# 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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## Table of abbreviations

The table of abbreviations below has been deliberately kept short as the parent group felt that it was often unnecessary and more confusing to include lots of abbreviations, so where feasible, we have tried to expand full words instead of using abbreviations. In particular, throughout this report, we have used the term rhabdomyosarcoma in full.

| | |
|---|---|
| AE | Adverse Event |
| CA | Conference Abstract |
| CAG | Clinical Advisory Group |
| CCLG | Children's Cancer and Leukaemia Group |
| CR | Complete Response |
| CRD | Centre for Reviews and Dissemination |
| CTR | Clinical Trial Registry/Registration |
| HSCT | Haematopoietic Stem Cell Transplantation |
| ORR | Objective Response Rate |
| PD | Progressive Disease |
| PICO | Population, Intervention, Comparator, Outcome |
| PPI | Patient/Parent and Public Involvement |
| PR | Partial Response |
| QoL | Quality of Life |
| SD | Stable Disease |
| SR | Systematic Review |
| UK | United Kingdom |
| USA | United States of America |

# Research Summary

## Introduction

Rhabdomyosarcoma is a form of cancer that most commonly affects children and young people. About one third of children and young people with rhabdomyosarcoma have disease that does not respond to treatment (refractory) or that comes back after treatment (relapse).

Only around one in five children with relapsed or refractory rhabdomyosarcoma can be cured, and so there are difficult decisions to be made about what treatment to give next, balancing the quality of life with the likelihood of successful outcome/cure. The options might include:

- aggressive treatment aiming to cure
- treatment to reduce the amount of disease, and therefore help symptoms
- experimental trials of new treatments (also called early phase studies)
- symptom control.

The research described in this report aimed to look for all early phase studies in relapsed or refractory rhabdomyosarcoma and to see how effective the different treatments are for different children, using an approach called a 'systematic review'.

This will help to give families and professionals more accurate information about what to expect from the options available. The systematic review is part of a larger research project called REFoRMS, which aims to support treatment decision making for children and young people with relapsed and refractory rhabdomyosarcoma.

## What we did

We worked with a group of families with experience of relapsed and refractory rhabdomyosarcoma, and healthcare professionals with expertise in this area, throughout the REFoRMS project. They helped to make sure the research answered the most important questions in the best way, and provided insight into what the research findings mean.

We searched for early phase studies that had been published in research journals using nine different databases (places where research is stored). We also looked at online registers of studies that researchers said they were going to do (called clinical trials registries). We did the searches in June 2021.

We looked for any early phase trials of treatments for children and young people (aged less than 18 years old) with relapsed and/or refractory rhabdomyosarcoma. We looked for studies which took place anywhere in the world and were written in any language. We looked for studies which took place after the year 2000 to help understand the best current treatments.

## Findings

We found 16,965 possibly relevant studies in the databases and registries. Two researchers looked at each of these possible studies. We found 129 studies that had been published, and 99 studies in the registries that were definitely relevant. Of the studies found in the registries, 63 say they are currently open to recruit people to take part in the study.

Before we looked at what the published studies found, we assessed whether they had been designed and carried out in a way that makes the results reliable and trustworthy. This was sometimes quite difficult as the research reports were short or did not provide the information to help us to know what the researchers did or what they found.

In the 129 published studies there were over 1,100 children and young people with relapsed or refractory rhabdomyosarcoma. Most studies looked at different kinds of chemotherapies (also referred to as systemic therapies), but others looked at treatments like stem cell transplants, vaccines, surgery and radiotherapy. Not many studies (21%) looked at how long children and young people survived after they received the experimental treatment, but for those that did, most (70%) said that the time until the disease progressed (the person became more unwell) was short - on average under six months.

Many studies looked at whether the experimental treatment made the tumours look smaller on a scan, and for those studies, this happened on average 21.6% of the time.

Many of the studies also looked at any bad things that happened during the studies (sometimes due to the experimental treatment, sometimes just because the children and young people were unwell). The most common things to happen were changes to the child or young person's blood count, but the bad things that did happen were different depending on the type of experimental treatment.

## What next

These are difficult findings for children and young people with relapsed/refractory rhabdomyosarcoma, their families and the people who care for them.

