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Consensus recommendations for systemic therapies in the management of relapsed Ewing sarcoma: A report from the National Ewing Sarcoma Tumor Board

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Ewing sarcoma (ES) is a bone and soft tissue cancer that most often occurs in teenagers and young adults. This paper uses the experience of the National Ewing Sarcoma Tumor Board, a multi-institution, multidisciplinary virtual tumor board that meets monthly to discuss challenging cases of ES and address questions related to treatment of patients with relapsed ES. While not intended to replace the clinical judgement of treating physicians and limited by available data, these consensus recommendations will support clinicians treating patients with this challenging malignancy, made even more difficult when it recurs.

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Debates remain in defining the standard of care for treating patients with relapsed Ewing sarcoma. This set of consensus recommendations from the National Ewing Sarcoma Tumor Board are intended to provide some clarity and recommendations for the management of patients with recurrent disease.

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Keywords: Ewing Sarcoma, Consensus, Relapse, Refractory, Stem Cell Transplantation, Metastasis

Ewing sarcoma (ES) is a malignant tumor of bone and soft tissue that most often occurs in children, adolescents, and young adults. Debate and controversy remain in the

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management of relapsed/refractory ES (RR-ES). We have leveraged the expertise assembled by the National Ewing Sarcoma Tumor Board, a multidisciplinary virtual tumor board that meets monthly to discuss challenging cases of ES. This review will focus on select topics that apply to the management of patients with RR-ES. The specific topics covered include the initial approach of such patients and discussion of goals of care, the role of molecular testing, chemotherapy regimens and novel agents to consider, the role of maintenance therapy, and the use of high-dose chemotherapy with autologous stem cell rescue. The data referenced are often limited to subgroup analyses and/or compiled from multiple sources. While not intended to replace the clinical judgement of treating physicians, these guidelines are intended to support clinicians and provide some clarity and recommendations for the management of patients with RR-ES.

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Introduction

Ewing sarcoma (ES) is an aggressive malignant tumor of bone and soft tissue of children, adolescents, and young adults. Despite advances in upfront treatment, relapses occur in approximately 25% of patients with localized disease and 70% of patients with metastatic disease.[1] Treatment of relapsed/refractory ES (RR-ES) remains a clinical challenge; 5-year survival is less than 15% and the majority of patients suffer a subsequent episode of progressive disease within 6 months of initial relapse.[2]

We leveraged the experience assembled by the formation of the National Ewing Sarcoma Tumor Board (NEWS), a multidisciplinary virtual conference that meets monthly to discuss challenging cases of ES, to construct a list of frequent clinical questions relevant to RR-ES. We previously published on controversies related to upfront therapy.[3] In this review, we focus on topics that apply to systemic therapies in the management of RR-ES. The topics are limited to those that have a clinical and practical impact and for which there are some, albeit limited, data to support general recommendations. While local control measures play a critical role in the management of RR-ES and will be explored in a separate manuscript, the current manuscript focuses on systemic therapies.

The data referenced are often limited to subgroup analyses and/or compiled from multiple sources. Although not intended to replace the clinical judgement of treating physicians, the recommendations are focused on providing pediatric and adult oncologists - who may or may not possess specific sarcoma expertise - some clarity and support for the management of patients with RR-ES.

Question 1: What should be considered when approaching RR-ES with curative intent?

The approach to a patient with RR-ES begins with a clear understanding of the initial diagnosis and treatment response, stage (localized *versus* metastatic *versus* combined relapse), difficult-to-treat locations, overall burden of disease at time of relapse (oligometastatic *versus* diffusely metastatic), and time to relapse. Each of these factors is prognostic, as reviewed below.

The most consistently reported determinant of prognosis is time to first relapse. Patients with a greater than 2-year relapse-free interval from time of initial diagnosis have superior event-free (EFS) and overall survival (OS) across multiple single and multi-institutional series.[4-9] In an analysis of cooperative group study INT-0091, patients whose disease relapsed two years or more after initiation of treatment had an estimated 5-year OS of 30% as compared to 7% in those whose disease relapsed within two years.[5]

Stage and sites of disease at diagnosis and relapse can also impact prognosis. A retrospective analysis of 55 patients reported that the 5-year OS in RR-ES patients with localized disease at initial diagnosis was 31% *versus* 12% for those with upfront metastatic disease.[4] For initially localized disease in first relapse, rates of second complete response (CR2) were 84% in patients with local recurrence *versus* 48% of patients with pulmonary-only metastases, 20% of patients with bone-only metastases, and 2.4% of patients with both.[10] 5-year OS was 35-50% for patients

