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RESEARCH ARTICLE

Cancer Therapy and Prevention

A systematic review of early phase studies for children and young people with relapsed and refractory rhabdomyosarcoma: The REFoRMS-SR project

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Abstract

Rhabdomyosarcoma is the commonest soft tissue sarcoma in children. Around one-third of children with rhabdomyosarcoma experience relapse or have refractory disease, which is associated with a poor prognosis. This systematic review of early phase studies in pediatric relapsed/refractory rhabdomyosarcoma was conducted to inform future research and provide accurate information to families and clinicians making difficult treatment choices. Nine databases and five trial registries were searched in June 2021. Early phase studies of interventions for disease control in patients under 18 years old with relapsed/refractory rhabdomyosarcoma were eligible. No language/geographic restrictions were applied. Studies conducted after 2000 were included. Survival outcomes, response rates, quality of life and adverse event data were extracted. Screening, data extraction and quality assessment (Downs and Black Checklist) were conducted by two researchers. Owing to heterogeneity in the included studies, narrative synthesis was conducted. Of 16,965 records screened, 129 published studies including over 1100 relapsed/refractory rhabdomyosarcoma patients were eligible. Most studies evaluated systemic therapies. Where reported, 70% of studies reported a median progression-free survival ≤ 6 months. Objective response rate was 21.6%. Adverse events were mostly hematological. One-hundred and seven trial registry records of 99 studies were also eligible, 63 of which report they are currently recruiting. Study quality was limited by poor and inconsistent reporting. Outcomes for children with relapsed/refractory rhabdomyosarcoma who enroll on early phase studies are poor. Improving reporting quality and consistency would facilitate the synthesis of early phase studies in relapsed/refractory rhabdomyosarcoma (PROSPERO registration: CRD42021266254).

Connor Evans and Lucy Shepherd are joint first authors.

Scott Crowther, Sara Wakeling, Andy Stewart and Claire Stewart are Parent Group Members.

Julia Chisholm and Faith Gibson are Clinical Advisory Group Members.

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KEYWORDS

childhood cancer, refractory, relapse, rhabdomyosarcoma, systematic review

What's new?

Rhabdomyosarcoma is the most common soft tissue cancer in children, and around one-third of patients will have relapse or refractory disease. Here, the authors reviewed early phase studies of relapsed/refractory rhabdomyosarcoma, conducted between 2000 and 2021, to provide accurate information to clinicians and families seeking treatment. Objective response rate was 21.6%, and 70% of studies reported a median progression-free survival of 6 months or less. However, the analysis was hindered by inconsistent reporting; the authors note that better reporting would improve the ability to synthesize data from early phase studies in relapsed/refractory rhabdomyosarcoma.

1 | INTRODUCTION

Rhabdomyosarcoma accounts for ~4.5 cases/million children/adolescents per year.¹ Overall around two-thirds of patients diagnosed with rhabdomyosarcoma are alive at 5 years after diagnosis, but outcomes vary by risk group. Around one in three children and young people treated for rhabdomyosarcoma experience relapsed or refractory disease.^{2,3} Outcomes are much poorer in this situation, where historically only 17% of patients survived.⁴ Importantly, the prognosis associated with relapsed and refractory rhabdomyosarcoma varies greatly with the timing and location of the relapse as well as the intensity of prior therapies used; for example, over 40% of children and young people with originally localized disease who relapse in the same location may be cured, but the chances of cure are much lower in those with metastatic relapse.⁵ With this in mind, it can be difficult for clinicians, parents and patients to decide what treatments should be given for relapsed and refractory rhabdomyosarcoma.

Across Europe, the standard of care treatment for first relapse of rhabdomyosarcoma that has already received an alkylating agent (ifosfamide or cyclophosphamide based induction therapy) is currently the combination of vincristine, irinotecan and temozolomide (VIT) together with appropriate local control measures including surgery and/or radiotherapy wherever feasible.⁶ Furthermore, the ongoing European pediatric Soft tissue Sarcoma study Group Frontline and Relapse Rhabdomyosarcoma Study (FaR-RMS) is exploring the combination of backbone vincristine and irinotecan chemotherapy with the tyrosine kinase inhibitor regorafenib.⁷

The options for subsequent lines of treatment are much less clear. Alongside symptom-directed interventions such as pain relief, anticancer treatment options may be considered and can include aggressive treatment with the intention to cure, palliative treatments to reduce treatment burden and early phase studies. These early phase studies involve investigating new treatments or combinations of treatments, such as, including systemic chemotherapy, novel agents and targeted therapies, radiotherapy, cellular therapy and/or vaccinations. As these treatments are new and experimental, the goal of these early phase studies is primarily to assess the dosing and/or safety of a novel treatment. The findings

of effectiveness within these types of studies are often secondary and therefore useful in generating knowledge of potentially effective treatments which need to be synthesized to support further investigations. Previous reviews have shown a low success rate in terms of tumor response and overall survival times in early phase studies,⁸ but this response for rhabdomyosarcoma patients specifically, has not been examined and thus warrants review.

Within the REFoRMS-SR project, we conducted a systematic review of early phase studies of interventions for children and young people with relapsed and refractory rhabdomyosarcoma with the aim of synthesizing the current evidence to inform clinicians, parents and patients about the effectiveness of interventions that have been evaluated in this way. This review has been conducted alongside a qualitative study to understand the decision-making process of patients and families with experience of relapsed and refractory rhabdomyosarcoma. Both work-streams will be combined to generate a best practice statement to support healthcare professionals in pediatric oncology services. This article reports the systematic review.

2 | METHODS

2.1 | Parent and clinical advisory groups

The REFoRMS-SR project was guided by a group of bereaved parents whose children had experienced relapsed and refractory rhabdomyosarcoma, and a clinical advisory group consisting of healthcare and research professionals with expertise in soft tissue sarcoma. The parent group were identified through a combination of open and closed invites to known contacts, and the clinical advisory group by invitation through professional contacts for their specific clinical and/or methodological interests. Both groups were involved continuously and through direct interaction as defined by the ACTIVE framework.⁹ The parent and clinical advisory groups were involved in influencing and/or controlling the study design (stages 1–4 of ACTIVE framework) and interpretation of findings (stages 10–12 of ACTIVE framework) throughout the REFoRMS-SR project and are co-authors to this article.

2.2 | Search strategy and selection criteria

This systematic review followed a protocol registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021266254¹⁰), and was written in accordance with the PRISMA 2020 guidelines.¹¹ It was conducted following standardized systematic review methods as depicted in Figure 1.

Searches were developed by an information specialist (HF); the full search strategies are provided in Data S1. MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Science Citation Index-Expanded, Database of Abstracts of Reviews of Effects (DARE), the International HTA database, PROSPERO and Conference Proceedings Citation Index-Science were searched to identify published articles. ClinicalTrials.gov, European Union Clinical Trials Register, WHO International Clinical Trials Registry Platform (WHO ICTRP), International Standard Randomised Controlled Trial Number (ISRCTN) and ANZCHOG Children's Cancer Clinical Trials Repository (ACCCTR) were searched to identify additional unpublished, ongoing or completed studies. No language or geographical limitations were applied, but studies were only included if they were published from 2000 onwards. All databases were searched on 30 June 2021 and were deduplicated in EndNote 20. Reference lists of relevant systematic reviews and included articles were searched on 11 April 2022.

Studies identified in the searches were screened using the Rayyan Software,¹² based on the following criteria:

- **Population:** Patients with relapsed and/or refractory rhabdomyosarcoma aged 0–17 years inclusive. Patients aged 18 years and above were considered adults and therefore excluded. Studies including patients with other conditions/ages were eligible for inclusion provided that the data relating to the population of interest could be extracted separately, or where 50% or more patients were from the population of interest. Pre-clinical and animal studies of treatments for rhabdomyosarcoma were excluded.
- **Intervention:** Any treatment given with the intention of disease control, including with palliative or curative intent. Studies which evaluated treatments for symptom management in patients with rhabdomyosarcoma were not eligible.
- **Comparator:** Studies did not need to have a comparator group but were still eligible if reporting relevant outcomes.
- **Outcomes:** Survival (progression free survival, overall survival), Radiological response rates by RECIST criteria, Quality of Life (measured by specific assessment tools [eg, PedsQL] and also by experiential or qualitative data), side effects/adverse events, burden of therapy, costs/measures of cost-effectiveness.
- **Study Design:** Early phase studies, including single arms or randomized between two or more options, including, but not limited to: “First in child” studies (traditionally phase 1), Dose finding studies (traditionally phase 1b/2a), Proof of concept/efficacy studies

(traditionally phase 2b), Early effectiveness studies (traditionally phase 2b/3). Studies were excluded if enrolment ceased before 2000. With regards to publication type, we included full-text articles, conference abstracts and clinical trial registry records.

Screening was conducted independently and in duplicate by at least two researchers (CE, LB, JEM and GB). Conflicts were resolved by a third reviewer or discussion with the review team. Authors of full-text publications were contacted to clarify whether studies were eligible for inclusion if the information provided was unclear (eg, if the study enrolled participants with rhabdomyosarcoma but the age of these participants was not reported). Authors of clinical trial registrations were contacted if the trial was completed but no corresponding publication could be identified.

2.3 | Data extraction

Before data extraction, eligible clinical trial registrations, conference abstracts and full-text publications were linked. For studies where multiple sources of data were available, data were extracted from the source with the most information.

Data extraction was performed by one reviewer (CE, LB and JEM) and checked by a second (CE, LB and JEM). Disagreements were resolved following discussion with the review team. For full-text publications and conference abstracts, patient demographic and disease characteristics were extracted for all patients unless rhabdomyosarcoma specific data were available; adverse event data were extracted for all participants; and data regarding clinical outcomes were extracted for rhabdomyosarcoma patients only (see Data S1 for the full-text data extraction template).

2.4 | Quality assessment

Quality assessment was conducted by one reviewer (CE, LB and JEM) and checked by a second (CE, LB and JEM), using a modified version of the Downs and Black Checklist¹³ (see Data S1), owing to the absence of any validated quality assessment tool for early phase studies. Two questions regarding the external validity (Questions 11 and 12) were removed as they were not deemed relevant for early phase studies. For single-arm studies, only 15 of the 27 items were applicable. Quality assessment was only conducted for full-text publications and conference abstracts. Disagreements were resolved by consensus.

2.5 | Synthesis

Meta-analyses were planned but were not performed due to significant heterogeneity in the included interventions. A narrative synthesis was performed. Results are presented in order of importance to the parent advisory group.

