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An update on rhabdomyosarcoma risk stratification and the rationale for current and future Children's Oncology Group clinical trials

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Abstract

Children and adolescents with rhabdomyosarcoma (RMS) comprise a heterogeneous population with variable overall survival rates ranging between approximately 6% and 100% depending on defined risk factors. Although the risk stratification of patients has been refined across five decades of collaborative group studies, molecular prognostic biomarkers beyond *FOXO1* fusion status have yet to be incorporated prospectively in upfront risk-based therapy assignments. This review describes the evolution of risk-based therapy and the current risk stratification, defines a new risk stratification incorporating novel biomarkers, and provides the rationale for the current and upcoming Children's Oncology Group RMS studies.

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CONFLICT OF INTEREST STATEMENT

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Keywords

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INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in children and adolescents, with approximately 350 cases annually in the United States. [1, 2] Patients are assigned a risk group based on clinicopathologic features, which then dictates treatment with multimodal therapy that may include chemotherapy, surgery, and/or radiation therapy. Despite improvements, there continues to be significant variability in survival across risk groups, from overall survival rates of less than 20% for patients with high-risk RMS (HR-RMS) to rates greater than 90% for patients with low-risk RMS (LR-RMS). [3] The current risk stratification system is based on findings from the Intergroup Rhabdomyosarcoma Study (IRS) trials I-IV.[4] A key element of risk stratification has been histology, and the two histologic subtypes that consistently predict outcomes are embryonal RMS (ERMS) and alveolar RMS (ARMS).[5] Recent studies have demonstrated the importance of molecular features, with *FOXO1* fusion status a critical prognostic biomarker second only to metastatic status [6–8], providing the rationale for the incorporation of *FOXO1* fusion status into the current Children's Oncology Group (COG) intermediate risk RMS (IR-RMS) study, ARST1431 (NCT02567435). However, additional molecular features that may be prognostic have yet to be utilized in the risk stratification of patients with RMS.[9]

In this article, we propose an updated risk stratification of RMS that incorporates molecular features and provide the rationale for the current and planned COG RMS studies for low, intermediate, and high-risk RMS.

RISK STRATIFICATION

Clinicopathologic Factors

Since the first IRS trial in 1972, the approach to the treatment of patients with RMS has been risk-based. IRS I and II employed a post-surgical clinical group (CG) that classified patients into CG I-IV based on the extent of surgical resection, lymph node status, and metastatic disease. [10, 11] IRS I and II demonstrated that patients with CG I disease maintained excellent outcomes with risk adapted therapy while those with CG IV disease had poor outcomes despite aggressive treatment.[12] Patients with CG II and III disease had variable outcomes and subsequent IRS protocols attempted to refine these subsets. IRS III and IV added a pretreatment TNM staging system and included primary tumor site (favorable/unfavorable) as a prognostic factor. [13, 14] The classification of site (favorable *versus* unfavorable) has stayed largely consistent through the years with the most recent change being that the biliary tract/liver will again be considered unfavorable in future protocols. Favorable sites include the orbit, head and neck (non-parameningeal), and genitourinary (non-bladder/non-prostate), with all other sites considered as unfavorable. The outcomes from IRS III and IV led to further refinement of risk-adapted therapy assignments with the creation of defined risk

groups (low, intermediate, and high). [15] The current IRS CG system and the RMS TNM Staging system are shown in Tables 1 and 2, respectively.

We validated these clinicopathologic factors in 2157 patients enrolled on the IRS V (D9602, D9802, and D9803) and the COG ARST studies (ARST0331, ARST0431, ARST0531, and ARST08P1). Patients ≥ 10 years old and those with tumors in unfavorable sites or with large tumors (>5cm) had inferior outcomes (Figures 1A-C). Similarly, nodal involvement and CG was prognostic in this large cohort of patients (Figure 2A-B), and patients with ARMS had an inferior outcome compared to patients with ERMS (Figure 2C). Since *FOXO1* fusion status is a better prognostic classifier [6, 7], it has now replaced histology in the COG risk stratification for RMS (Table 3).

Molecular factors

Approximately 80% of tumors that are morphologically ARMS carry a *FOXO1* fusion, while more than 95% of tumors that are morphologically ERMS have no *FOXO1* fusion [16], and we now understand that the presence or absence of the *FOXO1* fusion gene drives the clinical behavior of RMS. Recent molecular diagnostics have uncovered features beyond *FOXO1* fusion status, delineating novel molecular biomarkers that have yet to be incorporated into RMS risk stratification.

Fusion positive rhabdomyosarcoma (FP-RMS)

The presence of a *FOXO1* fusion refers to one of two chromosomal translocations – t(2;13) resulting in fusion of *PAX3* to *FOXO1* or t(1;13) resulting in fusion of *PAX7* to *FOXO1*. Although infrequent rearrangements of the *PAX3* gene (e.g. with *NCOA1* or *INO80D*) have been described, the rarity of these fusions preclude definitive outcome data. Because the *FOXO1* translocation represents the most common translocation observed in patients with rhabdomyosarcoma with well-defined outcome data, the term “fusion positive” in this manuscript refers to those harboring the *FOXO1* fusion. Several retrospective studies have found that *FOXO1* fusion status is an independent prognostic factor in all risk groups except for patients with metastatic disease.[6, 8, 17, 18] In a retrospective analysis that examined *FOXO1* fusion status in patients with histological ARMS and low risk stage and group, patients with FP RMS had worse outcomes than those with FN RMS. [17] In an analysis of 434 patients treated on D9803, those with FN ARMS had similar outcomes to those with ERMS, suggesting that fusion status rather than histology is what drives unfavorable outcome. [6] Finally, in the largest analysis published to date, 1727 evaluable patients from the IRS V and COG ARST studies were analyzed, and only metastatic status surpassed *FOXO1* fusion status as a poor prognostic predictor. [8] ARST1431 is the first COG study to use *FOXO1* fusion status in risk stratification.

Some studies have suggested that the *FOXO1* fusion partner (*PAX3* or *PAX7*) may be prognostic. In a series of 287 patients with RMS, the 5-year OS for patients with *PAX3* fusions was significantly worse than for those with *PAX7* fusions (39% vs 74%, p=0.001).[7, 19] However, this finding may be confounded by the association of the *PAX* fusion partner with tumor age (≥10 years) and size (>5cm). [20] The prognostic significance of the *FOXO1* fusion partner will be prospectively evaluated on ARST1431. Additionally, in the

upcoming HR-RMS COG study, tumor tissue will be banked at diagnosis, end of therapy, and relapse, allowing for potential future studies, including those examining the effects of alternative fusions seen in patients with ARMS.

FP-RMS tumors generally have a low mutational burden, but certain gene amplifications may carry prognostic significance. Specifically, the 12q13–14 amplification results in overexpression of *CDK4* and is associated with worse survival (HR 2.25, p=0.023 for FFS and HR 2.26, p=0.04 for OS). [21] Additionally, *MYCN* amplification has been associated with decreased survival in patients with ARMS, with a difference in FFS between those with high and low MYCN expression (log-rank statistic = 5.82, p=0.0158).[22] The prognostic significance of *CDK4* and *MYCN* amplification will be examined prospectively in the upcoming HR-RMS COG study, ARST2031.