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with local recurrence *versus* 10-20% for distant-only (lung *or* bone), and 0-10% for patients with both.[4,9] Patients who initially presented with appendicular primary tumors had an 18% chance of achieving CR2 versus 6% for pelvic primary tumors, and 9% for other sites, with 5-year EFS rates of 10.7, 4.1, and 0%, respectively.[8] In patients with upfront metastatic disease, 82% of these patients developed distant-only relapse, 5% relapsed locally-only, and 13% had both.[11] Those with pulmonary-only metastatic disease at diagnosis had a 3-year EFS of 54% compared to 26% for non-pulmonary metastatic disease.[12]

Medical providers should have an open discussion with the patient and family about their prognosis at relapse, factoring in all available data about their disease. Addressing patient priorities, which may evolve, will dictate how the medical team presents and recommends therapeutic options such as chemotherapy, local control, clinical trial enrollment, and supportive care. Additional factors to consider are the uncertainties of treatment efficacy, toxicities of therapy, and optimizing quality of life. For example, younger patients may feel differently about pursuing additional cancer-directed therapies than older patients. It is important to readdress goals of care at times of subsequent relapse or disease progression or following the development of treatment-related toxicity. Furthermore, patients with RR-ES may become "metavivors", a term used to describe people living with cancer as a chronic and terminal illness.[13] This group of patients experiences unique biopsychosocial challenges such as management of acute and chronic symptoms due to previous and current cancer treatment, psychological distress, financial toxicity and changing caregiver dynamics.[14] Early incorporation of palliative medicine in the care of patients with RR-ES is essential for symptom management and discussion of goals of care.[15]

New biomarkers are needed to better identify which patients with first recurrent ES may still be cured. Additionally, evaluation of health-related quality of life (HR-QoL) measures and patient-reported outcomes (PROs) are needed to fully understand the psychosocial impact and needs of RR-ES patients.

Consensus Statement: While the best outcomes in patients with RR-ES have been seen in patients with late and localized relapses, discussion with the patient should be informed by the circumstances of their current disease, predicted outcomes, current organ function, and patients' goals of care. Psychosocial support is critical for RR-ES patients. We strongly suggest consultation with Supportive/Palliative Care at time of relapse, if not already involved.

Question 2: What is the role of molecular testing at relapse in this tumor type?

Molecular testing for somatic aberrations, most commonly through DNA and RNA sequencing, has become customary in the diagnostic workup of high-risk solid tumors. Although identification of hallmark fusions between *EWSR1* and *ETS* family members is useful for diagnosis, patients with ES generally have fewer actionable alterations compared to other tumors. For example, of the 104 RR-ES patients screened on the National Cancer Institute Children's Oncology Group (NCI-COG) Pediatric MATCH trial, only 12 (11.5%) had study-defined actionable alterations, with four patients (3.8%) enrolling for treatment using a molecularly targeted agent.[16] Loss-of-function mutations in *STAG2* and *TP53* are among the most common[17] but unfortunately are not yet

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targetable. Alterations in other targetable genes are infrequently identified, such as *PIK3R1, FGFR1, EZH2,* along with alterations in cell cycle control and DNA damage repair genes.[18-20] In terms of germline findings, ES has been associated with as high as 13% germline pathogenic or likely pathogenic variants in genes involved in DNA damage repair, including FANCC, CHEK2, BRAC1 and BRCA2[21,22], which may justify sequencing normal cells (buccal cells, peripheral blood, etc.) plus either archival tumor from diagnosis or tumor tissue obtained at relapse.

Unfortunately, RR-ES has not proportionally benefitted from advances in the current molecular era. Further investigation is needed to identify genomic, epigenomic, proteomic and metabolomic abnormalities, as well as changes in the tumor microenvironment and immune response. Molecular biomarkers of response are also essential to understand why certain patients respond to targeted therapies.

Consensus Statement: Molecular testing of RR-ES occasionally can identify additional/pathogenic alterations, but targetable alterations are infrequent and the therapeutic efficacy of agents targeting these molecular alterations is not yet established. Biopsy of recurrent tumor may be beneficial in scenarios where confirmation of recurrence is needed or archival tissue is unavailable for families and physicians interested in comparative germline testing.