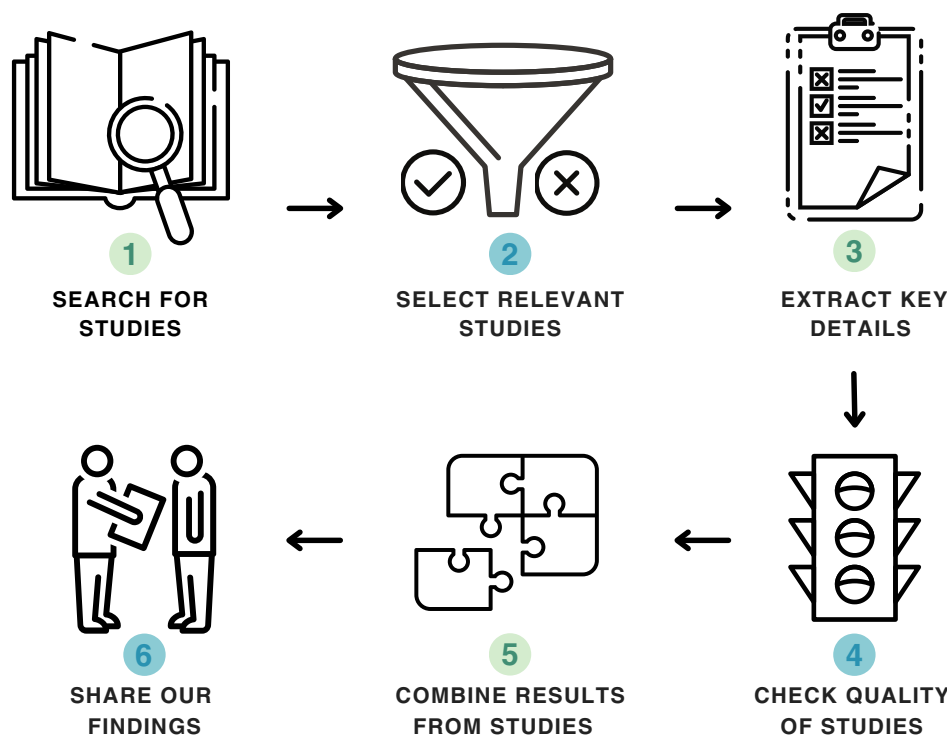


FIGURE 1 Infographic describing the systematic review process.

3 | RESULTS

3.1 | Study selection

From 16,965 studies identified from the database searches, 584 were deemed eligible at title and abstract screening, including 203 clinical trial registry records, 99 conference abstracts and 282 full-text publications. An additional 83 studies and clinical trial registry records were identified by additional searches, 32 of which were eligible for inclusion (Supporting Information Refs. S1–S32). Of the 75 authors contacted for further information, 32 replied (43% response rate) and four studies (Supporting Information Refs. S13, S24, S33, S34) were eventually included. Excluded studies information is provided in the Data S1.

Overall, 122 studies from 124 full-text articles (Supporting Information Refs. S1–S27, S33–S129) alongside seven studies from conference abstracts (Supporting Information Refs. S28, S130–S135), were included in the synthesis of published studies ($n = 129$). Three of these studies (Supporting Information Refs. S63, S92, S94) included seven non-comparative arms which have been extracted separately, resulting in a total of 133 individual cohorts being included in the synthesis. Where applicable, the data has been explicitly reported as either the number of cohorts or number of studies. An additional 107 clinical trial registry records of 99 trials were included in the synthesis of clinical trial data. Further details of the study selection process are provided in Figure 2.

3.2 | Quality assessment

One hundred and twenty single-arm studies (Supporting Information Refs. S1, S3–S27, S33–S47, S49–S62, S64–S89, S93, S95–S105,

S108–S111, S113–S135) and three non-comparative, multiarm studies (Supporting Information Refs. S63, S92, S94) were assessed using a 17-item modified Downs and Black checklist.¹³ In general, studies reported the methods and results well, although several studies did not report study selection criteria. Similarly, almost 20% did not provide random variation of the data, and almost 20% did not report adverse events appropriately. Internal validity was deemed to be at low risk of bias across the studies included.

Six multiarm, comparative studies (Supporting Information Refs. S2, S28, S90, S91, S106, S112) were assessed using the 27-item Downs and Black Checklist,¹³ with the majority of studies providing comprehensive reporting of their trial. The internal validity across the studies was mixed; although subjects were randomized in five of the six studies, randomization was only concealed in one of those studies. Only one study blinded participants to the intervention, and two blinded assessors to the intervention. Studies did use appropriate statistical tests and outcome measures.

For all studies, external validity was difficult to determine. By their very nature, early phase studies often investigate novel drugs only available in highly specialized centers and have stringent eligibility criteria. Risk of bias assessments are summarized in Figure 3, with further details provided in Data S1.

3.3 | Synthesis—Completed and included studies

3.3.1 | Demographics of completed, included studies

Across the 129 studies, over 1100 children and young people with relapsed/refractory rhabdomyosarcoma were included. A

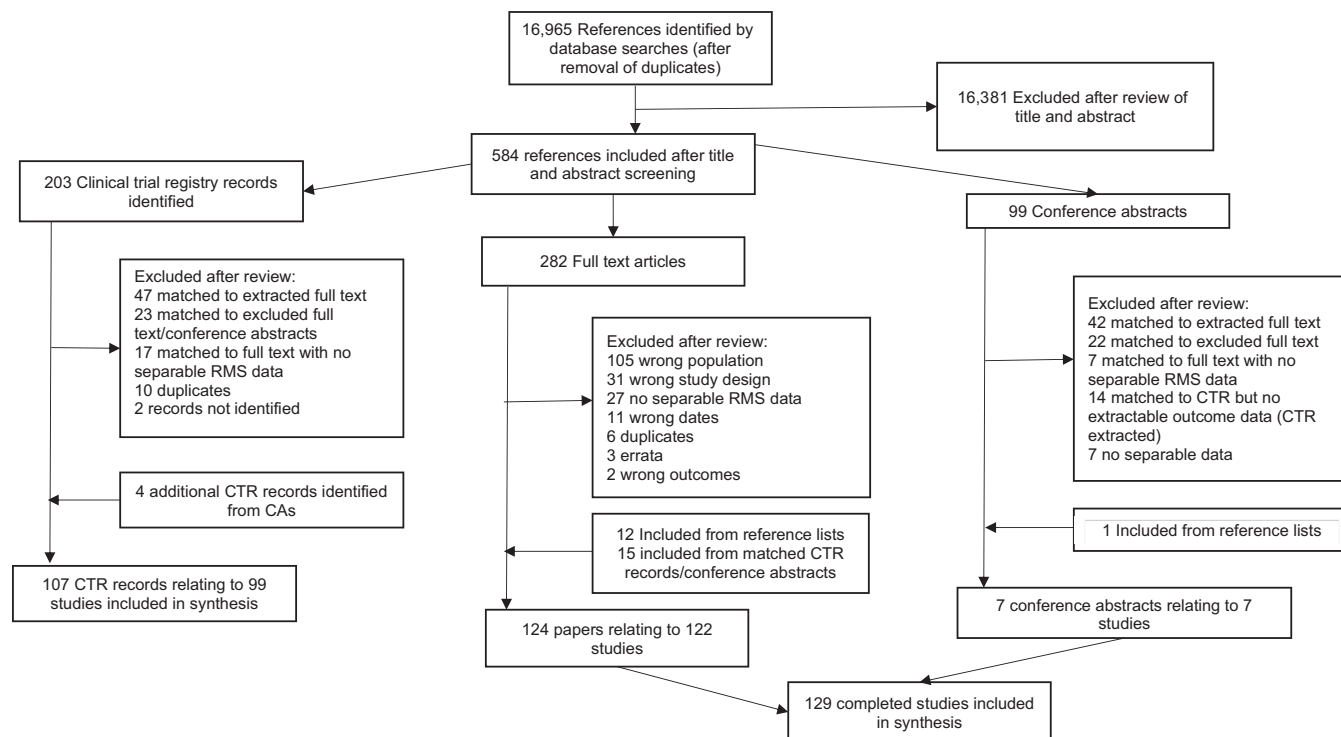


FIGURE 2 Flowsheet for study selection.

summary of characteristics of the included studies is provided in Table 1.

Studies primarily investigated systemic therapies. The majority of studies were conducted in the United States, and across Europe. Only 10% of studies were conducted in Low/Middle Income Countries according to World Bank criteria (Supporting Information Ref. S136). Where reported, most studies were conducted in multiple centers (76%).

Patient demographics for children and young people with rhabdomyosarcoma specifically were often not reported. Where it was reported, children and young people with rhabdomyosarcoma were mostly 10 years or older with only eight cohorts including children under the age of 3 years. There were slightly more males than females included (54.8% male), but this was deemed to be representative of children and young people with rhabdomyosarcoma. Where reported, most children and young people were white.

3.3.2 | Clinical effectiveness

Data relating to clinical effectiveness outcomes are presented in Table 2.

3.3.3 | Survival outcomes

Only 27 studies (21%) reported data on progression free survival (PFS) or time to progression (TTP) (Supporting Information Refs. S1, S2, S10, S12, S14, S15, S20, S22, S34–S36, S44, S51, S56, S67, S72, S88, S90, S91, S98, S106, S112, S115, S117, S131, S134). Where reported ($n = 19$), the

median PFS/TTP was ≤ 6 months in 70% of studies (Supporting Information Refs. S1, S2, S14, S15, S20, S22, S34–S36, S56, S67, S88, S91, S112, S115, S117, S134) and no single-agent therapy (either standard or novel interventions) reported a PFS of >2 months. Overall survival (OS) was reported in 26 studies (20%) (Supporting Information Refs. S1, S2, S12, S14, S16, S25, S35, S36, S44, S48, S56, S73, S78, S79, S88, S90–S92, S101, S105, S106, S115–S117, S128, S134). Where the median OS was reported ($n = 23$ cohorts [S1, S2, S12, S14, S35, S36, S56, S73, S78, S79, S88, S91, S101, S105, S106, S115–S117, S128, S134, S135]), it was ≤ 6 and 12 months in $\sim 30\%$ and $\sim 61\%$ of cohorts, respectively.

3.3.4 | Quality of life

Two studies reported data on quality of life (not rhabdomyosarcoma-specific). Pramanik et al reported no difference in self-reported quality of life between children and young people who received metronomic chemotherapy or placebo (Supporting Information Ref. S106). El Kababri et al reported an improvement in Karnofsky/Lansky scores for 15% of children and young people, although we note that Karnofsky/Lansky scores are performance status measures, rather than standard measures of quality of life (Supporting Information Ref. S57).

3.3.5 | Response rates

Overall, 59 of 1151 children and young people showed a complete response (CR), and 190 experienced a partial response (PR).