Fusion negative rhabdomyosarcoma (FN-RMS)

FN-RMS has classically referred to tumors that do not harbor the *FOXO1* fusion protein. However, these tumors may carry other rare translocations. One example is very young patients with sclerosing and spindle cell tumors that carry VGLL or NCOA translocations. Although the presence of the translocations is pathognomonic for congenital sclerosing/spindle cell RMS, the prognostic significance of the fusion protein is not clear. *FOXO1* FN RMS tumors are more likely to carry single nucleotide point mutations, particularly in the *RAS* pathway (*NRAS, KRAS, HRAS*) but also in other genes (*FGFR4, PIK3CA*, *TP53*, *MYOD1*). [23] The prognostic significance of *RAS* mutations remains unclear. However, mutations in *MYOD1* (L122R) and *TP53* are predictors of poor prognosis in patients with FN-RMS.[9, 24, 25]

Mutations in *MYOD1* (L122R) are associated with a sclerosing or spindle cell phenotype (without the *VGLL* or *NCOA* fusions described above), typically seen in older children, and confer a dismal prognosis, with small case series describing survival rates of 0–30%. [26–28] A retrospective analysis of pediatric RMS in the US and UK showed *MYOD1* mutations in 3% (n=17) of FN-RMS tumors (n=515).[9] In this cohort the presence of the *MYOD1* (L122R) mutation resulted in uniformly dismal outcomes irrespective of clinical risk stratification, with an associated HR of 6.839 (3.468–13.507, p<0.0001) in the 11 COG patients and a HR of 3.320 (1.212–9.099, p=0.0133) in the six UK patients.

In a small series *TP53* mutations were seen in 20% of FN-RMS, and the presence of a somatic *TP53* mutation was associated with worse overall survival (HR 2.3 [1.0–4.9], p=0.04).[24] In the larger US and UK cohort (n=515), *TP53* mutations were identified in 13% (n=69) of *FOXO1* FN tumors, with uniform distribution across risk groups. Both cohorts demonstrated a significantly worse prognosis for those with tumors harboring *TP53* mutations (US cohort: EFS p=0.0146; HR 1.973 [1.132–3.438], UK cohort: EFS p=0.0055; HR 2.105 [1.230–3.604]).[9] Patients with *TP53* or *MYOD1* mutated tumors may therefore benefit from a risk reassignment and potential intensification of therapy.

RATIONALE FOR CURRENT AND PLANNED COG RMS STUDIES

Based on the data presented above, we propose a revised risk stratification schema for future COG trials that incorporates molecular biomarkers (specifically *MYOD1* and *TP53* mutations) in treatment assignments. Below we describe the rationale for the current and planned COG RMS studies across all three risk groups, summarized in Table 4.

Low Risk

Patients with LR-RMS comprise over a quarter of all patients with RMS and carry an excellent prognosis with a 4-year EFS of approximately 90% following treatment with 48 weeks of vincristine and dactinomycin (VA, as in D9602) or 12 weeks of vincristine, dactinomycin and cyclophosphamide (VAC) followed by 12 weeks of VA (as in ARST0331).[29, 30] In D9602, patients with ERMS were divided into Subgroup A and Subgroup B. Subgroup A included patients with Stage 1, CG I/IIA or CG III (orbit only), or Stage 2, CG I disease, and these patients were treated with 48 weeks of VA chemotherapy. The 5-year failure free survival (FFS) and OS for Subgroup A patients were 89% (95% CI: 84–92%) and 97% (95% CI: 90–99%), respectively. Subset B patients included those with stage 1/CG IIB/C, Stage 1/CG III (non-orbital), Stage 2/CG II, and Stage 3/CG I or II patients. These patients also achieved good outcomes (5-year FFS 85% and OS 93%), albeit with substantially more alkylator exposure (cumulative cyclophosphamide dose 26.4 g/m^2 over 44 weeks). In ARST0331, patients with ERMS were divided into Subset 1 and Subset 2, with definitions refined based on the outcomes from D9602. Subset 1 included patients with Stage 1/2, CG I/II or CG III (orbit only) disease who were treated with 12 weeks of VAC followed by 12 weeks of VA in an attempt to decrease the duration of therapy compared to D9602 while adding minimal alkylator therapy. The 3-year FFS was 89% (95% CI: 85%−92%) and OS was 98% (95% CI: 95–99%).[30] Subset 2 patients had suboptimal outcomes when the cumulative cyclophosphamide dose was decreased from 26.4 g/m^2 to 4.8 g/m^2 and are now treated on the intermediate risk trial, whereas Subset 1 defines the current COG LR-RMS cohort. Recent literature has also shed light on the impact of the biliary tract, previously considered a favorable site in D9602 and ARST0331. An analysis of 17 patients with localized biliary RMS treated on D9602 and ARST0331 revealed a 5-year EFS and OS of 70.6% and 76.5%, respectively. [31] The biliary tract/liver site will be considered unfavorable in future studies.

Most patients with Stage 1, CG I tumors in D9602 and ARST0331 had paratesticular disease. These patients achieved excellent outcomes without alkylator therapy on D9602 (5-year EFS 96% and OS 100%)[29], comparable to the outcomes seen on ARST0331 (3-year FFS 93% and OS 99%).[30] IRS-IV also produced excellent outcomes among the paratesticular patients < 10 years (3 year FFS 90%) with the omission of cyclophosphamide and a shorter duration of therapy (36 weeks) with VA. Finally, the recently concluded European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) RMS 2005 trial showed excellent outcomes in their low risk patients (non-alveolar histology, CG I, age < 10 years, tumor size ≤ 5 cm) with 24 weeks of VA (5 year EFS of 95.5% [95% CI 86.8–98.5] and OS of 100%).[32] An analysis of 240 patients treated on D9602 and ARST0331 with Stage 1, CG I FN RMS, has defined a subset of patients with LR-RMS who experience exceedingly good

outcomes, achieving 5-year EFS of 91% (95% CI: 87–95%), suggesting that this subset of patients that may benefit from therapy reduction.[8] These patients will be classified as very low-risk (VLR) RMS in the future LR-RMS study ARST2032.

Patients with CG III orbital disease have very good outcomes but have suffered from incremental increases in local failure rate (while retaining a very high OS) with sequential reductions in alkylator and radiation doses. Although patients with CG III orbital disease had low local failure rates (2%) and higher 5-year FFS (94%) in IRS IV, it was achieved with a significant burden of therapy, using a high cumulative dose (26.4 g/m^2) of cyclophosphamide and higher doses of radiation (50.4–59.4 Gy).[33] In ARST0331, patients with orbital RMS had 3-year FFS and OS of 87% (95% CI: 77–92%) and 97% (95% CI: 90– 99%), respectively, and all relapses in patients with CG III orbital tumors were local.[30] ARST0331 treated these patients with a cumulative cyclophosphamide dose of 4.8g/m^2 and 45Gy of radiotherapy, resulting in a 21% local failure rate in those achieving partial response (PR) at 12 weeks versus 0% in those achieving complete response (CR) at 12 weeks.[34] Patients with orbital disease may therefore benefit from intensification of local control treatment while continuing minimal alkylator exposure. ARST2032 will increase radiation dose to 50.4 Gy (from 45Gy in ARST0331) for patients with Stage 1, CG III orbital RMS who do not achieve radiological CR at week 12.

Based on the adverse prognostic effect of *MYOD1* or *TP53* pathogenic mutations, patients whose tumors have these mutations will no longer be considered LR and will be treated in a separate arm in ARST2032. By reclassifying patients with adverse molecular features (*MYOD1* or *TP53* mutations), ARST2032 will be enriched with patients with a more favorable prognosis. This molecularly defined LR cohort will then be subdivided into two newly defined risk groups: 1) patients with VLR-RMS (FN, Stage 1, CG I, *MYOD1* and *TP53* wild type [WT]) who will receive a reduction in therapy with 24 weeks of VA and 2) patients with LR-RMS (FN, Stage 1 CG II, or Stage 2 CG I/II or CG III (orbit only), *MYOD1* and *TP53* WT) who will receive 12 weeks of VAC followed by 12 weeks of VA. Patients who have *MYOD1* or *TP53* pathogenic mutations will be treated on study with 42 weeks of VAC therapy using a cumulative cyclophosphamide dose of approximately 16.8 g/m^2.