We are working on a number of different next steps:

- We are working on an interview study where we speak to patients and families about how they have made, or are making, decisions about treatment in relapsed or refractory rhabdomyosarcoma. This will help us understand the decision-making process and how best to support families making these choices.
- The results of this systematic review and the interview study will be combined in a best practice statement which will provide advice and support to clinicians and families about important things to consider when discussing treatment options.
- We will be sharing our findings with families and professionals, including healthcare teams, researchers and policy makers, so that they can use the information in patient care, and in designing research studies in the future.
- We will work with researchers to think about better ways to design and report high quality research that is more helpful to answering these kinds of questions in the future.
- We are working on a project called Living-REFoRMS which will provide a regularly updated online resource of information about early phase trials for children and young people with relapsed and refractory rhabdomyosarcoma.

# Technical Abstract


## Background

Rhabdomyosarcoma is the commonest soft tissue sarcoma in children and young people affecting ~50 children in the UK annually. One third of children with rhabdomyosarcoma experience relapse or have refractory disease, which is associated with a poor prognosis. A systematic review of early phase trials in paediatric relapsed/refractory rhabdomyosarcoma was conducted to inform future research and provide accurate information to families and clinicians making difficult treatment choices.

## Methods

Nine databases and five trial registries were searched in June 2021. Early phase trials of interventions for disease control (curative or palliative) in patients <18 years 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 (Down's and Black Checklist) was conducted by two researchers. Owing to heterogeneity in included studies, narrative synthesis was conducted.

## Results

Of 16,965 records screened, 129 published studies including over 1,100 relapsed/refractory rhabdomyosarcoma patients were eligible. Most studies evaluated systemic therapies (n=74). Where reported, 70% of studies reported a median progression-free survival ≤6 months, and objective response rate was 21.6%. Adverse events were mostly haematological. 107 trial registry records were also eligible, 63 of which are active. Study quality was limited by inconsistent reporting.

## Conclusions

Response and survival rates for children and young people with relapsed/refractory rhabdomyosarcoma who enrol on early phase trials are low. Improving reporting quality and consistency would facilitate synthesis of early phase studies in relapsed/refractory rhabdomyosarcoma.