Question 3: What is the chemotherapy regimen of choice?

Several regimens have demonstrated efficacy in RR-ES in single-arm clinical trials including irinotecan and temozolomide with or without vincristine (IT/VIT), cyclophosphamide and topotecan (TC), high-dose ifosfamide (IFOS), gemcitabine and docetaxel (GD), oral etoposide, and others (Table 1).[23]

The rEECur trial, a European, multi-arm, multi-stage phase 2/3 randomized study, compared outcomes between four regimens (IT, TC, IFOS, and GD) in patients with recurrent and primary refractory ES[24-27]. Using a probability-based Bayesian approach with multiple pairwise comparisons, early termination of the GD arm at the first interim assessment, then IT arm at the second interim assessment, occurred after patients had a predicted inferior objective response rate (ORR) by RECIST 1.1 compared to the other arms. The phase 3 portion of the study compared the remaining arms, TC and IFOS, and demonstrated a 95% posterior probability that EFS and OS were better with IFOS than TC. Median EFS was 3.7 months (95% CI, 2.1-6.2) for TC and 5.7 months (95% CI, 3.8-7.0) for IFOS, and median OS was 10.4 months (95% CI, 7.5-15.5) for TC and 16.8 months (95% CI, 11.1-25.8) for IFOS. Additionally, a greater survival difference occurred in patients less than 14 years of age compared to those 14 years of age or older. Further pairwise comparisons demonstrated overlapping outcomes between TC and IT and high levels of confidence disfavoring GD against any of the other regimens.

In rEECur, the IT treatment arm did not contain vincristine, and irinotecan was dosed intravenously (IV) over 5 days. However, there is no standardized approach to the administration of IT/VIT in RR-ES, and data are mostly extracted from retrospective studies.[28,29] Recently, a randomized controlled phase 2 trial for RR-ES assessed a 10-day lower-dose versus a 5-day

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higher-dose IV irinotecan schedule in combination with vincristine.[30] The overall response rate (ORR) at 12 weeks was significantly higher for the protracted irinotecan schedule (54.5% versus 20.8%, p=0.019), but there was no difference in PFS (progression-free survival) or OS. Grade 3/4 gastrointestinal adverse events were higher in those who received 5-day irinotecan. These results align with a recent review that compared ORR of both dosing schemas across a variety of trials revealing an ORR of 53% (47 of 89) for the 10-day irinotecan schedule versus an ORR of 29% (52 of 180) for the 5-day irinotecan schedule.[29] While the ORR may be higher with a lower side effect profile using 10-day lower-dose irinotecan in combination with temozolomide +/- vincristine, the feasibility of this schedule for patients combined with lack of impact on PFS and OS should be considered by care teams. Another consideration is the use of oral irinotecan (usually mixed with cranberry-grape juice to mask the bitter taste) which has been studied using both 5- and 10-day schedules. Objective responses have been seen with both dosing schedules with greater toxicity in the protracted schedule.[31,32] However, the palatability of oral administration limits its use for many patients, and there are on-going efforts to address this.[33]

Interpretation of rEECur data is further limited by differences in sample size, prognostic indicators of survival, such as time to first recurrence and extent of disease at first recurrence, differences in the primary endpoint between interim analyses and the phase 3 portion of the study, local control measures, and number of cycles of therapy received.[5,28,34] Moreover, prior to the two-arm phase 3 portion, patients and investigators had the option of limiting the regimens to which a patient was eligible to be randomized, introducing the potential for bias.

Toxicity profiles affecting organ function and quality of life also need to be considered. In rEECur, GD was associated with fewer grade 3/4 adverse events compared to the other arms. IT was associated with more nausea, vomiting, and diarrhea compared to TC and IFOS, and IFOS was associated with more infection, renal toxicity, and encephalopathy compared to TC. Given the adverse profile of high-dose IFOS in heavily pretreated patients, alternative schedules of IFOS (e.g. continuous infusion) may be useful, albeit with limited data to support its use in ES.[35] Similarly, liposomal doxorubicin is a means of rechallenging with doxorubicin with decreased overall cardiotoxicity, although, data are limited to support its use in this setting.[36,37]

Ultimately, the choice of regimen, schedule, and duration should take into account the plan for local control, toxicity, response, and patient and family preferences. To briefly address optimal duration of therapy, it is important to note that the median EFS in the rEECur study was 4.6 months, with other single arm studies faring worse; thus, duration of therapy is tailored by the duration of disease control or tolerability.[38-40] In cases of patients with exceptional, enduring responses or stability with therapy, the optimal duration of therapy is unknown; for patients with no evidence of disease, six to 12 months of adjuvant therapy is commonly used, but the authors are unaware of any data to specifically support this timeframe.