ARST2032 will be the first study to incorporate real time molecular risk stratification into a prospective cooperative group RMS clinical trial and will simultaneously attempt to decrease therapy for the nearly 15% of patients with RMS who have Stage 1, CG I disease.

Intermediate Risk

Patients with intermediate risk RMS (IR-RMS) represent the most heterogeneous risk group with 5-year EFS rates between 50–75% and comprise more than half of newly diagnosed patients with RMS.[8, 35] The definition of what constitutes IR-RMS has evolved and as such, the eligibility criteria for the current IR-RMS study (ARST1431) differs from prior studies. While D9803 enrolled patients younger than 10 years with ERMS and metastatic disease, they were not eligible for ARST0531 and were treated on HR-RMS trials (ARST0431 and ARST08P1).[36, 37] ARST0431 and ARST08P1, the two most recent studies for patients with upfront metastatic RMS, both demonstrated that patients <10 years of age with metastatic

ERMS had superior outcomes compared to other patients with HR-RMS, with 3-year EFS between 60–64%, while patients ≥10 years of age with metastatic ERMS had 3-year EFS between 32–48%.[38, 39] These patient are therefore now reclassified as intermediate risk.[36, 38, 39] In addition, patients previously considered LR on Subset 2 of ARST0331 (ERMS Stage 1, CG III with non-orbit primary or Stage 3, CG I/II disease) had inferior outcomes when treated with a de-intensified regimen consisting of 48 weeks of therapy using a cumulative cyclophosphamide dose of only 4.8 g/m^2, compared to those treated on D9602, which used a higher cyclophosphamide dose [29, 40]. These patients are also now considered IR. In an additional refinement to the risk stratification, ARST1431 uses *FOXO1* fusion status instead of histology for study eligibility based on analyses demonstrating that it is more predictive of outcome [6, 7, 19, 41–43].

ARST1431 is the first IR-RMS study to test a molecularly targeted agent in upfront treatment for RMS. Patients are randomized to receive VAC alternating with vincristine and irinotecan (VAC/VI) or VAC/VI plus temsirolimus, an mTOR inhibitor. There is substantial preclinical data demonstrating that the mTOR pathway is frequently activated in RMS [44–54]. Furthermore, clinical data from a prior randomized COG study for patients with relapsed RMS (ARST0921) demonstrated superior 6-month EFS and response rates for the temsirolimus-containing regimen versus the bevacizumab-containing regimen.[55]

Following the initial 42 weeks of VAC/VI therapy, patients treated on ARST1431 receive 24 weeks of maintenance therapy consisting of continuous daily low dose oral cyclophosphamide (CPM^{PO}) plus weekly IV vinorelbine on 3 out of every 4 weeks. The inclusion of maintenance is based on results from EpSSG RMS 2005, designed to test the addition of maintenance to the standard 27 weeks of induction with ifosfamide, dactinomycin, and vincristine ± doxorubicin (IVA or IVADo) in patients with non-metastatic ARMS and locally advanced ERMS who had achieved complete remission post-induction. Patients were randomized to receive an additional 24 weeks of maintenance therapy on the same schedule as ARST1431 versus no maintenance therapy. Patients who received maintenance had improved 5-year OS of 86.5% vs. 73.7%, (p=0.0097), although improvement in 5-year disease free survival did not reach statistical significance (77.6% v. 69.8%, p=0.061]).[56] Despite the differences between the EpSSG and COG approaches to RMS, including the use of different agents and durations of induction in distinct patient populations, the overall conclusions of the study may be relevant for all patients with IR or HR-RMS. Maintenance has therefore been incorporated into ARST1431 for all patients on both study arms. Since all patients will be receiving maintenance on ARST1431, the effect of adding maintenance to a 42-week VAC/VI chemotherapy regimen will be assessed by comparing the outcome of patients treated on the non-temsirolimus arm of ARST1431 to the outcome of historical control patients who were treated with VAC/VI on ARST0531. This will help to contextualize the results of the RMS2005 study for COG patients and provide greater insight into the role of maintenance therapy added to a COG backbone in IR-RMS.

High Risk

Patients with HR-RMS comprise approximately 15% of all patients with RMS but represent the most challenging to treat, with dismal outcomes. While successive IRS trials (IRS

I-IV) have improved EFS and OS for localized RMS patients using VAC as the primary chemotherapy regimen, variations on VAC have failed to improve outcomes for HR-RMS patients.[4, 14, 35, 36, 39, 57]

Results from the two most recent HR-RMS COG trials, ARST0431 and ARST08P1, have defined HR-RMS to include patients with Stage 4 ERMS aged 10 years or greater and patients with Stage 4 ARMS or FP-RMS. These studies, in an attempt to maximize dose intensity, incorporated all known active agents (vincristine, doxorubicin, cyclophosphamide, ifosfamide/etoposide, and VAC) into an interval compressed, intensified backbone and also evaluated promising novel agents (irinotecan, temozolomide or cixutumumab).[38, 39] Both studies demonstrated that patients younger than 10 years of age with Stage 4 ERMS had superior outcomes when compared to other HR-RMS patients, with 3-year EFS ranging from 60–64%, an outcome similar to that observed on D9803, the IRS-V IR-RMS study. In contrast, the 3-year EFS for Stage 4 ERMS patients older than 10 years was 32–48%. Patients with ARMS continue to have the worst outcomes with 3-year EFS ranging from 6–16%.[38, 39] In D9802, window therapy with VI was added to a VAC backbone utilizing 2.2g/m^2/cycle of cyclophosphamide. Although response rates to VI window therapy were promising (ORR 42% [95% CI: 38–80%]), the FFS in patients with HR-RMS with and without window therapy remained equally dismal at under 20%.[58] Further, patients with FP-RMS enrolled on D9802 and ARST0431 had a 6% five year EFS (95% CI: 0–11%).[8]

Vinorelbine, a second generation vinca alkaloid has been tested as a single agent and in combination with cyclophosphamide in patients with heavily pre-treated RMS. In two phase 2 trials, the overall response rate (ORR) observed with single agent vinorelbine (30mg/m^2) was 36% and 50%, including one CR and nine PRs.[59, 60] A lower dose of vinorelbine (25 mg/m^2) was evaluated in combination with CPM^{PO} in a larger cohort of heavily pre-treated patients with relapsed/refractory RMS. Four CRs and 14 PRs were observed, with an ORR of 36%.[61] These response rates are superior to those seen in other phase 2 trials for patients with relapsed RMS, and comparable to response rates with other agents tested in upfront phase 2 windows in treatment-naïve patients[62–71], suggesting that vinorelbine is a highly active agent in RMS that warrants further investigation. Additionally, a recent meta-analysis of five studies for patients with relapsed or refractory RMS demonstrated that patients with ARMS have a 41% improved response rate compared to those with ERMS when treated with vinorelbine alone or in combination with lower dose or oral cyclophosphamide.[72]

Because neither the cyclophosphamide dose intensity on D9802, nor the intensified backbones utilized on ARST0431 and ARST08P1 improved outcomes for patients with HR-RMS, ARST2031 will employ a VAC backbone with an intermediate cyclophosphamide dose (1.2 g/m^2/cycle) and utilize vinorelbine in the experimental arm. Additionally, the role of maintenance as published in the EpSGG RMS 2005 study is unknown in patients with COG-defined HR-RMS. ARST2031 will compare induction using VAC versus Vinorelbine-AC (VINO-AC) in a randomized fashion for patients with HR-RMS, while adding maintenance with Vinorelbine-CPM^{PO} to both arms to improve outcomes of patients with HR-RMS. Finally, ARST2031 will prospectively examine the potential association of *CDK4* and *MYCN* amplification with EFS and OS in patients with newly diagnosed

HR-RMS, given data suggesting that amplification of *CDK4* and *MYCN* are associated with a poorer prognosis.[21, 22]

FUTURE DIRECTIONS

Through collaborative, large scale next generation sequencing efforts, significant progress has been made in understanding the genomic landscape of RMS and the potential effects of these alterations on the clinical behavior of RMS tumors. More nuanced risk stratification that incorporates molecular prognostic factors may allow for the reduction of therapy in patients with excellent prognoses while also identifying those who may benefit from therapy intensification and/or the use of novel agents.