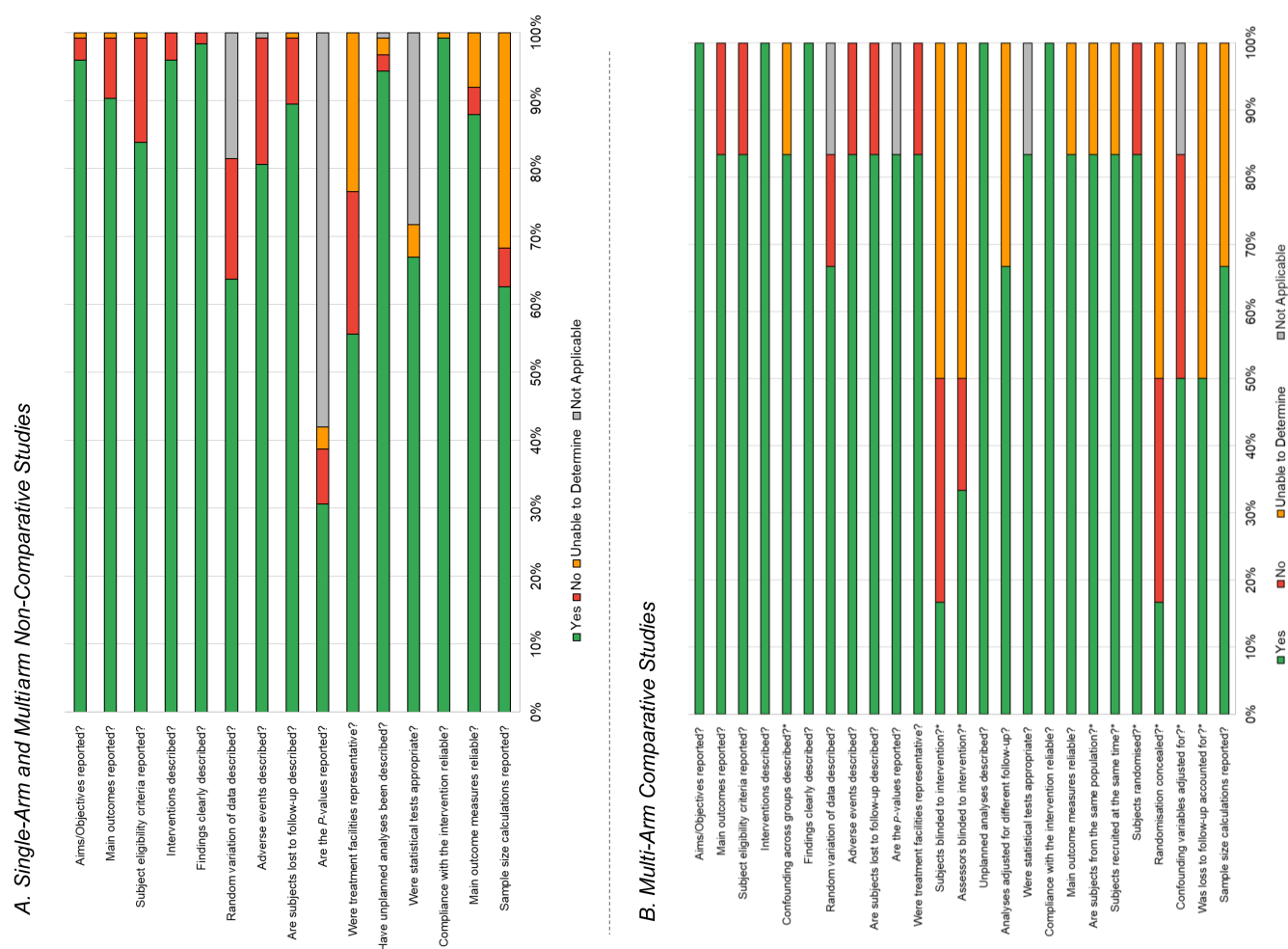


FIGURE 3 Risk of bias assessment for single arm and multiarm non-comparative studies (A) and multiarm comparative studies (B).

Therefore, the objective response rate (CR + PR) across all interventions for children and young people with relapsed and refractory rhabdomyosarcoma was 21.6%. Cohorts reporting more than 10 children and young people with relapsed and refractory rhabdomyosarcoma, where the objective response rate is greater than 30% have been identified in blue fill within Table 2. Ten cohorts reported a 100% response rate amongst children and young people with rhabdomyosarcoma, but these studies all had fewer than five participants, so results should be interpreted with caution (Supporting Information Refs. S8, S10, S14, S33, S62, S72, S96, S105, S128, S131). Where data was reported separately for children and young people with a first-relapse, the overall response rate was 33.7% (29/86 children and young people, from seven cohorts [Refs. S12, S42, S53, S74, S92, S108, S112]). No studies assessed differential efficacy by ethnicity or sex. Other planned subgroup analyses were unable to be performed due to availability of data.

3.3.6 | Adverse events

Data on adverse events of interventions included in this systematic review were available for over 4500 children and young

people (not rhabdomyosarcoma-specific). Although the majority of studies used a standardized tool (including the Common Terminology Criteria for Adverse Events [CTCAE], and the World Health Organisation [WHO] classification), the reporting of adverse events varied across studies making it difficult to synthesize the data. Hematological adverse events were most common. Laboratory test abnormalities were also common, although the impact of these on children and young people's symptoms was unclear.

3.3.7 | Deaths

Nineteen studies (15%) explicitly reported deaths (Supporting Information Refs. S1, S3, S5, S10, S11, S19, S22, S24, S65–S67, S76, S82, S91, S103, S112, S115, S128, S134). From these studies 69 deaths were reported out of a total of 1011 patients. Nine deaths were deemed to be related to the study treatment, while 32 were due to progressive disease. Children and young people progressed both early within a study (either before the intervention was administered or within the first cycle of the intervention) and within 30 days of treatment administration.

TABLE 1 Summary of study characteristics and demographics of included children and young people from the included studies.

Demographics	Provided by	Findings
Intervention characteristics		
Intervention	133 cohorts (100%)	Single-Arm/Non-Comparative: 127 cohorts Chemotherapy: 106 cohorts <i>Standard single-agent systemic therapy</i> (29, 21.8% of all cohorts), <i>standard multiagent systemic therapy</i> (24 [18.0%]), <i>novel single-agent systemic therapy</i> (24 [18.0%]), <i>novel multiagent systemic therapy</i> (22 [16.5%]), <i>biomarker-driven therapies</i> (4 [3.0%]), <i>metronomic chemotherapy</i> (3 [2.3%]) Other interventions: 21 cohorts [15.8%] <i>Cellular therapies</i> (6 [4.5% of all cohorts]), <i>vaccine therapies</i> (6 [4.5%]), <i>HSCT</i> (5 [3.8%]), <i>other approaches</i> (4 [3.0%]) Comparative Studies: six cohorts <i>Comparing standard systemic therapy regimens</i> (2 [1.5% of all cohorts]), <i>comparing dosing schedules</i> (1 [0.8%]), <i>comparing novel agents added to multiagent systemic therapy</i> (1 [0.8%]), <i>comparing metronomic chemotherapy vs best supportive care</i> (1 [0.8%]), <i>sibling vs matched donor allogeneic HSCT</i> (1 [0.8%]) (112)
Method of administration	128 cohorts (95%)	<i>Intravenous</i> (71 [55.5%]), <i>Intravenous and Oral</i> (22 [17.2%]), <i>Oral</i> (22 [17.2%]), <i>Intradermal</i> (3 [2.3%]), <i>Intravenous and Subcutaneous</i> (2 [1.6%]), <i>Other</i> (8 [6.3%])
Study characteristics		
Country	115 studies (89%)	North America: <i>Canada</i> (8), <i>USA</i> (71) Europe: <i>Austria</i> (1)(122), <i>Belarus</i> (1), <i>Czech Republic</i> (1), <i>Denmark</i> (1), <i>Europe NOS</i> (3), <i>France</i> (13), <i>Germany</i> (8), <i>Hungary</i> (1), <i>Italy</i> (16), <i>Netherlands</i> (6), <i>Poland</i> (1), <i>Russia</i> (2), <i>Slovakia</i> (1), <i>Spain</i> (6)(2, 3, 6, 87, 105, 109, 134), <i>Sweden</i> (1), <i>Switzerland</i> (1), <i>UK</i> (8) Asia: <i>China</i> (2), <i>India</i> (1), <i>Japan</i> (7), <i>South Korea</i> (2) Africa/Middle East: <i>Egypt</i> (1), <i>Israel</i> (2), <i>Morocco</i> (1), <i>Turkey</i> (2) Oceania: <i>Australia</i> (3), <i>New Zealand</i> (1) South America: <i>Brazil</i> (3) *Note that the number of studies is greater than 115 as many studies were conducted across multiple countries
Single or multicenter	96 studies (74%)	Single center: 23 studies [24.0%] Multicenter: 73 studies [76.0%]
Trial phase	101 studies (78%)	Phase I: 54 studies [53.5%] Phase I/II: 10 studies [9.9%] Phase II: 35 studies [34.7%] Phase III: 1 study [1.0%] Molecular Registry Study: 1 study [1.0%]
Population eligibility	129 studies	Seven studies [5.4%] recruited rhabdomyosarcoma patients only Most studies only included patients with relapsed/refractory disease ($n = 94$ [73%])
Population characteristics		
Age	49 cohorts (37%) RMS specific	22 cohorts (45%) included patients with a median age ≥ 10 years. Eight cohorts (16%) included children and young people under the age of 3 years. Of the 34 studies that reported the age range for patients with RMS, nine [26%] included a minority of participants over the age of 18 years, whose data could not be separated from that of younger participants (2, 25, 40, 44, 51, 56, 67, 120)
Sex/gender	34 cohorts (26%) RMS specific	Where both male and female children and young people were reported, 54.8% were male. Sex/gender was reported as a single binary characteristic.
Ethnicity/race	7 cohorts (5%) RMS specific	Ethnicity and race were reported variably. White: 44 [70%]; Black: 9 [14%]; Other: 6 [10%], Unknown/Not Reported: 4 [6%]

Note: Detailed demographic information for each study can be found in the project's full report.²⁴

Abbreviations: HSCT, hematopoietic stem cell transplant; NOS, not otherwise specified; RMS, rhabdomyosarcoma; UK, the United Kingdom; USA, the United States.

TABLE 2 Disease response and survival outcomes for the included, published studies.

