1321 has a phase II design with two arms: (1) to compare ID and RT ± pazopanib in chemotherapy-sensitive NRSTS, anticipating an increase in pathologic response rate from 40% to 60%; and (2) to compare RT ± pazopanib for chemotherapy-resistant NRSTS, anticipating an increase in pathologic response rate from 10% to 30%.

DT

Newly diagnosed and relapsed DT. Sorafenib, a multi-targeted tyrosine kinase inhibitor, has single agent activity adult DT, with a 25% partial response and 71% stable disease rates [112]. Whether sorafenib response is correlated with CTNNB1 mutation status is unknown [36]. Given the rarity of pediatric desmoid tumor, randomized phase II studies are not feasible. Instead, POG 9650 and ARST0321 provide a well-defined historic cohort against which to compare response rate and EFS for the proposed phase II study of sorafenib, ARST1223.

KEY TRIALS TO BE PURSUED

RMS

Phase 3 trials. ARST0531 is the pivotal phase III RMS study that will complete accrual by December 2012, with mature results

by December 2014. The results from ARST0921 (bevacizumab vs. temsirolimus) and ARST08P1 (IMC-A12 vs. temozolomide) are anticipated at the same time. Should either of these studies demonstrate superiority of the investigational agent over the contemporary control treatment, a randomized phase III trial in intermediate-risk RMS compared to VAC would be well-supported. If IMC-A12 is superior but not available for clinical development, the COG STS Committee could pursue an alternative IGF-1R antibody, such as AMG479. A randomized selection design study comparing VAC ± sorafenib with FDG PET as an early endpoint for activity could be conducted prior to receiving the results from ARST0531. If none of these five agents is promising, the COG STS Committee will consider a trial comparing VAC to interval-compressed VDC/IE, which improved outcome for localized Ewing sarcoma [90]. A case–control comparison of non-interval-compressed VDC/IE to VAC on IRS-IV suggested improvement in outcome with the five-drug regimen [113]. In addition, the positive outcome seen on ARST0431 in high-risk RMS could be due to the use of interval-compressed VDC/IE [23]. Any future phase III study will use *PAX-FOXO1* fusion status rather than ARMS/ERMS for treatment allocation. In addition, future phase III studies will incorporate standard requirements for lymph node evaluation, since regional lymph node involvement is associated with outcome in ARMS [114] and is an important site of relapse [115]. Phase III studies will include local treatment pathways that maximize local control and minimize morbidity [116–120].

Randomized phase 2 studies. Several promising new agents could be tested in future randomized phase II studies in high-risk or recurrent RMS, including crizotinib, a combined ALK and c-MET inhibitor [91,93], ponatinib, an FGFR4 inhibitor [121], eribulin, a novel microtubule inhibitor [122], or TH-302, a hypoxia activated alkylating agent [123].

Prioritization strategy. Agents with pediatric phase I dose definition and favorable preclinical results will be prioritized for randomized phase II development, which could include intermediate-risk, high-risk, or recurrent RMS populations depending upon the anticipated toxicity of the agent and the population to be studied. It is possible that a highly targeted agent could be evaluated in a single agent phase II study. However, it is more likely that agents will be evaluated in combination, necessitating randomized trial designs to determine their relative activity. Only agents with substantial single agent phase II activity or success in a randomized phase II study would be tested in a randomized phase III trial.

NRSTS

Phase 3 trials. ARST1321 will be designed with an option to expand to a phase III study with EFS as the primary endpoint. Assuming an improvement in the rate of pathologic response with the addition of pazopanib (assessed separately for the chemotherapy-sensitive and chemotherapy-resistant cohorts), accrual would be expanded to answer a definitive outcome question.

DT

ARST1223 will be a single arm phase II study conducted over 5 years. There are no active efforts in new agent discovery for DT. Instead, the COG STS Committee will encourage DT specimen banking on D9902 and explore collaboration to investigate novel biologic insights into DT therapy.

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