DNA minor groove binders, such as trabectedin or lurbinectedin, have shown preclinical activity in ES, with evidence that these agents can sequester the fusion oncoprotein in the nucleolus.[65] These agents have entered clinical trials for patients with RR-ES. A phase 1 study of trabectedin as a 3-hour infusion reported one of three (33%) patients with RR-ES had a complete response.[66]

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A subsequent phase 2 trial administered trabectedin as a 24-hour infusion and no responses were observed.[67] A follow-up phase 1/2 trial evaluating a 1-hour infusion together with low-dose irinotecan recently reported five out of 18 (28%) patients with objective responses in the phase 2 portion of the trial, or eight out of 23 (35%) if phase I patients treated at the RP2D were included.[68,69] Median duration of response in the phase 2 portion was 7.5 months and the study reported a 6-month PFS of 40%. A phase 2 trial of lurbinectedin monotherapy reported a 14.3% ORR, though median duration of response was only 4.2 months.[39] While the results of this phase 1/2 trial evaluating trabectedin with irinotecan are promising, interpretation of these findings must consider that it is based on only 23 patients additional study may be warranted before moving this combination into the front-line treatment of RR-ES outside of the setting of a clinical trial.

Additional studies are required in order to identify the best sequence, intensity, and schedule of agents in the setting of first RR-ES. Quality of life considerations may take precedence over therapeutic efficacy, since it is unknown which patients have the greatest benefit from more aggressive approaches, outside of patients younger than 14 years of age.

Consensus Statement: We recommend considering enrollment in a clinical trial at first relapse and beyond. In the absence of an accessible clinical trial, we recommend consideration of individual patient factors including cumulative toxicities and goals of care in choosing between IT/VIT, TC, IFOS or any other regimen at first or subsequent relapse. GD is no longer recommended for first recurrent disease.

Question 4: What is the role of novel agents?

Several multitargeted tyrosine kinase inhibitors (mTKIs) have been investigated in RR-ES. Cabozantinib was evaluated in a phase 2 trial (CABONE) in patients with RR-ES, with a 26% ORR.[41] Regorafenib has been tested in two phase 2 trials. The Sarcoma Alliance through Research and Collaboration (SARC) trial reported an ORR of 10% and a median PFS of 14.8 weeks.[42] A separate randomized, placebo-controlled phase 2 trial (REGOBONE) reported a 21.7% ORR and a median PFS of 11.4 weeks.[43] Regorafenib was combined with vincristine and irinotecan in a phase 1 trial for pediatric patients with relapsed solid tumors. Discontinuous dosing was tolerable and three out of five patients with ES on the trial had objective responses.[44] Catequentinib (anlotinib) has also been studied in a phase 1b/2 trial with vincristine and irinotecan in Chinese patients with RR-ES without CNS metastases.[45] Patients in phase 1b that were treated with the recommended phase 2 dose (RP2D) were included in the phase 2 analysis, resulting in a total of 24 adults (16 years or older in this study) and 12 children. In the phase 2 portion, the majority of patients (92%) had metastatic disease, 44% had lung-only target lesions, and 64% had only one prior line of chemotherapy. Irinotecan was given over 10 days (RP2D was 15mg/m^2 in adults and 20mg/m^2 in children) and catequentinib concurrently over 14 days. Toxicity data was not available on a per-patient basis, but overall the regimen appeared to be myelosuppressive. The ORR was 69%, with a higher response rate of 83% in children. WLI or surgical resection was allowed for patients achieving PR and patients were censored at those timepoints, leading to a high rate of protocol violations and an overall PFS of 8-10 months. These results have not yet been validated.