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Standard systemic therapy—single agent										
Pegylated Liposomal Doxorubicin (Doxil)	Marina, 2002 (S89)	2 ^c R + R RMS	0	0			0% ^d	NR	NR	No objective responses. Two RMS patients either SD, PD or non-evaluable (at least one evaluable)
Etoposide	Kebudi, 2004 (S79)	2 relapsed, 2 refractory RMS	1	1	0	2	50% ^d	NR	8.5 (2 to >94)	Three of four patients had previously received etoposide. Response duration: 10 months for patient with PR, 87 months for patient with CR
Gemcitabine	Wagner-Bohn, 2006 (S122)	3 relapsed RMS	0	0	0	3	0% ^d	NR	NR	
High-dose Ifosfamide	Meazza, 2010 (S97)	5 R + R RMS	0	1	1	3	20% ^d	NR	NR	
High dose Ifosfamide	Yalcin, 2004 (S128)	1 R + R RMS	1	0	0	0	100% ^d	NR	97.5	
Temozolomide	De Sio, 2006 (S56)	2 R + R RMS	0	0	0	2	0% ^d	1 (range N/A)	2.5 ^d (2, 3)	
Irinotecan	Vassal, 2007 (S117)	20 1st relapse, 10 2nd relapse, 5 refractory	1	3	6	24	11.4% (95% CI: 3.2%– 26.7%)	1.38 (95% CI: 1.22–1.61)	5.81 (95% CI: 4.27–9.36)	1 not assessable. Response durations: 7.8 months for patient with CR and 2.8, 3.7 and 6.4 months for patients with PR
Irinotecan	Makimoto, 2019 (S7)	4 R + R RMS	0	0	3	1	0% ^d	NR	NR	SD lasted >8 weeks for 1 patient with RMS, and >24 weeks for a second patient with RMS
Irinotecan	Shitara, 2006 (S111)	3 R + R RMS	0	1	0	2	33.3% ^d	NR	NR	
Irinotecan	Bomgaars, 2007 (S46)	18 R + R RMS	0	1			5.6% ^d	NR	NR	17 other evaluable RMS patients not clearly reported
Irinotecan	Bisogno, 2005 (S43)	12 R + R RMS		2		6	16% ^d	NR	NR	3 minor responses, 1 no response Response outcomes inconsistent with demographic data
Irinotecan	Furman, 2006 (S64)	4 ^c R + R RMS	0	0	0		0% ^d	NR	NR	No complete or partial responses. Between 0 and 3 patients with RMS had PD (based on number evaluable)
Irinotecan	Blaney, 2001 (S17)	2 ^c Refractory RMS	0	0	0	At least 1	0% ^d	NR	NR	At least 1 patient had PD. One patient unclear if PD or non-evaluable
Irinotecan (weekly)	Bomgaars, 2006 (S45)	2 R + R RMS	0	0	1		0% ^d	NR	NR	1 pt NR but assumed PD. One patient in each stratum (where stratified by previous treatment)

TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Topotecan	Hawkins, 2006 (S71)	9 R + R RMS	0	0			0% ^d	NR	NR	9 RMS patients evaluable with no objective response and either SD/PD. 2 patients with SD had STS but unclear if these had RMS or not
Topotecan	Santana, 2003 (S24)	1 R + R RMS	0	0	0	1	0% ^d	NR	NR	Response data provided via email communication with authors
Docetaxel	Zwerdling, 2006 (S129)	8 R + R RMS	1	0	1	6	12.5% ^d	NR	NR	
Ixabepilone	Widemann, 2009 (S126)	3 R + R RMS	0	0	0		0% ^d	NR	NR	3 evaluable RMS, assumed PD but not explicitly reported
Ixabepilone	Jacobs, 2010 (S76)	10 R + R RMS	0	0			0% ^d	NR	NR	No partial or complete responses were observed
Nab-paclitaxel	Amoroso, 2020 (S36)	14 R + R RMS	0	1	0	11	7.1%	5.1 weeks (95% CI: 2.1–7.9)	19.6 weeks (95% CI: 4.0–25.7)	2 additional unconfirmed PR
Nab-paclitaxel	Moreno, 2018 (S102)	12 R + R RMS	0	1	1	9	8.3% ^d	NR	NR	
Oxaliplatin	Beaty, 2010 (S40)	10 R + R RMS	0	0	0	10	0% ^d	NR	NR	
Oxaliplatin	Geoerger, 2008 (S18)	2 ^c R + R RMS	0	0			0% ^d	NR	NR	At least one PD or SD, and one unclear if PD/SD or non-evaluable
Oxaliplatin	Spunt, 2007 (S26)	1 Refractory RMS	0	0	0	1	0% ^d	NR	NR	
Pemetrexed	Warwick, 2013 (S123)	8 R + R RMS	0	0	0	8	0% ^d	NR	NR	
Trabectedin	Baruchel, 2012 (S39)	20 R + R RMS	0	1	1	18	5% ^d	NR	NR	
Vinorelbine	Kuttesch, 2009 (S84)	11 R + R RMS	1	3	6	1	36%	NR	NR	DOR: 2 courses for pt with CR and 2 with PR; 3 course for other pt with PR. No responses observed among 3 patients with embryonal RMS.
Vinorelbine	Casanova, 2002 (S50)	12 R + R RMS	0	6	1	4	50% (21%–79%)	NR	NR	Response rate for alveolar RMS 83% (95% CI: 36%–99%) 1 patient had minor response DOR for patients with PR: median 10 months (range 3.5+ to 15 months)
Vinorelbine	Johansen, 2006 (S19)	At least 1 relapsed RMS		1			NR	NR	NR	7 patients with STS, at least one relapsed RMS, who had PR and completed 16 weeks of therapy before disease progression

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TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Standard systemic therapy—multiple agents										
Cisplatin, Irinotecan, Amifostine	Souid, 2003 (S113)	3 Refractory RMS	0	0	3	0	0% ^d	NR	NR	Median number of course (1.5). One patient with RMS received at least 3 course (~18 weeks)
Cisplatin + topotecan	Wells, 2002 (S125)	6 R + R RMS		1			NR	NR	NR	Five other RMS pts, unclear if all evaluable or their response
Escalation of cyclophosphamide in VETOPEC regimen	McCowage, 2011 (S95)	4 R + R RMS	1	3	0	0	100% ^d	NR	NR	One RMS patient with PR still alive after 48 months from study entry
Cyclophosphamide + topotecan	Saylors, 2001 (S110)	15 R + R RMS	0	10		2	67%	NR	NR	Three had mixed response or SD. Outcomes for each RMS subgroup also reported
Decitabine, Doxorubicin, Cyclophosphamide	George, 2010 (S69)	1 R + R RMS	0	0	1	0	0% ^d	NR	NR	
Etoposide, Vincristine, Epirubicin, High dose cyclosporin (EVE/cyclosporin)	Davidson, 2002 (S53)	2 1st relapse, 1 2nd relapse, 1 7th relapse	0	1	2	1	25% ^d	NR	NR	Two RMS patients had vincristine only, 1 doxorubicin/vincristine/etoposide and 1 etoposide/vincristine
Gemcitabine + oxaliplatin	Geoerger, 2011 (S66)	12 R + R RMS	0	1	0	11	8.3% ^d	NR	NR	
Ifosfamide, Carboplatin, Etoposide	Loss, 2004 (S22)	1 relapsed, 1 refractory RMS	0	1	1	0	50% ^d	6 ^d (5–7)	NR	One RMS patient had partial response after 4 courses and was alive with SD at the end of study. The other RMS patient had SD after 6 courses but died from toxicity
Ifosfamide, Oxaliplatin, Etoposide	Lam, 2015 (S85)	3 R + R RMS	0	0	2	1	0% ^d	NR	NR	
Irinotecan + VAC	Bisogno, 2021 (S42)	7 first relapse RMS	2	3	2	0	71.4% ^d	NR	NR	Response after 3 cycles RMS patients with CR alive with NED at 48 months and 3 months. All other patients DOD
Oxaliplatin + Doxorubicin	Mascarenhas, 2013 (S93)	2 R + R RMS	0	0	0	2	0% ^d	NR	NR	
Oxaliplatin + Irinotecan	McGregor, 2009 (S8)	2 ^c R + R RMS	1	0	0		NR	NR	NR	1 RMS patient not clearly reported—PD or not evaluable
Topotecan + Temozolomide	Le Teuff, 2020 (S87)	8 R + R RMS	0	0	3	5	0% ^d	NR	NR	
	Rubie, 2010 (S23)	1 R + R RMS	0	0	1	0	0% ^d	7	NR	

TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Topotecan + temozolomide										
Temozolomide, Irinotecan, Temozolomide	Bagatell, 2014 (S38)	4 ^c R + R RMS	0	0	1		0% ^d	NR	NR	3 RMS patients NR, may not be evaluable for response SD lasted at least 9 cycles for this RMS patient
Topotecan, carboplatin, Cyclophosphamide, Etoposide	Compostella, 2019 (S51)	32 R + R RMS	2	7	9	11	28%	14% at 5 years	NR	3 had minor response Response rate by histology: • 35% (6/17) for alveolar RMS • 20% (3/15) for non-alveolar RMS Response did not significant differ between patients with an early vs late relapse (33% vs 26%)
Topotecan + ifosfamide	Kawamoto, 2010 (S133)	4 R + R RMS	0	1			25% ^d	NR	NR	3/4 RMS did not respond but not sure of their exact outcome
Topotecan, Ifosfamide, Carboplatin	Radhakrishnan, 2015 (S108)	1 1st relapsed RMS			1		0% ^d	NR	NR	RMS patient received only 1 cycle
Topotecan, Vincristine, Doxorubicin	Meazza, 2009 (S98)	6 R + R RMS (most relapsed)	1	4			83% ^d	7 (3–15)	NR	1 RMS patient had minor response 5/6 evaluable patients later relapsed
Vincristine, Irinotecan, Temozolomide	McNall-Knapp, 2010 (S96)	1 R + R RMS	1	0	0	0	100% ^d	NR	NR	RMS patient had PR after 2 cycles, and CR after cycle 6—then went on to have autologous HSCT.
Vincristine, Oral Irinotecan, Temozolomide (VOIT)	Wagner, 2010 (S121)	6 ^c R + R RMS	0	0	0		0% ^d	NR	NR	All RMS patients (between 3 and 6 evaluable) had PD but unclear how many were evaluable
Vinorelbine + low-dose cyclophosphamide	Casanova, 2004 (S49)	8 R + R RMS	1	2	2	3	37.5% ^d	NR	NR	DOR: Embryonal RMS Male (9 year) SD alive at 1 month; Embryonal RMS Female (18 year) PR DOR = 8 month, DOD 12 month; Embryonal RMS Female (12 year) PR, DOR = 5 month, DOD 10 month; Embryonal RMS Female (13 year) SD, DOR = 8+ month, receiving treatment; Alveolar RMS Male (16 year), CR, DOR = 10+ month, receiving treatment

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TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Vinorelbine + low-dose cyclophosphamide	Minard-Colin, 2012 (S101)	50 R + R RMS Results after 2 cycles	3	14	12	21	34% (95% CI: 21–47%)	NR	9 (95% CI: 6– 12)	3/4 RMS patients who achieved CR relapsed at 10, 12 and 56 months after CR. The 4th patient remains alive with no evidence of recurrence of disease, 3.6 years after achieving a CR Median DOR for 14 PR patients = 7 months (range 0.5– 35 months) Response was dependent on disease status at enrolment: patients with an untreated relapse achieved a 45% ORR (95% CI: 27%–63%), versus only 16% (95% CI: 0%–32%) of patients with a refractory disease or a refractory relapse (P = .04). None of the five patients with primary refractory RMS achieved a CR or a PR
		Results over whole duration of treatment	4	14	11	21	36% (95% CI: 23–49%)			
Novel agents—single agent										
Everolimus (MoA:mTORs) <i>(This conference abstract represents data from a study with an unknown trial status, and so the trial registry record has also been extracted— NCT01216839)</i>	Epelman, 2015 (S132)	6 ^c R + R RMS		1			NR	NR	NR	5 RMS NR—either SD, PD or non- evaluable. PR in RMS patient lasted 11 months
Temsirolimus (MoA: mTORs)	Geoerger, 2012 (S67)	13 R + R RMS (most refractory)	0	0	4	9	0% ^d	39 days (95% CI: 23– 48 days)	NR	One patient with RMS who achieved SD at 12 weeks achieved confirmed PR during week 18. Median duration of SD or better for RMS was 75 days (95% CI: 56–256)
Alisertib (MoA:AKI)	Mosse, 2019 (S11)	10 R + R RMS	0	0	1	7	0% ^d	NR	NR	Two non-responders (unclear if these are SD) Patient with SD had 15 cycles RMS patient followed-up for 48 days
Apatinib (MoA:VEGFR-2 TKI)	Liu, 2020 (S33)	1 R + R RMS	0	1	0	0	100% ^d	NR	NR	
Lenvatinib (MoA:multi-TKI)	Gaspar, 2021 (S4)	5 ^c R + R RMS	0	0			0% ^d	NR	NR	Unclear whether RMS patients had SD, PD or not evaluable (at least 4 were evaluable)

TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Regorafenib (MoA:multi-TKI) (This full-text represents data from the dose escalation stage of a trial. As trial remains active, not recruiting, the trial registry record has also been extracted—NCT02085148)	Geoerger, 2021 (S68)	3 ^c R + R RMS	0	1	1		NR	NR	NR	1 PR reported as unconfirmed (tumor shrinkage—35%) Patient with SD for 16.2 weeks 1 RMS NR (could be SR, PD or non-evaluable)
Pazopanib (MoA:multi-TKI)	Lee 2015 (conference abstract). Clinical trial registry 2020 (S134)	12 R + R RMS					8.3% (90% CI: 0.4–33.9%)	1.8 (90% CI: 1.0–1.8)	5.6 (90% CI: 2.2–14.2)	1 RMS patient achieved either confirmed CR or confirmed PR or SD for at least two protocol-scheduled disease assessments
Pazopanib (MoA:multi-TKI)	Glade Bender, 2013 (S70)	5 ^c R + R RMS	0	0	1		0% ^d	NR	NR	Four RMS patients either PD or not evaluable. RMS patient with SD had SD for ≥6 months
Sorafenib (MoA:multi-TKI)	Kim, 2015 (S81)	10 R + R RMS	0	0			0% (0%–26%)	NR	NR	10 had no objective response, and not SD so PD assumed
Sorafenib (MoA:multi-TKI)	Widemann, 2012 (S127)	4 ^c Refractory RMS	0	0			0% ^d	NR	NR	No confirmed objective response but the number of RMS evaluable is unclear
Ispinesib (MoA:kinesin spindle protein inhibitor)	Soud, 2010 (S114)	2 R + R RMS	0	0			0% ^d	NR	NR	2 RMS patients evaluable but not clearly reported and assumed PD
Sonidegib (LDE225) (MoA: hedgehog pathway inhibitor)	Kieran, 2017 (S80)	4 ^c R + R RMS	0	0	0		0% ^d	NR	NR	3–4 patients with PD
Bevacizumab (MoA:Anti-VEGF mab)	De Pasquale, 2011 (S55)	2 Relapsed RMS	1				NR	NR	NR	1 RMS response NR Duration on treatment: 1 and 5 months
Cixutumumab (MoA:insulin like growth factor mab)	Weigel, 2014 (S124)	20 R + R RMS	0	1	3	16	5% ^d	NR	NR	RMS patient with PR completed 10 cycles. RMS patients with SD completed 5, 7 and 22 cycles
Depsipeptide (MoA: histone deacetylase inhibitor)	Fouladi, 2006 (S60)	4 R + R RMS	0	0	1		NR	NR	NR	Three patients could have had PD or not evaluable SD was for 7 courses
Ipilimumab (MoA:CTLA-4 mab)	Merchant 2016b (S100)	2 ^c R + R RMS	0	0			0% ^d	NR	NR	RMS could have been SD, PD or non-evaluable
Lexatumumab (MoA: TRAIL-R2 mab)	Merchant, 2012 (S9)	3 ^c relapsed RMS	0	0			0% ^d	NR	NR	Unclear if RMS patients were evaluable, had PD or SD

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TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Lorvotuzumab Mertansine (IMGN901) (MoA: antibody-drug conjugate [CD56 and mertansine])	Geller, 2020 (S65)	16 ^c R + R RMS		1			NR	NR	NR	15 other RMS patients NR but not clear if all evaluable or what their response was. RMS patient with PR was after cycle 2 then progressed after 11 cycles
Nivolumab (MoA:PDL1 inhibitor)	Davis, 2020 (S54)	11 R + R RMS	0	0	3	6	0% ^d	NR	NR	Two additional patients evaluable but response not clearly reported
Ontuxizumab (MORAb-004) (MoA: anti-endosialin mab)	Norris, 2018 (S104)	4 R + R RMS	0	0	0	4	0% ^d	NR	NR	One additional RMS patient had PD so did not complete cycle 1 (thus non-evaluable)
Rebeccamycin Analog (NSC no. 655649) (MoA: topoisomerase inhibitor)	Langevin, 2008 (S86)	20 R + R RMS	1	2			15% (4.3%–37.6%)	NR	NR	One not assessable, 16 evaluable patients NR – assumed to have PD Response duration: 19 months for pt with CR, 5 and 6 months for patients with PR
Rebeccamycin Analog (NSC no. 655649) (MoA: topoisomerase inhibitor)	Langevin, 2003 (S21)	1 Refractory RMS	0	0	1	0	0% ^d	NR	NR	
Seprehvir (MoA:protease inhibitor)	Streby, 2019 (S115)	1 R + R RMS	0	0	0	1	0% ^d	14 days	2 months	RMS patient had disease progression on day 14 and was taken off trial and given seprehvir + pazopanib at another institution—did have SD but eventually disease progressed and died from disease
<i>Novel agents—multiple agents</i>										
Vinblastine + Sirolimus	Morgenstern, 2014 (S52)	2 ^c R + R RMS		1			NR	NR	NR	One RMS patient response NR (could be non-evaluable). Reported patient had PR after 3 cycles, then PD 5 months after starting study medications
Sirolimus, Cyclophosphamide, Topotecan	Vo, 2017 (S118)	3 R + R RMS	0	0	0	3	0% ^d	NR	NR	
Celecoxib + vinblastine	Stempak, 2006 (S27)	3 R + R RMS	0	0	1		0% ^d	NR	NR	Two other RMS patients evaluable with either SD or PD One RMS patient had SD and was taken off study at 30 weeks.
Erlotinib ± Temozolomide	Jakacki, 2008 (S77)	8 ^c R + R RMS	0	0			0% ^d	NR	NR	Between 5 and 8 RMS patients had either SD or PD. Up to 3 patients non-evaluable

TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Regorafenib, Vincristine, Irinotecan (<i>This conference abstract represents a subset of patients. As trial remains active, not recruiting, the trial registry record has also been extracted—NCT02085148</i>)	Casanova, 2020 (S130)	12 R + R RMS	1	5			50% ^d	NR	NR	6 other RMS did not have a response but exact outcome NR (one did have PR after data cut-off)
Sorafenib + Topotecan	Reed, 2016 (S34)	1 R + R RMS	0	0	0	1	0% ^d	44 days	NR	
Talazoparib + Irinotecan	Federico, 2020b (S59)	3 R + R RMS	0	0	0	3	0% ^d	NR	NR	PD after 1 course in 2 patients, and 2 courses in 1 patient
Talazoparib + Temozolomide	Schafer, 2020 (S13)	1 R + R RMS	0	0	0	1	0% ^d	NR	NR	RMS patient progressed after 1 cycle
Bevacizumab, Sorafenib, Low-Dose cyclophosphamide	Federico, 2020a (S58)	1 R + R RMS	0	0	1	0	0% ^d	NR	NR	
Bevacizumab, Sorafenib, Low-Dose cyclophosphamide	Navid, 2013 (S103)	2 ^c R + R RMS	0	1	0		NR	NR	NR	1 patient with RMS who had either PD or was not evaluable for response
Vincristine, oral Irinotecan + Temozolomide (VOIT) + Bevacizumab	Wagner, 2013 (S119)	1 R + R RMS	0	0	0	1	0% ^d	NR	NR	PD after 3 cycles
Cixutumumab + Temsirolimus	Fouladi, 2015 (S61)	9 ^c R + R RMS	0	0	1		NR	NR	NR	Up to 8 more RMS patients, either PD or not evaluable for response. Patient with SD had over 3 cycles
Cixutumumab + Temsirolimus	Wagner, 2015 (S120)	11 R + R RMS	0	0	2		0% ^d	NR	NR	9 not clearly reported but not CR/PR/SD. Of the two RMS patients with SD, 1 received 6 cycles and the other received 4 cycles
Perifosine + Temsirolimus	Becher, 2017 (S41)	1 R + R RMS	0	0	0	1	0% ^d	NR	NR	
Reovirus (Reolysin) ± Cyclophosphamide	Kolb, 2015 (S82)	6 ^c R + R RMS	0	0			0% ^d	NR	NR	Between 1 and 6 RMS patients (based on number of patients evaluable) progressed. Either within 28 days, or after a second or third cycle following SD

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TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Tariquidar + Doxorubicin	Fox, 2015 (S62)	1 R + R RMS	0	1	0	0	100% ^d	NR	NR	PR after 4 cycles. Further protocol therapy was declined and radiation was received to achieve CR. They later died of complications of recurrent RMS
Tirapazamine + Cyclophosphamide	Aquino, 2004 (S37)	3 ^c Refractory RMS	0	1	1		NR	NR	NR	1 RMS patient NR—either PD or non-evaluable RMS patient with PR received 11 cycles. RMS patient with CR received at least 3 cycles
<i>Biomarker-driven studies</i>										
Atezolizumab (known or expected PDL1 involvement)	Geoerger, 2020b (S6)	9 R + R RMS	0	0	0	9	0% ^d	NR	NR	
Pembrolizumab (PDL1 positive only)	Geoerger, 2020a (S5)	5 R + R RMS	0	0	3	2	0% ^d	NR	NR	
Ceritinib (ALK-positive tumors)	Fischer, 2021 (S3)	12 ^c R + R RMS			2		NR	NR	NR	1 patient with “no-complete response or no-progressive disease.” Other 9 unreported
Personalized medicine (RMS patients both received crizotinib)	Worst, 2016 (S15)	2 relapsed RMS	0	0	0	2	0% ^d	(6 weeks to 6 months)	NR	Both RMS patients had PAX3:FOXO1 fusions. 1 had MET overexpression (intermediate priority) and KAT6A (very low priority). 1 had ALK overexpression (intermediate), FGFR overexpression (intermediate) and MET overexpression (intermediate)
<i>Metronomic chemotherapy</i>										
Metronomic—Thalidomide, Celecoxib, alternating Etoposide/ Cyclophosphamide	Kieran, 2005 (S20)	2 R + R RMS	0	0	0	2	0% ^d	10.5 weeks ^d (9–12 weeks)	NR	
Metronomic—Celecoxib, Vinblastine, Cyclophosphamide, Methotrexate; plus radiotherapy	Ali, 2016 (S16)	14 R + R RMS					NR	NR	70.7% at 1 year	Response rate NR
Metronomic—Cyclophosphamide, Etoposide, Valproic acid	El Kababri, 2020 (S57)	14 RMS (most R + R; possibly not all)	1	2	4	7	21.4% ^d	NR	NR	

TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
HSCT										
High-dose chemotherapy with autologous HSCT	Shiriae, 2013 (S131)	3 R + R RMS (of total 8 RMS patients)	0	3	0	0	100% ^d	See comment	NR	All patients received busulfan and melphalan whilst those who had tandem HDCT also received carboplatin and etoposide followed by etoposide and cyclophosphamide Whole RMS population (n = 8) had median PFS 142 days
Allogeneic HSCT	Prete, 2010 (S135)	8 ^c relapsed, 3 ^c refractory RMS					NR	NR	See comment	At time of transplant, 10 had PR and 1 had PD 5 RMS patients relapsed, other 6 RMS patients not clearly reported 1 year EFS 0.14 (standard error 0.12) 1 year OS 0.37 (standard error 0.16) 100 days probability of treatment-related mortality was 0.29 (standard error 0.14) for RMS patients.
Haplo-SCT with non- myeloablative conditioning	Perez-Martinez, 2012 (S105)	1 R + R RMS	1	0	0	0	100% ^d	NR	>56 (N/A)	RMS patient had PR before receiving SCT
Haplo SCT with reduced intensity conditioning (This full-text represents a subset of patients. The trial remains recruiting so the trial registry has also been extracted— NCT01804634)	Llosa, 2017 (S88)	2 R + R RMS					NR	102.5 (61– 144) days	7.9 (6–9.8) months	1 RMS patient in CR4 before treatment Responses NR
Reduced intensity allogeneic HSCT	Baird, 2012 (S1)	2 R + R RMS					NR	85 days ^d (70– 100)	45 months ^d (13–77+)	
Cellular therapies										
Autologous MSCs with oncolytic virus Icovir-5 (Celyvir)	Ruano, 2020 (S109)	1 R + R RMS	0	0	0	1	0% ^d	NR	NR	
Autologous lymphocyte infusion (D2) and dendritic cell vaccines, plus CYT107 (recombinant human IL7)	Merchant, 2016a (S99)	3 1st relapse, 1 2nd relapse RMS					NR	NR	NR	Of 4 relevant patients—3 alive no recurrence (no residual disease at immunotherapy), 1 DOD (had residual disease at immunotherapy).

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TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Consecutive donor-derived adoptive cellular immunotherapy after allogeneic HSCT	Merker, 2019 (S10)	1 relapsed RMS	1	0	0	0	100% ^d	11	NR	Patient died of relapsed disease
HER2 CAR-T cells (<i>This trial remains recruiting so total population number is up to date of current publication</i>)	Hegde, 2020 (S72)	1 Refractory RMS	1	0	0	0	100% ^d	See comment	NR	Fusion negative, HER2 positive Patient relapsed 6 months after initial course of CAR-T cells, received further CAR-T cells (with pembrolizumab) and achieved a second CR
LAK-cell therapy + whole-body hyperthermia	Ismail-zade, 2010 (S75)	4 ^c R + R RMS		2			NR	NE	NE	One RMS with “no result”—unclear if PD or unevaluable. 1 MR
TAA cytotoxic T cells (TAA-Ts)	Hont, 2019 (S74)	1 1st relapse, 2 2nd relapse RMS	0	0	3	0		NR	NR	Note: Patients had to express 1+ of the target tumor antigens: WT1, PRAME and/or survivin DOR: 12.5+, 10.9+ and 4.1+ months
<i>Other approaches</i>										
AMORE	Blank, 2009 (S44, S48)	9 relapsed RMS (1st or 2nd relapse only)						82% at 5 years (whole group B popn, includes 2 residual disease patient)	See comment	Three patients died (0.7, 0.8 and 9.9 years of follow-up)—one of local recurrence and lung metastases, 1 of distal metastases only and one of a second primary tumor: fibrosarcoma, respectively. Four patients had NED at the end of follow-up (14.1, 13.1, 6.0 and 9.2 years). 2 patients were alive (at 0.8 and 1.6 years, neither had recent follow-up data)
Intratumoral injection of HSV1716 (oncolytic herpes virus)	Streby, 2017 (S116)	1 relapsed RMS	0	0	1	0	0% ^d	NR	8	Patient had SD at 14 and 28 days
Radiofrequency Ablation + chemotherapy	Hoffer, 2009 (S73)	2 R + R RMS					NR	NR	5 (5–5)	1 RMS patient died from pneumonia, 1 RMS patient DOD
Transarterial chemoembolization (TACE)	Jiang, 2016 (S78)	6 ^c R + R RMS					NR	NR	16.7 (95% CI: 9.679–26.654)	Responses NR Differences in cancer pain VAS scores reported in article
<i>Non-comparative multiarm cohorts</i>										
Dalotuzumab (<i>monotherapy arm of study</i>)	Frappaz, 2016 (S63)	3 ^c R + R RMS	0	0			0% ^d	NR	NR	None of the RMS patients experienced a response or prolonged SD

TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Dalotuzumab + Ridaforolimus (combination arm of study)	Frappaz, 2016 (S63)	1 ^c R + R RMS	0	0			0% ^d	NR	NR	The RMS patient did not experience a response or prolonged SD
Doxorubicin, Cyclophosphamide, Etoposide, Ifosfamide, Tirapazamine (Regimen 2 of study)	Mascarenhas, 2019b (S92)	24 1st relapse RMS (ineligible for phase 2 window)	6	7			54%	NR	See comments	11 evaluable but response NR (either SD or PD) 3 year OS 39% (95% CI: 20%–57%) FFS: 21% (95% CI: 8%–37%)
		49 1st relapse RMS (failed phase 2 window)	0				22%	NR	See comments	3 year OS 24% (95% CI: 13%–37%) FFS: 17% (95% CI: 8%–29%)
Doxorubicin, Cyclophosphamide, Etoposide, Ifosfamide (Regimen 3 of study)	Mascarenhas, 2019b (S92)	14 1st relapse RMS					NR	NR	See comments	3 year OS 84% (95% CI: 50%–96%) FFS: 79% (95% CI: 47%–93%)
Olaratumab + Doxorubicin (Specific arm of study)	Mascarenhas, 2021 (S94)	5 R + R RMS	0	2	2	1	40% ^d	NR	NR	Response rate relates to patients with measurable disease
Olaratumab, Irinotecan, Vincristine (Specific arm of study)	Mascarenhas, 2021 (S94)	5 R + R RMS	1	0	2	2	20% ^d	NR	NR	Response rate relates to patients with measurable disease
Olaratumab + Ifosfamide (Specific arm of study)	Mascarenhas, 2021 (S94)	1 R + R RMS	0	0			0% ^d	NR	NR	RMS patient had either SD or PD
<i>Comparative studies</i>										
Carboplatin + Irinotecan	Petrilli, 2004 (S28)	NR ^c (all RMS patients refractory)					NR	NR	NR	
Irinotecan		At least 2 ^c refractory RMS		2			NR	NR	NR	
Allogeneic HSCT with minimal conditioning regimen—sibling donor	Shook, 2013 (S112)	1 second relapse, 1 refractory RMS	0	0	1	1	0% ^d	49.5 days ^d (28– 71 days)	NR	All RMS patients died from PD
Allogeneic HSCT with minimal conditioning regimen—MUD		1 first relapse RMS	0	0	1	0	0% ^d	195 days	NR	

(Continues)

TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Bevacizumab, Vinorelbine, Cyclophosphamide	Mascarenhas, 2019a (S90)	40 primary refractory or 1st relapse RMS	4	7		11	28% (13.7%–41.3%)	See comment	See comment	18 responses NR EFS: <ul style="list-style-type: none"> 6 months 54.6% (95% CI: 39.8%–69.3%) 12 months 18.2% (95% CI: 6.8%–29.6%) 24 months 6.8% (95% CI: 0%–14.3%) OS: <ul style="list-style-type: none"> 6 months 84.1% (95% CI: 73.3%–94.9%) 12 months 59.1% (95% CI: 44.6%–73.6%) 24 months 29.6% (95% CI: 16.1%–43%)
Temsirolimus, Vinorelbine, Cyclophosphamide		38 primary refractory or 1st relapse RMS	5	13		4	47% (31.5%–63.2%)	See comment	See comment	16 responses NR EFS: <ul style="list-style-type: none"> 6 months 69.1% (95% CI: 55.1%–83%) 12 months 40.5% (95% CI: 25.6%–55.3%) 24 months 19.1% (95% CI: 7.2%–30.9%) OS: <ul style="list-style-type: none"> 6 months 90.5% (95% CI: 81.6%–99.4%) 12 months 78.4% (95% CI: 65.8%–91.1%) 24 months 39.2% (95% CI: 24.2%–54.2%) ORR were not significantly different between the two groups. EFS was significantly better for the TEM arm compared to the BEV arm ($P = .018$), but no significant difference in OS ($P = .23$)
Irinotecan—prolonged schedule (with other multimodal chemotherapy)	Mascarenhas, 2010 (S91)	42 first relapse or refractory RMS	5	6	12	19	26% (16–42%)	0.5 years	1.4 years	1 year FFS: 37% (95% CI: 23%–51%) 3 year FFS: 14% (95% CI: 5%–27%) 1 year OS: 55% (95% CI: 39%–68%) 3 year OS: 34% (95% CI: 20%–49%)

TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Irinotecan—short schedule (with other multimodal chemotherapy)		47 first relapse or refractory RMS	0	17	14	16	36% (25–51%)	0.7 years	1.3 years	1 year FFS: 38% (95% CI: 25%–52%) 3 year FFS: 15% (95% CI: 7%–26%) 1 year OS: 60% (95% CI: 44%–72%) 3 year OS: 22% (95% CI: 11%–35%)
Vincristine + Irinotecan	Defachelles, 2021 (S2)	41 first relapse, 14 undifferentiated relapse, 5 refractory RMS	2	16	21	19	After 2 cycles: 31% (20%– 45%)	3.2 (95% CI: 2.4–7.3)	10.3 (95% CI: 7.1–12.6)	2 not evaluable after 2 cycles or best response PFS: • 6 months 42% (95% CI: 29%–54%) • 1 year 28% (95% CI: 17%–40%) • 2 years 15% (95% CI: 8%–26%) OS: • 6 months 70% (95% CI: 57%–80%) • 1 year 43% (95% CI: 30%–55%) • 2 years 22% (95% CI: 12%–34%)
			4	18	17	19	Best ORR: 38% (26%– 52%)			
Vincristine, Irinotecan, Temozolomide		40 first relapse, 12 undifferentiated relapse, 8 refractory RMS	2	19	21	10	After 2 cycles: 44% (30%– 58%)	4.7 (95% CI: 4.1–8.5)	15.0 (95% CI: 10.0–21.2)	5 not evaluable after 2 cycles, 2 not evaluable as best response PFS: • 6 months 45% (95% CI: 32%–57%) • 1 year 33% (95% CI: 21%–45%) • 2 years 18% (95% CI: 9%–29%) • Unadjusted HR 0.74 (0.49–1.11) OS: • 6 months 80% (95% CI: 67%–88%) • 1 year 56% (95% CI: 42%–67%) • 2 years 33% (95% CI: 21%–45%) • Unadjusted HR 0.73 (0.47–1.13) (Additional outcome data available in article)
			9	24	16	9	Best ORR: 57% (43%– 70%)			
Metronomic—thalidomide, celecoxib, alternating etoposide/ cyclophosphamide	Pramanik, 2017 (S106, S107) <i>Some outcome data provided via email communication with authors</i>	3 R + R RMS	0	0	2	1	0% ^d	130 days ^d (69– 178 days)	218 days ^d (87– 282 days)	
Best supportive care		5 R + R RMS	0	0	0	4	0% ^d	41 days ^d (9– 67 days)	46 days ^d (9– 141 days)	1 RMS patient outcome unclear but OS 9 days
Vaccines										
Dendritic cell vaccine + Decitabine	Krishnadas, 2015 (S83)	1 relapsed RMS	0	0	0	1	0% ^d	NR	NR	Patient had 3 relapses