Although knowledge of the molecular mechanisms driving RMS have advanced quickly, the availability of agents that target these molecular drivers has lagged. Current investigational therapies for patients with relapsed or refractory RMS include the use of kinase inhibitors, insulin-like growth factor antibodies, histone deacetylase inhibitors, and poly ADP ribose polymerase (PARP) inhibitors among other agents and are used alone or in combination with various salvage chemotherapy backbones.[73, 74] As the data utilizing molecular biomarkers for risk stratification mature, thus identifying smaller cohorts of patients with different prognoses, our ability to offer appropriate risk-based therapy for all patients should improve, including for those with the most dismal prognoses.

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Abbreviations Table:

ARMS	Alveolar rhabdomyosarcoma
CG	Clinical group
CI	Confidence interval
CPM^{PO}	Daily oral cyclophosphamide
COG	Children's Oncology Group
CR	Complete Response
EFS	Event free survival
EpSSG	European Paediatric Soft Tissue Sarcoma Study Group
ERMS	Embryonal rhabdomyosarcoma
FFS	Failure free survival
HR	Hazard ratio

HR-RMS	High-risk rhabdomyosarcoma
IR-RMS	Intermediate-risk rhabdomyosarcoma
IRS	Intergroup Rhabdomyosarcoma Study
LR-RMS	Low-risk rhabdomyosarcoma
ORR	Overall response rate
OS	Overall survival
PR	Partial response
RMS	Rhabdomyosarcoma
VA	Vincristine, Actinomycin
VAC	Vincristine, Actinomycin, Cyclophosphamide
VI	Vincristine Irinotecan
WHO	World Health Organization

REFERENCES:

1. Howlader N NA KM, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatlovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2014. In: Institute NC, editor. 2016 ed. https://seer.cancer.gov/csr/1975_2014/2016.
2. Shern JF, Yohe ME, Khan J. Pediatric Rhabdomyosarcoma. Crit Rev Oncog. 2015;20(3–4):227–43. doi:10.1615/critrevoncog.2015013800 [PubMed: 26349418]
3. Skapek SX, Ferrari A, Gupta AA, et al. Rhabdomyosarcoma. Nat Rev Dis Primers. Jan 7 2019;5(1):1. doi:10.1038/s41572-018-0051-2 [PubMed: 30617281]
4. Raney RB, Maurer HM, Anderson JR, et al. The Intergroup Rhabdomyosarcoma Study Group (IRSG): Major Lessons From the IRS-I Through IRS-IV Studies as Background for the Current IRS-V Treatment Protocols. Sarcoma. 2001;5(1):9–15. doi:10.1080/13577140120048890 [PubMed: 18521303]
5. Rudzinski ER, Kelsey A, Vokuhl C, et al. Pathology of childhood rhabdomyosarcoma: A consensus opinion document from the Children's Oncology Group, European Paediatric Soft Tissue Sarcoma Study Group, and the Cooperative Weichteilsarkom Studiengruppe. Pediatr Blood Cancer. Mar 2021;68(3):e28798. doi:10.1002/pbc.28798 [PubMed: 33306276]
6. Skapek SX, Anderson J, Barr FG, et al. PAX-FOXO1 fusion status drives unfavorable outcome for children with rhabdomyosarcoma: a children's oncology group report. Pediatr Blood Cancer. Sep 2013;60(9):1411–7. doi:10.1002/pbc.24532 [PubMed: 23526739]
7. Missiaglia E, Williamson D, Chisholm J, et al. PAX3/FOXO1 fusion gene status is the key prognostic molecular marker in rhabdomyosarcoma and significantly improves current risk stratification. J Clin Oncol. May 10 2012;30(14):1670–7. doi:10.1200/JCO.2011.38.5591 [PubMed: 22454413]
8. Hibbitts E, Chi YY, Hawkins DS, et al. Refinement of risk stratification for childhood rhabdomyosarcoma using FOXO1 fusion status in addition to established clinical outcome predictors: A report from the Children's Oncology Group. Cancer Med. Oct 2019;8(14):6437–6448. doi:10.1002/cam4.2504 [PubMed: 31456361]
9. Shern JF, Selfe J, Izquierdo E, et al. Genomic Classification and Clinical Outcome in Rhabdomyosarcoma: A Report From an International Consortium. J Clin Oncol. Jun 24 2021:JCO2003060. doi:10.1200/JCO.20.03060

10. Maurer HM, Moon T, Donaldson M, et al. The intergroup rhabdomyosarcoma study: a preliminary report. Cancer. Nov 1977;40(5):2015–26. doi:10.1002/1097-0142(197711)40:5<2015::aid-cncr2820400505>3.0.co;2-k [PubMed: 336175]
11. Maurer HM, Gehan EA, Beltangady M, et al. The Intergroup Rhabdomyosarcoma Study-II. Cancer. Mar 1 1993;71(5):1904–22. doi:10.1002/1097-0142(19930301)71:5<1904::aid-cncr2820710530>3.0.co;2-x [PubMed: 8448756]
12. Crist WM, Garnsey L, Beltangady MS, et al. Prognosis in children with rhabdomyosarcoma: a report of the intergroup rhabdomyosarcoma studies I and II. Intergroup Rhabdomyosarcoma Committee. J Clin Oncol. Mar 1990;8(3):443–52. doi:10.1200/JCO.1990.8.3.443 [PubMed: 2407808]
13. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. J Clin Oncol. Mar 1995;13(3):610–30. doi:10.1200/JCO.1995.13.3.610 [PubMed: 7884423]
14. Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. J Clin Oncol. Jun 15 2001;19(12):3091–102. doi:10.1200/JCO.2001.19.12.3091 [PubMed: 11408506]
15. Meza JL, Anderson J, Pappo AS, Meyer WH, Children's Oncology G. Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on intergroup rhabdomyosarcoma studies III and IV: the Children's Oncology Group. J Clin Oncol. Aug 20 2006;24(24):3844–51. doi:10.1200/JCO.2005.05.3801 [PubMed: 16921036]
16. Parham DM, Barr FG. Classification of rhabdomyosarcoma and its molecular basis. Adv Anat Pathol. Nov 2013;20(6):387–97. doi:10.1097/PAP.0b013e3182a92d0d [PubMed: 24113309]
17. Arnold MA, Anderson JR, Gastier-Foster JM, et al. Histology, Fusion Status, and Outcome in Alveolar Rhabdomyosarcoma With Low-Risk Clinical Features: A Report From the Children's Oncology Group. Pediatr Blood Cancer. Apr 2016;63(4):634–9. doi:10.1002/pbc.25862 [PubMed: 26756883]
18. Rudzinski ER, Anderson JR, Chi YY, et al. Histology, fusion status, and outcome in metastatic rhabdomyosarcoma: A report from the Children's Oncology Group. Pediatr Blood Cancer. Dec 2017;64(12)doi:10.1002/pbc.26645
19. Duan F, Smith LM, Gustafson DM, et al. Genomic and clinical analysis of fusion gene amplification in rhabdomyosarcoma: a report from the Children's Oncology Group. Genes Chromosomes Cancer. Jul 2012;51(7):662–74. doi:10.1002/gcc.21953 [PubMed: 22447499]
20. Heske CM, Chi YY, Venkatramani R, et al. Survival outcomes of patients with localized FOXO1 fusion-positive rhabdomyosarcoma treated on recent clinical trials: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. Cancer. Mar 15 2021;127(6):946–956. doi:10.1002/cncr.33334 [PubMed: 33216382]
21. Barr FG, Duan F, Smith LM, et al. Genomic and clinical analyses of 2p24 and 12q13-q14 amplification in alveolar rhabdomyosarcoma: a report from the Children's Oncology Group. Genes Chromosomes Cancer. Aug 2009;48(8):661–72. doi:10.1002/gcc.20673 [PubMed: 19422036]
22. Williamson D, Lu YJ, Gordon T, et al. Relationship between MYCN copy number and expression in rhabdomyosarcomas and correlation with adverse prognosis in the alveolar subtype. J Clin Oncol. Feb 1 2005;23(4):880–8. doi:10.1200/JCO.2005.11.078 [PubMed: 15681534]
23. Shern JF, Chen L, Chmielecki J, et al. Comprehensive genomic analysis of rhabdomyosarcoma reveals a landscape of alterations affecting a common genetic axis in fusion-positive and fusion-negative tumors. Cancer Discov. Feb 2014;4(2):216–31. doi:10.1158/2159-8290.CD-13-0639 [PubMed: 24436047]
24. Agaram NP, LaQuaglia MP, Alaggio R, et al. MYOD1-mutant spindle cell and sclerosing rhabdomyosarcoma: an aggressive subtype irrespective of age. A reappraisal for molecular classification and risk stratification. Mod Pathol. Jan 2019;32(1):27–36. doi:10.1038/s41379-018-0120-9
25. Casey DL, Wexler LH, Pitter KL, Samstein RM, Slotkin EK, Wolden SL. Genomic Determinants of Clinical Outcomes in Rhabdomyosarcoma. Clin Cancer Res. Mar 1 2020;26(5):1135–1140. doi:10.1158/1078-0432.CCR-19-2631 [PubMed: 31699828]