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DNA damage response (DDR) inhibitors that target PARP, ATR, WEE1, CDC7, and others have demonstrate robust preclinical activity in ES.[46-50] However, multiple early phase trials of PARP inhibitors alone and in combination with chemotherapy have had disappointing results.[40,51-53] Scheduling and dosing may make a difference, as a more recent phase 1/2 trial of a protracted PARP inhibitor schedule plus low-dose irinotecan (arm D of the AcSé-ESMART trial) found 1 CR and 1 PR with 7 SD out of 26 patients (35%).[46,47,54] In a phase 1 trial of WEE1 inhibitor with irinotecan, one of four patients with ES had the single confirmed PR on study.[55] Ongoing studies include the ONITT protocol (NCT04901702), which is examining the combination of liposomal irinotecan with a PARP inhibitor or temozolomide and a phase 1/2 study of an ATR inhibitor, both with RR-ES-specific cohorts.[56,57]

Preclinical investigations identified a role for targeting CDK4 in ES[58,59], leading to at least three clinical trials. One trial combined palbociclib with the IGF-1R monoclonal antibody ganitumab. No patients responded to this combination, though five out of 10 (50%) patients had stable disease.[60] Two ongoing trials are evaluating palbociclib (NCT03709680) or abemaciclib (NCT05440786) with chemotherapy in patients with RR-ES. Other cyclin dependent kinase inhibitors, including CDK9 inhibition, are earlier in clinical development.

Several strategies targeting ES fusion oncoprotein have been investigated. LSD1 inhibition is thought to impede the transcriptional re-programming by the fusion oncoprotein.[61] The LSD1 inhibitor seclidemstat was tested as monotherapy[62] and in combination with TC in patients with RR-ES with minimal efficacy.[63] Another drug, TK216, is thought to block the fusion oncoprotein transcriptional activity through RNA helicase A. This agent was evaluated as monotherapy and in combination with vincristine, but with only two out of 28 (7%) patients with complete response, further development in ES is yet to be determined.[64]

Patients with RR-ES have not derived significant benefit from immune checkpoint inhibitors and tumor vaccines. A phase 2 trial of pembrolizumab included a RR-ES cohort, with no responses.[70] A pediatric phase 2 trial of nivolumab / ipilimumab showed one out of 14 (7%) patients with RR-ES with a complete response.[71] An autologous tumor vaccine gemogenovatucel-T (Vigil) has been evaluated in patients with RR-ES both with and without irinotecan/temozolomide, with two out of ten (20%) patients demonstrating partial responses in the most recent study.[72,73] A number of antigens of potential interest for cellular immunotherapies are expressed in ES, including GD2[74], B7H3[75], STEAP1, etc.[76,77] No clinical results targeting these or other antigens have yet been published in this population.

Given the limited practical understanding of the genomics and epigenomics of ES outside of the characteristic fusion, and the high toxicity of currently successful approaches in RR-ES, the interest in targeted therapies is well-founded, but unfortunately has had limited success. Research to better understand the reasons for which subset of patients respond to agents such as mTKIs, PARP inhibitors, CDK inhibitors, fusion oncoprotein inhibitors, DNA minor groove binders, or immunotherapy and why the majority of patients do not is critically needed. The ethics of aggressive care in the setting of poor outcomes may also be a field in need of better

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illumination to help clinicians, patients, and families optimize patient-centered decision-making.

Consensus Statement: We recommend enrollment in clinical trials to explore novel therapies. Several targeted therapies have either shown activity in patients with RR-ES or are undergoing evaluation at various stages of clinical development in this population. The risks and benefits of these potential options and/or of participating in clinical trials must be weighed in the context of overall goals of care for this group of patients with very poor outcomes.

Question 5: What is the role of maintenance-styled therapy in CR2?

Maintenance chemotherapy has been proven to be effective in acute lymphoblastic leukemia and rhabdomyosarcoma.[78,79] Efficacy has not been established in RR-ES. Two randomized trials utilizing maintenance therapy (ganitumab[80] or zoledronic acid[81]) after completion of standard treatment in newly diagnosed patients have shown no benefit. Other studies utilizing oral trofosphamide[82], or oral cyclophosphamide plus either celecoxib[83] or vinorelbine[84] have demonstrated feasibility, but the precise benefit is difficult to determine due to short follow-up or absence of a randomized control. Studies exploring maintenance therapy as part of upfront treatment for newly-diagnosed patients with metastases are ongoing (INTER-EWING1 and iEuroEwing), yet to be reported (NCT03011528), or planned.[85] Studies to address maintenance therapy approaches in the second remission setting including the use of tyrosine kinase inhibitors are ongoing (NCT05135975).[86] It is hoped that more sensitive disease assessments, such as circulating tumor DNA monitoring,[87] will better inform the necessity, length and effectiveness of maintenance therapies.