(Continues)

TABLE 2 (Continued)

Regimen	Author, date (Supporting Information Reference) ^a	Total number of relevant CYP ^b	Responses (number of CYP)				Response rate % (95% CI) CR + PR	Median survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Glypican-3-derived peptide vaccine therapy	Tsuchiya, 2018 (S14)	1 R + R RMS	0	1	0	0	100% ^d	4	9	Note: Patients with histological confirmation of GPC3 expression in tumor cells, HLA-A24- or HLA-A2-positive status
NCCV cocktail-1 vaccine	Akazawa, 2019 (S35)	3 Refractory RMS			1	1	0% ^d	2.33 (0.43 to >12.91)	>15.93 (>13.83 to >17.15)	Two patients had SD status before vaccination and one was in remission. One patient maintained remission on treatment
Personalized peptide vaccine	Oda, 2020 (S12)	1 1st Relapse RMS	0	0		0	0% ^d	37+	37+	Patient disease-free before administration of PPV
Seneca Valley Virus (NTX-010) ± Cyclophosphamide	Burke, 2015 (S47)	3 ^c R + R RMS	0	0	1		NR	NR	NR	Two patients NR—either PD or not evaluable
WT1 peptide vaccination	Sawada, 2016 (S25)	2 relapsed, 1 refractory RMS				1	NA (see comments)	NR	See comment	Note: Patients had to have HLA-A*24:02, tumor cells or leukemic cells expressing WT1 mRNA or protein One RMS patient DOD 3 months after receiving the first vaccine—PD after first vaccine, then received rescue chemotherapy before receiving further vaccines (total 12). Two RMS patients were still alive and in CR (after 5+ and 7+ years) and received all 12 vaccines—these patients were in CR at start of vaccine treatment

Abbreviations: AMORE, Ablative surgery, Moulage technique brachytherapy and surgical Reconstruction; ALK, anaplastic lymphoma kinase; AKI, aurora kinase inhibitor; CAR-T, chimeric antigen receptor T-cells; CR, complete response; CI, confidence interval; CYP, children and young people; DOD, died of disease; DOR, duration of response; EVE, etoposide, vincristine, epirubicin; EFS, event free survival; FFS, failure free survival; HSCT, hematopoietic stem cell transplant; HDCT, high-dose chemotherapy; HER2, human epidermal growth factor receptor 2; LAK, lymphokine-activated killer; MUD, matched unrelated donor; MoA, mechanism of action; mTOR, mechanistic target of rapamycin; MSC, mesenchymal stem cell; MR, minimal regression; NED, no evidence of disease; NA, not applicable; NE, not extractable (foreign language report); NR, not reported; ORR, overall response rate; OS, overall survival; PR, partial response; PDL1, programmed death ligand 1; PFS, progression free survival; PD, progressive disease; R + R, relapsed and refractory (where not able to differentiate); RMS, rhabdomyosarcoma; STS, soft tissue sarcoma; SD, stable disease; SCT, stem cell transplant; TTP, time to progression; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; VEGF/VEGFR, vascular endothelial growth factor/vascular endothelial growth factor receptor; VAC, vincristine-actinomycin D-cyclophosphamide; VETOPEC, vincristine, etoposide and dose-escalated cyclophosphamide; VOIT, vincristine, oral irinotecan and temozolomide; VAS, visual analogue scale.

^aMean, (SE).

^bEvaluable, RMS patients.

^cPlus italicized indicates studies where exact number of evaluable RMS patients is unknown but is definitively >1.

^dCalculated from provided information.

3.4 | Synthesis—Clinical trial registrations

One-hundred and seven trial registry records of 99 studies that were not associated with a published study were also included in our review (Supporting Information Refs. S29–S32, S137–S239).

3.4.1 | Currently open

Sixty-three studies (64% of CTR studies) (Supporting Information Refs. S32, S137–S142, S144, S148, S149, S151, S154, S156, S158–S164, S166, S167, S169, S171–S173, S175–S181, S183–S187, S190, S191, S193–S195, S201, S204, S205, S207, S208, S211, S215, S220, S222, S224–S226, S229, S233, S234, S236–S238) were reported to be currently open at the time of data extraction, 39 of which stated they were recruiting participants (Supporting Information Refs. S29, S32, S137, S138, S140, S141, S151, S152, S156, S160–S164, S169, S172, S175–S178, S180, S181, S183–S185, S190, S191, S194, S195, S204, S205, S220, S222, S224–S226, S234, S236, S238). Overall, 53 studies (84% of currently open studies) were focused on participants with relapsed and refractory disease (Supporting Information Refs. S29, S32, S138–S142, S144, S148, S151, S152, S154, S156, S158, S159, S161, S163, S164, S166, S167, S172, S173, S175–S181, S183, S184, S186, S187, S193–S195, S201, S204, S205, S207, S208, S211, S215, S222, S224, S226, S233, S234, S236, S238, S240). The vast majority of studies were recruiting participants with multiple tumor types (97%), with two studies (Supporting Information Refs. S224, S225) focusing only on children and young people with rhabdomyosarcoma. In 15 studies (24%), eligibility was limited to those with a specific biomarker/mutation (Supporting Information Refs. S148, S149, S154, S159, S167, S173, S175, S178–S181, S185, S186, S208, S233). The majority of studies included the United States as a country of recruitment (87%) (Supporting Information Refs. S29, S32, S137–S141, S144, S148, S149, S151–S154, S156, S158, S159, S161, S162, S164, S168, S171–S173, S175, S176, S178–S181, S184, S185, S187, S190, S191, S193, S194, S204, S205, S207, S208, S220, S224, S226, S233, S236). Studies primarily focused on systemic therapies (73%; standard or novel agents, including biomarker-driven approaches, [Refs. S29, S138–S141, S144, S148, S149, S151, S152, S154, S158, S159, S169, S172, S173, S175, S177–S181, S184, S187, S190, S191, S194, S195, S201, S205, S207, S211, S215, S220, S222, S224–S226, S229, S233, S234, S236–S238]).

3.4.2 | Discontinued studies

Twelve studies (12% of CTR studies) were discontinued, either due to insufficient participant recruitment (4 studies, Refs. S146, S168, S210, S217), issues with the investigational drug (3 studies, Refs. S155, S165, S189), amendments to trials (3 studies, Refs. S153, S174, S182), being replaced by another study (1 study, Ref. S147) and due to investigator choice (1 study, Ref. S209). An additional five studies were

extracted with an unknown trial status so it was unclear if these were completed or not (Supporting Information Refs. S31, S192, S199, S202, S213). Overall, 12 studies (71%) were focused on recruiting relapsed and refractory participants (Supporting Information Refs. S153, S155, S165, S168, S174, S182, S189, S192, S202, S210, S217). One study was designed for rhabdomyosarcoma participants only (Supporting Information Ref. S213). The majority of these studies included the United States as a recruitment country (71%, Refs. S146, S147, S153, S155, S165, S168, S174, S182, S189, S209, S210, S217). Ten studies (59%) investigated systemic therapies (Supporting Information Refs. S153, S155, S158, S165, S168, S174, S182, S189, S202, S210).

3.4.3 | Completed not yet reported

Nineteen completed studies with no identifiable publications of the full dataset were extracted (19%, Refs. S30, S143, S145, S150, S157, S170, S188, S196–S198, S200, S203, S206, S212, S214, S218, S219, S221, S239). The date range for completion of these studies was 2004–2021 with the majority being completed before 2019 ($n = 12$), 63% of completed studies (Supporting Information Refs. S143, S145, S150, S170, S196, S198, S206, S214, S218, S221, S239), including two studies where the end date was not reported but the clinical trial records were last updated before 2019 (Supporting Information Refs. S150, S214). Two studies were focused on recruiting only participants with rhabdomyosarcoma (Supporting Information Refs. S206, S212) and one study included participants of all ages (Supporting Information Ref. S206). Again, most of these studies were recruiting in the United States (74%, Refs. S30, S143, S145, S150, S157, S170, S188, S196, S198, S200, S203, S206, S212, S239). The majority of studies investigated systemic therapies (68%, Refs. S30, S150, S157, S188, S196, S197, S203, S206, S212, S214, S218, S219, S239).

4 | DISCUSSION

The REFoRMS-SR represents a comprehensive synthesis of early phase studies of interventions for children and young people with relapsed and refractory rhabdomyosarcoma from 2000 to 2021. Within the 129 published studies of over 1100 children and young people, response rates to evaluated interventions were generally poor, and reporting of more clinically meaningful outcomes was rare. Survival and response rates in studies of single-agents (either standard or novel agents) were generally lower than for combination therapy studies, though these often have the benefit of being informed by single agent studies and thus select more promising agents. Most early phase research reported to date, or registered as currently ongoing, relates to systemic anticancer therapies. Studies predominantly involved white children and young people, located in the United States with a focus on older children and young people. The quality of reporting of studies was limited, with inconsistencies

BOX 1 Future research recommendations from the REFoRMS systematic review.

Future Research Recommendations

- To determine the most appropriate tool for quality assessment within systematic reviews of early phase studies, either through the development of a new tool, or assessment of currently available tools.
- To reach methodological consensus regarding the reporting of early phase studies to improve transparency and allow for easier comparison across trials.
- To create a core outcome set for early phase studies in relapsed and refractory pediatric malignancies developed alongside patients, families, clinicians and researchers, with the aim of outlining the most important outcomes for these kinds of studies, facilitating transparent reporting and enabling future syntheses.
- To establish whether the methods used within the REFoRMS-SR and the Living-REFoRMS resource can be translated across to other childhood malignancies. This would provide all families experiencing relapsed and refractory disease, and their clinicians, to access the most up-to-date, quality assessed, evidence syntheses.

making synthesis challenging. A small, but not insignificant proportion, of registered early phase studies in this population are not publicly reported by 2 years after completion. Recommendations for future research are summarized in Box 1.