26. Agaram NP, Chen CL, Zhang L, LaQuaglia MP, Wexler L, Antonescu CR. Recurrent MYOD1 mutations in pediatric and adult sclerosing and spindle cell rhabdomyosarcomas: evidence for a common pathogenesis. Genes Chromosomes Cancer. Sep 2014;53(9):779–87. doi:10.1002/gcc.22187 [PubMed: 24824843]
27. Rekhi B, Upadhyay P, Ramteke MP, Dutt A. MYOD1 (L122R) mutations are associated with spindle cell and sclerosing rhabdomyosarcomas with aggressive clinical outcomes. Mod Pathol. Dec 2016;29(12):1532–1540. doi:10.1038/modpathol.2016.144 [PubMed: 27562493]
28. Kohsaka S, Shukla N, Ameur N, et al. A recurrent neomorphic mutation in MYOD1 defines a clinically aggressive subset of embryonal rhabdomyosarcoma associated with PI3K-AKT pathway mutations. Nat Genet. Jun 2014;46(6):595–600. doi:10.1038/ng.2969 [PubMed: 24793135]
29. Raney RB, Walterhouse DO, Meza JL, et al. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 protocol, using vincristine and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low-risk embryonal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol. Apr 1 2011;29(10):1312–8. doi:10.1200/JCO.2010.30.4469 [PubMed: 21357783]
30. Walterhouse DO, Pappo AS, Meza JL, et al. Shorter-duration therapy using vincristine, dactinomycin, and lower-dose cyclophosphamide with or without radiotherapy for patients with newly diagnosed low-risk rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol. Nov 1 2014;32(31):3547–52. doi:10.1200/JCO.2014.55.6787 [PubMed: 25267746]
31. Aye JM, Xue W, Palmer JD, et al. Suboptimal outcome for patients with biliary rhabdomyosarcoma treated on low-risk clinical trials: A report from the Children's Oncology Group. Pediatr Blood Cancer. Apr 2021;68(4):e28914. doi:10.1002/pbc.28914 [PubMed: 33501771]
32. Bergeron C, Jenney M, De Corti F, et al. Embryonal rhabdomyosarcoma completely resected at diagnosis: The European paediatric Soft tissue sarcoma Study Group RMS2005 experience. Eur J Cancer. Mar 2021;146:21–29. doi:10.1016/j.ejca.2020.12.025 [PubMed: 33567392]
33. Donaldson SS, Meza J, Breneman JC, et al. Results from the IRS-IV randomized trial of hyperfractionated radiotherapy in children with rhabdomyosarcoma--a report from the IRSG. Int J Radiat Oncol Biol Phys. Nov 1 2001;51(3):718–28. doi:10.1016/s0360-3016(01)01709-6 [PubMed: 11597814]
34. Ermoian RP, Breneman J, Walterhouse DO, et al. 45 Gy is not sufficient radiotherapy dose for Group III orbital embryonal rhabdomyosarcoma after less than complete response to 12 weeks of ARST0331 chemotherapy: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. Pediatr Blood Cancer. Sep 2017;64(9)doi:10.1002/pbc.26540
35. Hawkins DS, Chi YY, Anderson JR, et al. Addition of Vincristine and Irinotecan to Vincristine, Dactinomycin, and Cyclophosphamide Does Not Improve Outcome for Intermediate-Risk Rhabdomyosarcoma: A Report From the Children's Oncology Group. J Clin Oncol. Sep 20 2018;36(27):2770–2777. doi:10.1200/JCO.2018.77.9694 [PubMed: 30091945]
36. Arndt CA, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. J Clin Oncol. Nov 1 2009;27(31):5182–8. doi:10.1200/JCO.2009.22.3768 [PubMed: 19770373]
37. Casey DL, Chi YY, Donaldson SS, et al. Increased local failure for patients with intermediate-risk rhabdomyosarcoma on ARST0531: A report from the Children's Oncology Group. Cancer. Sep 15 2019;125(18):3242–3248. doi:10.1002/cncr.32204 [PubMed: 31174239]
38. Weigel BJ, Lyden E, Anderson JR, et al. Intensive Multiagent Therapy, Including Dose-Compressed Cycles of Ifosfamide/Etoposide and Vincristine/Doxorubicin/Cyclophosphamide, Irinotecan, and Radiation, in Patients With High-Risk Rhabdomyosarcoma: A Report From the Children's Oncology Group. J Clin Oncol. Jan 10 2016;34(2):117–22. doi:10.1200/JCO.2015.63.4048 [PubMed: 26503200]
39. Malempati S, Weigel BJ, Chi YY, et al. The addition of cixutumumab or temozolomide to intensive multiagent chemotherapy is feasible but does not improve outcome for patients with

metastatic rhabdomyosarcoma: A report from the Children's Oncology Group. Cancer. Jan 15 2019;125(2):290–297. doi:10.1002/cncr.31770 [PubMed: 30351457]