Consensus Statement: The clinical value of maintenance therapy in RR-ES patients is not established. Consequently, we recommend that the use of maintenance therapy be restricted to a clinical trial setting or after a robust conversation with the patient regarding the lack of data and risks and benefits of such an approach.

Question 6: What is the role of high-dose therapy with autologous stem cell rescue?

Dating back forty years, high-dose therapy with autologous stem cell rescue (HDT) has been attempted for the treatment of patients with ES, in both the upfront and relapsed setting.[8,88] While HDT has been incorporated in the treatment of patients with high-risk neuroblastoma and high-risk medulloblastoma, its role in the treatment of patients with ES remains controversial.[89] Whether due to the retrospective nature of studies comparing patients treated with and without HDT, or the few prospective studies comparing the same, there are consistent concerns regarding potential selection bias and modest benefit. Patients who proceed with HDT often have clinical features associated with good response to conventional salvage chemotherapy,[4] prompting questions as to the true impact of HDT in patients with RR-ES. Importantly, while generally considered less toxic than allogeneic stem cell transplant, HDT has significant morbidity and mortality. A recent investigation compared 64 patients with RR-ES who received HDT, 98 patients who received standard therapy without HDT (non-HDT), and 34 patients who received no systemic therapy.[90] The median post-relapse survival (PRS) was significantly longer in the HDT

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cohort compared to the non-HDT, 76 months compared with 10.5 months ($p < 0.0005$), and PRS was higher in the HDT group compared to the non-HDT group at 2 years (67.9% vs 52.7%) and 5 years (20.5% vs 2%). However, the authors keenly point out that the patients with the worst prognosis based on sites of relapse, those with concomitant local and pulmonary relapse and those with extra-pulmonary sites of relapse, were disproportionately represented in the non-HDT group. It is therefore unclear if HDT provides benefit in RR-ES. More data is required in the form of randomized controlled trials to prove that any benefit offsets the known toxicity associated with this treatment approach.

Consensus Statement: The clinical value of HDT in RR-ES patients is not established due to the lack of randomized or prospective data. While some patients with chemotherapy responsive disease appear to achieve modest benefit from HDT, it is unclear if this is a result of this specific treatment approach versus selection bias of a cohort likely to experience superior results with any therapy. Consequently, we recommend that the use of HDT be restricted to a clinical trial setting or after a robust conversation with the patient regarding the lack of data and risks and benefits of such an approach.

Conclusion

In conclusion, this review offers consensus recommendations for the management of common clinical questions relevant to systemic therapies for the care of patients with RR-ES, as identified through the National Ewing Sarcoma Tumor Board. We provide a curated, high-level review of the available literature to inform these recommendations and highlight the work that remains to be done for the RR-ES population. For example, prospective clinical trials for RR-ES should collect known and anticipated prognostic data including time to relapse, prior treatment regimens, and disease burden at initial presentation (size and location of primary, metastatic sites if present) to help contextualize results. Additionally, while molecular evaluation of RR-ES has yet to yield benefits proportional to other diseases in the current molecular era, collection of these data with clinical annotation, including enrollment in prospective precision oncology endeavors, may be key to catalyzing clinically relevant progress (identification of prognostic, predictive and surveillance biomarkers). Finally, many important questions exist beyond those discussed in this review, and we recommend bringing these questions to multidisciplinary discussions with experts in the field, like those that occur at the NEWS tumor board.

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Table 1 - Characteristics of various systemic therapy regimens for RR-ES