While early phase studies are intended to predominantly focus on toxicities, and proxy measures of treatment effect (eg, RECIST response), our parent group were very clear that the outcomes most meaningful to them when considering these studies related to duration of survival and quality of life (including burden of therapy and opportunity costs). Involving children, young people and families in the design and delivery of early phase studies, including in outcome selection and definition, would strengthen this field of research. Furthermore, although disease response by RECIST was the most reported outcome, frequently this was simply stated as “no objective responses.” As such, it was unclear whether children and young people experienced stable disease or progressive disease, which may be clinically significant in this population. Inconsistencies in outcomes reported by studies, and how these are described or defined, limits comparisons across the field and reduces the ability to draw together findings to inform future clinical practice and research.¹⁴ This is potentially most obvious in the variation in how adverse events are described; variability which seems even more challenging given the principal intent of early phase studies. Newer approaches with patient-reported-adverse-outcomes and integration of electronic patient record capture methods could harmonize and improve

detection.¹⁵ A core outcome set for early phase studies in pediatric, teenage and young adult cancer would ensure that reporting priorities of key stakeholders are met, reduce selective reporting of certain outcomes and improve evidence syntheses in the future. The International Childhood Cancer Outcome Project has already started work in this area, by developing core outcome sets to measure the quality of survival for 17 common childhood cancer subtypes including rhabdomyosarcoma, based on outcomes that are valued by patients.¹⁶

The quality assessment of studies included in this review was challenging for a number of reasons, but primarily due to the sparsity of validated tools to assess the risk of bias of early phase studies. Indeed, many other systematic reviews of early phase studies have not included quality assessment.^{17–19} The common tools used in comparative efficacy (often randomized) trials do not apply, and quality assessment is focused around assessing the risk of the estimates of outcomes being valid. Methodological consensus regarding reporting of early phase studies would improve transparency and allow for easier comparison across trials. This has been highlighted by other systematic reviews of phase 1 trials and thus seems a consistent challenge for those undertaking evidence syntheses.^{20,21} Quality assessment tools for early phase studies have been developed, but as yet, seem to be poorly implemented. We thus recommend the development and implementation of both reporting guidelines and quality assessment tools for early phase studies in order to improve future evidence syntheses.²² Additionally, we consider it important to highlight that the majority of included studies within the REFoRMS-SR are single arm studies. This is an appropriate study design for much early phase work, but these should be recognized as in their very nature at higher risk of bias compared to multiarm studies. Thus, any interventions which indicate possible promise within single arm studies would be recommended to be further investigated using later stage, comparative designs.

We identified a small number of completed studies without full published results. This could be due to our search strategy, though this was extensive, or to researchers not publishing results. The failure to publish easily identifiable results, preferably linked to the relevant clinical trial registration record, has been highlighted as of particular concern within academic practice.^{14,23} If data are unpublished, then participants have taken part in research, often toward the end of their lives and with altruistic motivations, which does not benefit the wider community and funders have used resources which might reasonably have been used elsewhere. We believe this is ethically unacceptable. Furthermore, there is a risk of publication bias, and thus compromise within systematic reviews given that unpublished studies are more likely to identify negative findings. It is the responsibility of all those involved in childhood cancer research, including children and young people, families, clinicians, researchers and funders, to hold researchers to account for publishing the findings of their early phase studies.

The strengths of this review lie in its standardized methodologies completed by a specialized evidence synthesis team, in collaboration with parent and clinical expertise. This engagement with key stakeholders in both shaping the research and its dissemination, including through non-standard routes (eg, Twitter: @REFoRMS_Rhabdo), has

ensured this project will have significant impact within the community. As in much evidence synthesis work, the main challenges related to the poor reporting of data within included studies. In particular, data relating to outcomes of children and young people with rhabdomyosarcoma was frequently not separable from other tumor types; 35 studies on 31 therapies including almost 80 potentially eligible children and young people were excluded for this reason. Trials including multiple tumor types are essential in pediatric oncology; nonetheless we encourage reporting of patient demographics and outcomes by tumor type to improve the transparency and clinical utility of these data. We selected a search strategy focused on soft tissue sarcoma. This facilitated screening more broadly than a pure rhabdomyosarcoma search, but may potentially have missed a small number of studies which included “all relapsed/refractory pediatric malignancies.” Testing of strategies in advance, including screening samples of broader searches, suggests this number is likely minimal and is unlikely to have included data which would substantially impact on the review conclusions. Furthermore, additional strategies within the study identification process (including linking clinical trial registries and conference abstracts to published studies, and reference list searching) will have helped to mitigate any potential deficiencies in the database searches.

In relapsed and refractory rhabdomyosarcoma, one of the greatest future research challenges is the speed at which early phase studies are conducted, and thus the risk of any evidence synthesis becoming rapidly out of date. Children, young people, families and clinicians require innovative solutions to provide high quality data syntheses in a form that is continually updated. To address this, the REFoRMS-SR will now become the first living systematic review in childhood cancer: Living-REFoRMS. The Living-REFoRMS team will perform regular updates of the evidence synthesis, whilst also working on the methodological challenges of living reviews, including evaluating different methods for searching, screening, quality assessment and synthesis. The first update review is in progress and an interactive and user-friendly online resource is being developed to facilitate access to the Living-REFoRMS data for children, young people, families, clinicians and researchers.

AUTHOR CONTRIBUTIONS

Connor Evans: Involved in the details of study design and development of the study protocol; Screened titles and abstracts as well as full texts for study selection; Performed data extraction and quality assessment; Performed the analyses, with insights from all other authors into interpretation and presentation. **Lucy Shepherd:** Involved in the details of study design and development of the study protocol; Screened titles and abstracts as well as full texts for study selection; Performed data extraction and quality assessment; Performed the analyses, with insights from all other authors into interpretation and presentation. **Gemma Bryan:** Involved in the details of study design and development of the study protocol; Screened titles and abstracts as well as full texts for study selection. **Helen Fulbright:** Involved in the details of study design and development of the study protocol; Search strategies were designed and implemented by HF in collaboration with the research team. **Scott Crowther:** Involved in the details

of study design and development of the study protocol. **Sara Wakeling:** Involved in the details of study design and development of the study protocol. **Andy Stewart:** Involved in the details of study design and development of the study protocol. **Claire Stewart:** Involved in the details of study design and development of the study protocol. **Julia Chisholm:** Involved in the details of study design and development of the study protocol. **Faith Gibson:** Involved in the details of study design and development of the study protocol. **Bob Phillips:** Designed the overarching study and obtained funding as detailed; Involved in the details of study design and development of the study protocol. **Jessica E. Morgan:** Designed the overarching study and obtained funding as detailed; Involved in the details of study design and development of the study protocol; Screened titles and abstracts as well as full texts for study selection; Performed data extraction and quality assessment; Performed the analyses, with insights from all other authors into interpretation and presentation. The work reported in the article has been performed by the authors, unless clearly specified in the text. All authors were involved in the writing and editing of the article, and have approved the final version for publication.

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CONFLICT OF INTEREST STATEMENT

The authors have no other conflicts of interest to report.

DATA AVAILABILITY STATEMENT

Data sources and handling of the publicly available datasets used in our study are described in the Materials and Methods. Further details and other data that support the findings of our study are available from the corresponding authors upon request.

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REFERENCES

- Ognjanovic S, Linabery AM, Charbonneau B, Ross JA. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975-2005. *Cancer*. 2009;115(18):4218-4226.
- Malempati S, Hawkins DS. Rhabdomyosarcoma: review of the Children's Oncology Group (COG) soft-tissue sarcoma committee experience and rationale for current COG studies. *Pediatr Blood Cancer*. 2012;59(1):5-10.
- Yang L, Takimoto T, Fujimoto J. Prognostic model for predicting overall survival in children and adolescents with rhabdomyosarcoma. *BMC Cancer*. 2014;14(1):654.
- Pappo AS, Anderson JR, Crist WM, et al. Survival after relapse in children and adolescents with rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. *J Clin Oncol*. 1999; 17(11):3487-3493.
- Chisholm JC, Marandet J, Rey A, et al. Prognostic factors after relapse in nonmetastatic rhabdomyosarcoma: a nomogram to better define patients who can be salvaged with further therapy. *J Clin Oncol*. 2011; 29(10):1319-1325.
- Defachelles AS, Bogart E, Casanova M, et al. Randomized phase 2 trial of the combination of vincristine and irinotecan with or without temozolomide, in children and adults with refractory or relapsed rhabdomyosarcoma (RMS). *J Clin Oncol*. 2019;37:10000.
- WHO International Clinical Trials Registry Platform (ICTRP). Far-rms: An overarching study for children and adults with frontline and relapsed rhabdomyosarcoma; 2020. <http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-000515-24-IE>
- Waligora M, Bala MM, Koperny M, et al. Risk and surrogate benefit for pediatric phase I trials in oncology: a systematic review with meta-analysis. *PLoS Med*. 2018;15(2):e1002505.
- Pollock A, Campbell P, Struthers C, et al. Development of the ACTIVE framework to describe stakeholder involvement in systematic reviews. *J Health Serv Res Policy*. 2019;24(4):245-255.
- Morgan J, Evans C, Beresford L, Bryan G, Fulbright H, Phillips B. A systematic review of early phase studies for children and young people with relapsed and refractory rhabdomyosarcoma. PROSPERO; 2021. https://www.crd.york.ac.uk/prospere/display_record.php?ID=CRD42021266254
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210.
- Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-384.
- Bittlinger M, Bicer S, Peppercom J, Kimmelman J. Ethical considerations for phase I trials in oncology. *J Clin Oncol*. 2022;40(30):3474-3488.
- Sung L, Miller TP, Phillips R. Improving symptom control and reducing toxicities for pediatric patients with hematological malignancies. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1): 280-286.
- van Kalsbeek RJ, Hudson MM, Mulder RL, et al. A joint international consensus statement for measuring quality of survival for patients with childhood cancer. *Nat Med*. 2023;29(6):1340-1348.
- Fang P, Hu J-h, Cheng Z-g, Liu Z-f, Wang J-l, Jiao S-c. Efficacy and safety of bevacizumab for the treatment of advanced hepatocellular carcinoma: a systematic review of phase II trials. *PLoS One*. 2012;7(12):e49717.
- Glasmacher A, Hahn C, Hoffmann F, et al. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. *Br J Haematol*. 2006; 132(5):584-593.
- Omer N, Le Deley M-C, Piperno-Neumann S, et al. Phase-II trials in osteosarcoma recurrences: a systematic review of past experience. *Eur J Cancer*. 2017;75:98-108.
- Cohen JW, Akshintala S, Kane E, et al. A systematic review of pediatric phase I trials in oncology: toxicity and outcomes in the era of targeted therapies. *Oncologist*. 2020;25(6):532-540.
- Mackley MP, Fernandez NR, Fletcher B, Woolcott CG, Fernandez CV. Revisiting risk and benefit in early oncology trials in the era of precision medicine: a systematic review and meta-analysis of phase I trials of targeted single-agent anticancer therapies. *JCO Precis Oncol*. 2021;5:17-26.
- Yap C, Bedding A, de Bono J, et al. The need for reporting guidelines for early phase dose-finding trials: dose-finding CONSORT extension. *Nat Med*. 2022;28(1):6-7.
- AllTrials.Net. All Trials Registered. All Results Reported 2014. <https://www.alltrials.net/>
- Beresford L, Evans C, Bryan G, et al. A systematic review of early phase studies for children and young people with relapsed and refractory rhabdomyosarcoma: the reforms-sr project; 2023. <https://www.cclg.org.uk/our-research-projects/reforms-project>

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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