40. Walterhouse DO, Pappo AS, Meza JL, et al. Reduction of cyclophosphamide dose for patients with subset 2 low-risk rhabdomyosarcoma is associated with an increased risk of recurrence: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. Cancer. Jun 15 2017;123(12):2368–2375. doi:10.1002/cncr.30613 [PubMed: 28211936]
41. Gallego S, Zanetti I, Orbach D, et al. Fusion status in patients with lymph node-positive (N1) alveolar rhabdomyosarcoma is a powerful predictor of prognosis: Experience of the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). Cancer. Aug 1 2018;124(15):3201–3209. doi:10.1002/cncr.31553 [PubMed: 29797665]
42. Davicioni E, Finckenstein FG, Shahbazian V, Buckley JD, Triche TJ, Anderson MJ. Identification of a PAX-FKHR gene expression signature that defines molecular classes and determines the prognosis of alveolar rhabdomyosarcomas. Cancer Res. Jul 15 2006;66(14):6936–46. doi:10.1158/0008-5472.CAN-05-4578 [PubMed: 16849537]
43. Anderson J, Gordon T, McManus A, et al. Detection of the PAX3-FKHR fusion gene in paediatric rhabdomyosarcoma: a reproducible predictor of outcome? Br J Cancer. Sep 14 2001;85(6):831–5. doi:10.1054/bjoc.2001.2008 [PubMed: 11556833]
44. Hawkins DS, Spunt SL, Skapek SX, Committee COGSTS. Children's Oncology Group's 2013 blueprint for research: Soft tissue sarcomas. Pediatr Blood Cancer. Jun 2013;60(6):1001–8. doi:10.1002/pbc.24435 [PubMed: 23255356]
45. Le X, Pugach EK, Hettmer S, et al. A novel chemical screening strategy in zebrafish identifies common pathways in embryogenesis and rhabdomyosarcoma development. Development. Jun 2013;140(11):2354–64. doi:10.1242/dev.088427 [PubMed: 23615277]
46. Petricoin EF 3rd, Espina V, Araujo RP, et al. Phosphoprotein pathway mapping: Akt/mammalian target of rapamycin activation is negatively associated with childhood rhabdomyosarcoma survival. Cancer Res. Apr 1 2007;67(7):3431–40. doi:10.1158/0008-5472.CAN-06-1344 [PubMed: 17409454]
47. Cen L, Arnoczky KJ, Hsieh FC, et al. Phosphorylation profiles of protein kinases in alveolar and embryonal rhabdomyosarcoma. Mod Pathol. Sep 2007;20(9):936–46. doi:10.1038/modpathol.3800834 [PubMed: 17585318]
48. Slotkin EK, Patwardhan PP, Vasudeva SD, de Stanchina E, Tap WD, Schwartz GK. MLN0128, an ATP-competitive mTOR kinase inhibitor with potent in vitro and in vivo antitumor activity, as potential therapy for bone and soft-tissue sarcoma. Mol Cancer Ther. Feb 2015;14(2):395–406. doi:10.1158/1535-7163.MCT-14-0711 [PubMed: 25519700]
49. Kaylani SZ, Xu J, Srivastava RK, Kopelovich L, Pressey JG, Athar M. Rapamycin targeting mTOR and hedgehog signaling pathways blocks human rhabdomyosarcoma growth in xenograft murine model. Biochem Biophys Res Commun. Jun 14 2013;435(4):557–61. doi:10.1016/j.bbrc.2013.05.001 [PubMed: 23665330]
50. Houghton PJ, Morton CL, Kolb EA, et al. Initial testing (stage 1) of the mTOR inhibitor rapamycin by the pediatric preclinical testing program. Pediatr Blood Cancer. Apr 2008;50(4):799–805. doi:10.1002/pbc.21296 [PubMed: 17635004]
51. Houghton PJ, Morton CL, Gorlick R, et al. Stage 2 combination testing of rapamycin with cytotoxic agents by the Pediatric Preclinical Testing Program. Mol Cancer Ther. Jan 2010;9(1):101–12. doi:10.1158/1535-7163.MCT-09-0952 [PubMed: 20053767]
52. Wan X, Shen N, Mendoza A, Khanna C, Helman LJ. CCI-779 inhibits rhabdomyosarcoma xenograft growth by an antiangiogenic mechanism linked to the targeting of mTOR/Hif-1alpha/VEGF signaling. Neoplasia. May 2006;8(5):394–401. doi:10.1593/neo.05820 [PubMed: 16790088]
53. Hosoi H, Dilling MB, Shikata T, et al. Rapamycin causes poorly reversible inhibition of mTOR and induces p53-independent apoptosis in human rhabdomyosarcoma cells. Cancer Res. Feb 15 1999;59(4):886–94. [PubMed: 10029080]
54. Dilling MB, Dias P, Shapiro DN, Germain GS, Johnson RK, Houghton PJ. Rapamycin selectively inhibits the growth of childhood rhabdomyosarcoma cells through inhibition of signaling via the type I insulin-like growth factor receptor. Cancer Res. Feb 15 1994;54(4):903–7. [PubMed: 7508822]

55. Mascarenhas L, Chi YY, Hingorani P, et al. Randomized Phase II Trial of Bevacizumab or Temsirolimus in Combination With Chemotherapy for First Relapse Rhabdomyosarcoma: A Report From the Children's Oncology Group. J Clin Oncol. Nov 1 2019;37(31):2866–2874. doi:10.1200/JCO.19.00576 [PubMed: 31513481]
56. Bisogno G, De Salvo GL, Bergeron C, et al. Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. Nov 2019;20(11):1566–1575. doi:10.1016/S1470-2045(19)30617-5 [PubMed: 31562043]
57. Breneman JC, Lyden E, Pappo AS, et al. Prognostic factors and clinical outcomes in children and adolescents with metastatic rhabdomyosarcoma--a report from the Intergroup Rhabdomyosarcoma Study IV. J Clin Oncol. Jan 1 2003;21(1):78–84. doi:10.1200/JCO.2003.06.129 [PubMed: 12506174]
58. Pappo AS, Lyden E, Breitfeld P, et al. Two consecutive phase II window trials of irinotecan alone or in combination with vincristine for the treatment of metastatic rhabdomyosarcoma: the Children's Oncology Group. J Clin Oncol. Feb 1 2007;25(4):362–9. doi:10.1200/JCO.2006.07.1720 [PubMed: 17264331]
59. Casanova M, Ferrari A, Spreafico F, et al. Vinorelbine in previously treated advanced childhood sarcomas: evidence of activity in rhabdomyosarcoma. Cancer. Jun 15 2002;94(12):3263–8. doi:10.1002/cncr.10600 [PubMed: 12115359]
60. Kuttesch JF Jr., Krailo MD, Madden T, Johansen M, Bleyer A, Children's Oncology G. Phase II evaluation of intravenous vinorelbine (Navelbine) in recurrent or refractory pediatric malignancies: a Children's Oncology Group study. Pediatr Blood Cancer. Oct 2009;53(4):590–3. doi:10.1002/pbc.22133 [PubMed: 19533657]
61. Minard-Colin V, Ichante JL, Nguyen L, et al. Phase II study of vinorelbine and continuous low doses cyclophosphamide in children and young adults with a relapsed or refractory malignant solid tumour: good tolerance profile and efficacy in rhabdomyosarcoma--a report from the Societe Francaise des Cancers et leucemies de l'Enfant et de l'adolescent (SFCE). Eur J Cancer. Oct 2012;48(15):2409–16. doi:10.1016/j.ejca.2012.04.012 [PubMed: 22633624]
62. Weigel B, Malempati S, Reid JM, et al. Phase 2 trial of cixutumumab in children, adolescents, and young adults with refractory solid tumors: a report from the Children's Oncology Group. Pediatr Blood Cancer. Mar 2014;61(3):452–6. doi:10.1002/pbc.24605 [PubMed: 23956055]
63. Warwick AB, Malempati S, Krailo M, et al. Phase 2 trial of pemetrexed in children and adolescents with refractory solid tumors: a Children's Oncology Group study. Pediatr Blood Cancer. Feb 2013;60(2):237–41. doi:10.1002/pbc.24244 [PubMed: 22745043]
64. Soft Tissue Sarcoma Committee of the Children's Oncology G, Lager JJ, Lyden ER, et al. Pooled analysis of phase II window studies in children with contemporary high-risk metastatic rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol. Jul 20 2006;24(21):3415–22. doi:10.1200/JCO.2005.01.9497 [PubMed: 16849756]
65. Schuetze SM, Wathen JK, Lucas DR, et al. SARC009: Phase 2 study of dasatinib in patients with previously treated, high-grade, advanced sarcoma. Cancer. Mar 15 2016;122(6):868–74. doi:10.1002/cncr.29858 [PubMed: 26710211]
66. Schoffski P, Wozniak A, Leahy MG, et al. The tyrosine kinase inhibitor crizotinib does not have clinically meaningful activity in heavily pre-treated patients with advanced alveolar rhabdomyosarcoma with FOXO rearrangement: European Organisation for Research and Treatment of Cancer phase 2 trial 90101 'CREATE'. Eur J Cancer. May 2018;94:156–167. doi:10.1016/j.ejca.2018.02.011 [PubMed: 29567632]
67. Pappo AS, Vassal G, Crowley JJ, et al. A phase 2 trial of R1507, a monoclonal antibody to the insulin-like growth factor-1 receptor (IGF-1R), in patients with recurrent or refractory rhabdomyosarcoma, osteosarcoma, synovial sarcoma, and other soft tissue sarcomas: results of a Sarcoma Alliance for Research Through Collaboration study. Cancer. Aug 15 2014;120(16):2448–56. doi:10.1002/cncr.28728 [PubMed: 24797726]
68. Kim A, Widemann BC, Krailo M, et al. Phase 2 trial of sorafenib in children and young adults with refractory solid tumors: A report from the Children's Oncology Group. Pediatr Blood Cancer. Sep 2015;62(9):1562–6. doi:10.1002/pbc.25548 [PubMed: 26207356]

69. Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1–2 trial. Lancet Oncol. Apr 2020;21(4):541–550. doi:10.1016/S1470-2045(20)30023-1 [PubMed: 32192573]

70. Beaty O 3rd, Berg S, Blaney S, et al. A phase II trial and pharmacokinetic study of oxaliplatin in children with refractory solid tumors: a Children's Oncology Group study. Pediatr Blood Cancer. Sep 2010;55(3):440–5. doi:10.1002/pbc.22544 [PubMed: 20658614]

71. Baruchel S, Pappo A, Krailo M, et al. A phase 2 trial of trabectedin in children with recurrent rhabdomyosarcoma, Ewing sarcoma and non-rhabdomyosarcoma soft tissue sarcomas: a report from the Children's Oncology Group. Eur J Cancer. Mar 2012;48(4):579–85. doi:10.1016/j.ejca.2011.09.027 [PubMed: 22088484]

72. W A-R. Alveolar rhabdomyosarcoma has superior clinical response rates to vinorelbine compared to embryonal rhabdomyosarcoma in patients with refractory or relapsed disease. In: Lupo P SM, Chi Y, Kuttesch J, Meyer WH, Venkatramani R, Mascarenhas L, editor.: CTOS Abstract; 2020.

73. Pacenta HL, Allen-Rhoades W, Langenau D, et al. Prioritization of Novel Agents for Patients with Rhabdomyosarcoma: A Report from the Children's Oncology Group (COG) New Agents for Rhabdomyosarcoma Task Force. J Clin Med. Apr 1 2021;10(7)doi:10.3390/jcm10071416

74. Heske CM, Mascarenhas L. Relapsed Rhabdomyosarcoma. J Clin Med. Feb 17 2021;10(4)doi:10.3390/jcm10040804

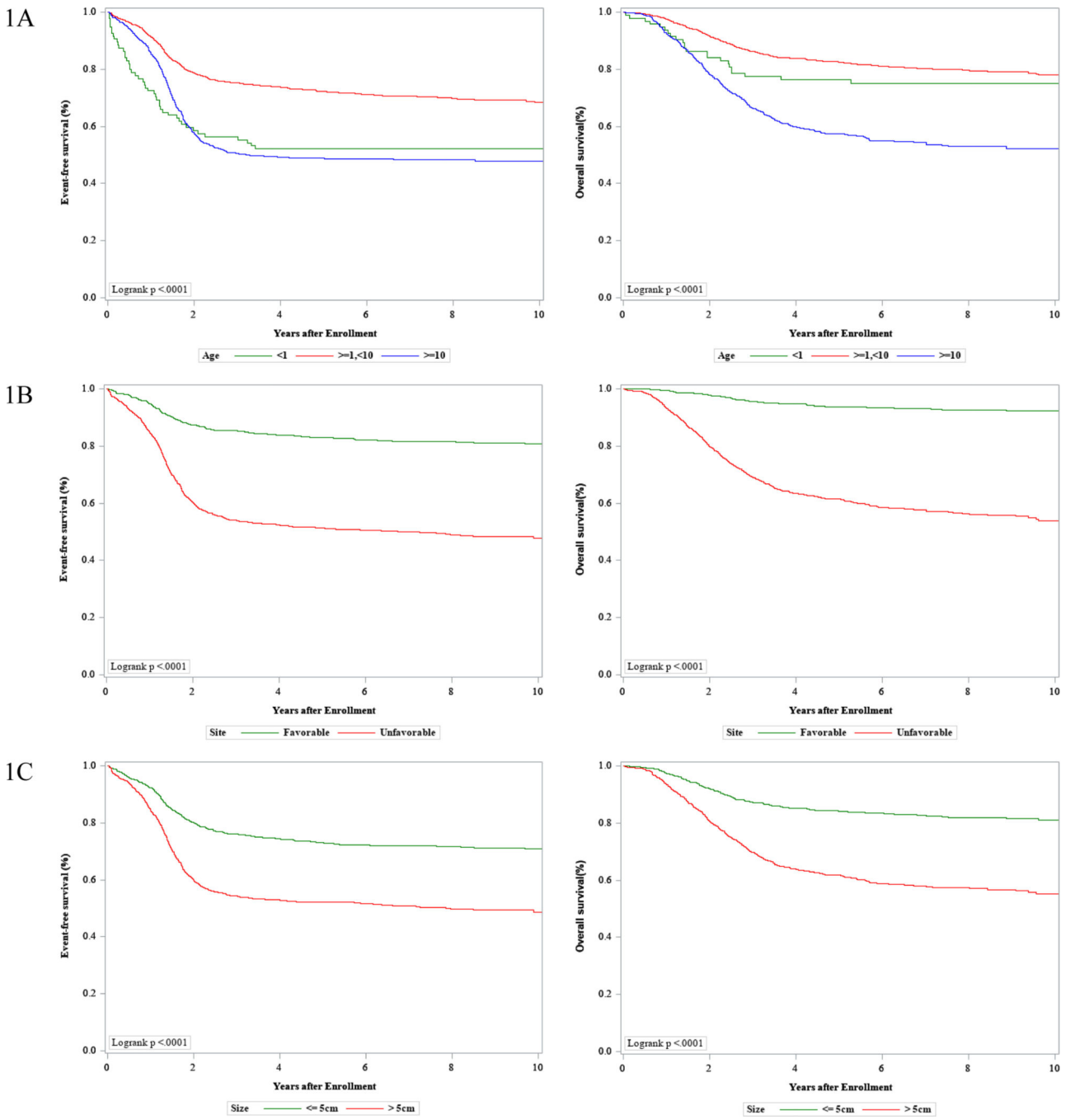

Figure 1:

Outcomes of 2157 patients enrolled on IRS V (D9602, D9803, and D9802) and COG ARST (ARST0331, ARST0531, ARST0431 and ARST08P1) studies based on clinical factors. 1A: EFS and OS by age at diagnosis; 1B: EFS and OS by tumor site; 1C: EFS and OS by tumor size