Regimen	Agents	Schedule	Cycle Length	GCSF	Toxicity profile	Reference	Design	N	ORR	Partial Response	Complete Response	6-month PFS	Median TTP (months)
IT/VIT 5 Day	Irinotecan 50 mg/m2/day IV or Irinotecan 90 mg/m2/day PO	Days 1-5	21 days	No	N/V/D, Less Alopecia (unless vincristine used)	PMID: 23776128,[91] PMID: 29533113[92]	Retrospective, Retrospective	22, 51	55%, 34%	32%, 24%	23%, 10%	NR, 49%	3, 3.9
	Temozolomide 100-150 PO mg/m2/day	Days 1-5											
	Vincristine 1.5 mg/m2/day IV	Day 1											
IT/VIT 10 day	Irinotecan 10-20 mg/m2/day IV or Irinotecan 35 mg/m2/day PO[31]	Days 1-5, Days 8-12	21 days	No	N/V/D, Less Alopecia (unless vincristine used)	PMID: 36622702,[30] PMID: 19637327[93]	Prospective RCT, Retrospective	22, 20	55%, 63%	50%, 37%	5%, 26%	41%*, NR	4.3, 8.3
	Temozolomide 100-150 PO mg/m2/day	Days 1-5											
	Vincristine 1.5 mg/m2/day IV	Days 1,8											
TC	Topotecan 0.75 mg/m2/day	Days 1-5	21 days	Yes	Marrow suppression, N/V, Alopecia	PMID: 16411206[94]	Retrospective	54	33%	33%	0%	NR	NR
	Cyclophosphamide 250 mg/m2/day	Days 1-5											
IFOS	Ifosfamide 3 g/m2/day IV	Days 1-5	21 days	Yes	Marrow suppression, N/V, Alopecia, renal insufficiency	PMID: 19142994[95]	Prospective single arm	35	34%	29%	6%	NR	NR
	Mesna 3 g/m2/day IV	Days 1-5											
GD	Gemcitabine 675-900 mg/m2/day IV	Days 1,8	21 days	Yes	Marrow suppression, N/V, Alopecia, neuropathy, edema	DOI:10.1200/JCO.2019.37.15_suppl.11007[24]	Prospective RCT	66	11.5%	NR	NR	NR	3
	Docetaxel 75-80 mg/m2/day IV	Day 8											
	Dexamethasone 3 mg/m2/day (up to 8mg) PO/IV	Days 7 - 9											
ICE	Ifosfamide 1.8 g/m2/day IV	Days 1-5	21 days	Yes	Marrow suppression, N/V, Alopecia, renal insufficiency, ototoxicity	PMID: 15503297[96]	Prospective single arm strata	22	48%	22%	29%	NR	NR
	Carboplatin 400 mg/m2/day IV	Days 1,2											
	Etoposide 100 mg/m2/day IV	Days 1-5											
CE	Carboplatin AUC 2.2 /day IV	Days 1,8,15	21 days	Yes	Marrow suppression, N/V, Alopecia, renal insufficiency, ototoxicity	PMID: 25251256[97]	Retrospective	61	51%	20%	31%	50%*	NR
	or Carboplatin AUC 7.5/day IV	Day 1											
	Etoposide 100 mg/m2/day IV	Days 1-3											
Trabectedin / Irinotecan	Trabectedin 1mg/m2 IV	Day 1	21 days	No	Fatigue, transaminitis, marrow suppression, N/V	DOI: 10.1200/JCO.2024.42.16_suppl.11508[69]	Prospective single arm	23	35%	35%	0%	40%	2.9
	Irinotecan 25mg/m2 IV	Days 2, 4											
Cabozantinib	Cabozantinib 60 mg/day (or 40 mg/m2/day in patients less than 16 years old) PO	Days 1-28	28 days	No	Rash, HTN, nephrotoxic, hepatoxicity, impaired wound healing	PMID: 32078813[41]	Prospective single arm	45	26%	26%	0%	33%	4.4 (?)
Regorafenib	Regorafenib 160 mg/day (or 82 mg/m2/day in patients less than 16 years old) PO	Days 1-21	28 days	No	Rash, HTN, nephrotoxic, hepatoxicity, impaired wound healing	PMID: 37914801,[43] PMID: 35950293[42]	Prospective, Prospective RCT	23, 30	13%, 10%	13,% 10%	0%	26%, 36 % (4 month)	2.9, 3.7
Oral Etoposide	Etoposide 40-50 mg/m2/day PO	Days 1-21	28 days	No	N/V, mild marrow suppression	PMID: 26797935[98]	Retrospective	58	19%	19%	<5%	NR	NR

* - Estimated PFS from graphical data

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Legend: GCSF – granulocyte colony stimulating factor, HTN – hypertension, IV – intravenous, mg/m2 – milligrams per metered squared, NR – not reported, N/V – nausea/vomiting, ORR – overall response rate, PFS – progression-free survival, PO – per mouth, RCT – randomized clinical trial, TTP – time to progression

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