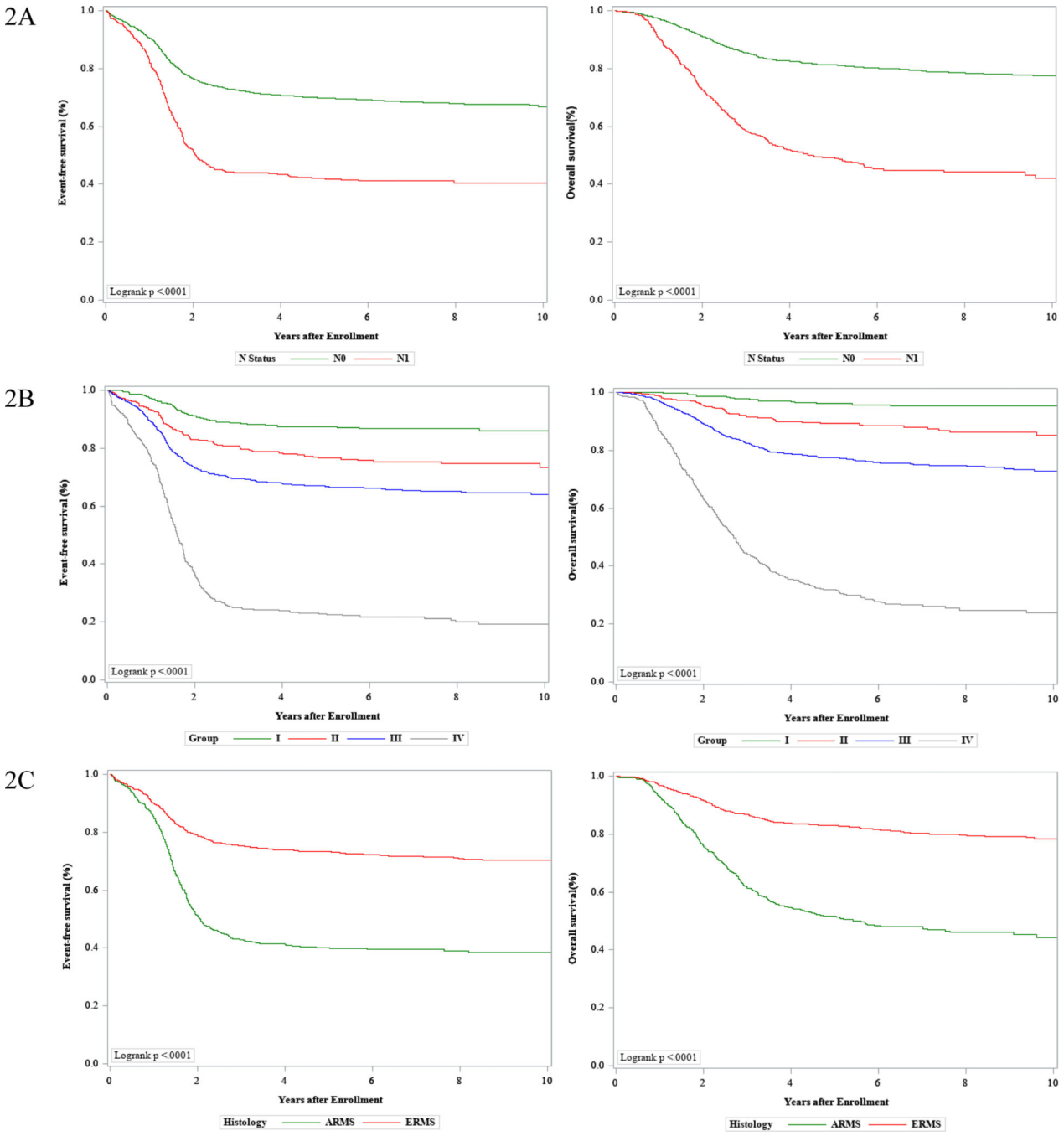

Figure 2:

Outcomes of 2157 patients enrolled on IRS V (D9602, D9803 and D9602) and COG ARST (ARST0331, ARST0531, ARST0431 and ARST08P1) studies based on clinical factors.

2A: EFS and OS by nodal status; 2B: EFS and OS by Clinical Group; 2C: EFS and OS by histology

TABLE 1:

Intergroup Rhabdomyosarcoma Study Clinical Groups

Group	Description
I	Localized disease, completely resected (no regional lymph node involvement)
II (A-C)	Localized disease, gross total resection with microscopic positive margins and/or evidence of regional spread A. Grossly resected tumor with microscopic residual disease. No evidence of regional node involvement. B. Regional disease with involved nodes, completely resected with no microscopic residual disease, including most distal node is histologically negative. C. Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual disease and/or histologic involvement of the most distal regional node (from the primary site) in the dissection.
III	Localized disease, incomplete resection with gross residual disease or biopsy only
IV	Distant metastatic disease present at onset

TABLE 2:

Rhabdomyosarcoma TNM Staging

Stage	Site	T	Size	N	M
1	Orbit, Head and neck (excluding parameningeal), GU – non-bladder/ non-prostate,	T_1 or T_2	a or b	N_0 or N_1 or N_x	M_0
2	Bladder/Prostate, Extremity, Cranial parameningeal, Other * (includes trunk, retroperitoneum, etc.)	T_1 or T_2	a	N_0 or N_x	M_0
3	Bladder/Prostate, Extremity, Cranial parameningeal, Other (includes trunk, retroperitoneum, etc.)	T_1 or T_2	a b	N_1 N_0 or N_1 or N_x	M_0 M_0
4	All	T_1 or T_2	a or b	N_0 or N_1	M_1

* Biliary tract/liver will be considered unfavorable site in future COG clinical trials

Tumor (T):

$T(site)_1$ – confined to anatomic site of origin

a. ≤5cm in diameter in size

b. >5cm in diameter in size

$T(site)_2$ – confined to anatomic site of origin

a. ≤5cm in diameter in size

b. >5cm in diameter in size

Regional Nodes (N):

N_0: Regional nodes not clinically involved

N_1: Regional nodes clinically involved by neoplasm defined as >1cm by CT or MRI

N_X: Clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation)

Metastasis (M):

M_0: No distant metastasis

M_1: Distant metastasis present

TABLE 3:

Current Children's Oncology Group Rhabdomyosarcoma Risk Stratification

Risk Group	Stage	Clinical Group	Age	Fusion Status
Low	1	I, II, III (orbit only)	Any	*FOXO1* −
	2	I, II		
Intermediate	1	III (non-orbit)	Any	*FOXO1* −
	1, 2, 3	I, II, III		*FOXO1* +
	2, 3	III		*FOXO1* −
	3	I, II		*FOXO1* −
	4	IV	<10 years	*FOXO1* −
High	4	IV	>10 years	*FOXO1* −
			Any	*FOXO1* +

Table 4:

Current and Planned Children's Oncology Group Rhabdomyosarcoma Studies

Risk Group	Stage	Clinical Group	Age	Fusion Status	COG Study	Therapy
Very Low Risk	1	I	Any	*FOXO1* −	ARST2032 * (anticipated activation spring 2022)	VA x 24w
Low Risk	1	II, III (orbit only)				VAC/VA X 24w
	2	I, II				
Intermediate	1	III (non-orbit)	Any	*FOXO1* −	ARST1431	VAC/VI vs VAC/VI + Temsirolimus x 42w + Maintenance (CPM^{PO}Vino) x 24w (all patients)
	1, 2, 3	I, II, III		*FOXO1* +		
	2, 3	III		*FOXO1* −		
	3	I, II		*FOXO1* −		
	4	IV	<10 years	*FOXO1* −		
High	4	IV	>10 years	*FOXO1* −	ARST2031 (anticipated activation summer 2021)	VAC vs VinoAC x 42w + Maintenance (CPM^{PO}Vino) x 24w (all patients)
			Any	*FOXO1* +		

* Patients treated on VLR or LR arms of ARST2032 must have *MYOD1*/*TP53* wildtype tumors

CPM^{PO}: Daily oral cyclophosphamide

Vino: Vinorelbine

VAC: Vincristine, Dactinomycin, Cyclophosphamide regimen using Cyclophosphamide dose of 1.2g/m^2/cycle

VinoAC: Vinorelbine, Dactinomycin, Cyclophosphamide regimen using Cyclophosphamide dose of 1.2g/m^2/cycle