PROSPERO registration: CRD42021266254

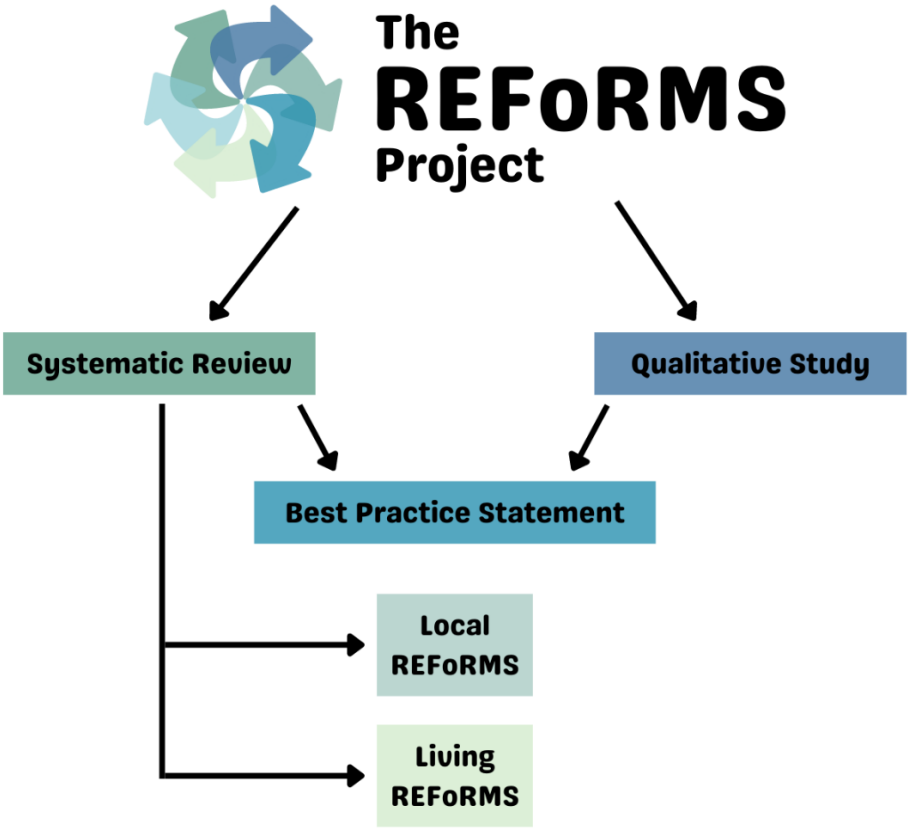
# Background

Rhabdomyosarcoma is the commonest soft tissue sarcoma in children, affecting between 40-50 children under 15 years old in England each year.[1] Upfront treatment is risk stratified, and is associated with >90% overall survival for low risk groups, compared with <10% for those with metastatic fusion-positive disease.[2] Overall, around one-third of children and young people treated for rhabdomyosarcoma experience relapsed (where the disease comes back after treatment) or refractory (where the disease does not respond to treatment) disease. For some children second line treatment with curative intent may be available, but for around four out of five this will not be successful.[3-5] This overall proportion of long-term cure varies extensively with the timing and location of relapse, along with the intensity of prior therapies used; for example, one-third of children with a relapse in the same location as their original tumour may be cured, but the chances of cure are much lower in those with metastatic relapses.[6]

Standard of care chemotherapy treatment for first relapse of rhabdomyosarcoma across Europe has been defined recently as the combination of vincristine, irinotecan and temozolomide (VIT) along with appropriate local control measures, including surgery and/or radiotherapy.[7] This chemotherapy combination is well tolerated, with a response rate of 44% and improved progression free and overall survival compared to vincristine and irinotecan alone.[8] Beyond this, there are a range of options which may be considered, from only symptom-directed interventions such as pain relief, through palliative anti-cancer treatments, given to reduce disease burden or symptoms, to experimental therapies, including in early phase clinical trials. This last option, entering a trial of an 'experimental' therapy which has limited experience and lack of knowledge about its effectiveness, is chosen by some families. Previous reviews have demonstrated a low rate of success overall in these early phase trials[9], when measured in tumour response and overall survival times, when all patients entered into these studies are analysed. Other studies have shown that families with poor-prognosis cancer may have an unrealistic view of the chance of cure.[10] The particular response rates of patients with rhabdomyosarcoma have not been specifically examined. Providing accurate information about these options, and understanding how patients and their parents make these difficult decisions, can enable healthcare professionals to support families and reduce the amount of decisional regret they experience in the future.

The REFoRMS project was funded by the Children's Cancer and Leukaemia Group (CCLG) in 2021 to address this challenge. It initially involved two key workstreams: 1) a systematic review of early phase studies for children and young people with relapsed and refractory rhabdomyosarcoma, and 2) a qualitative study to explore the decision-making process of patients and families with experience of relapsed and refractory rhabdomyosarcoma. These two work-streams will then be combined to create a best practice statement, guiding healthcare professionals in paediatric oncology services. Since the initial project commenced, there have been a number of additions to the REFoRMS project, including: 1) a review of studies exploring surgical and brachytherapy approaches for relapsed and refractory rhabdomyosarcoma (Local-REFoRMS), and 2) a funded project to convert the original systematic review into a living systematic review (Living-REFoRMS), which will update the evidence syntheses regularly and be reported through an accessible online resource.[11] This report focuses solely on the initial baseline systematic review, but will mention other aspects of the research as necessary for context (see Figure 1).

**Figure 1.** The REFoRMS project workstream




The entire REFoRMS project has been guided by our parent and clinical advisory groups. Full details of their contributions to the work are provided at relevant points within the report, and we have added boxes to make these elements more identifiable to readers.

## Aims and objectives

To systematically review the responses in early phase studies for children and young people with relapsed and refractory rhabdomyosarcoma and how effective these are likely to be in different patient groups.

# Methods

## Parent and Clinical Advisory Groups

The REFoRMS-SR was guided throughout by a group of parents whose children had experienced relapsed or refractory rhabdomyosarcoma, who are co-authors of this work. The parents were involved in setting aims and objectives of the review, in particular, the inclusion within the review of open and ongoing registered clinical trials. They were involved in defining the key outcomes to be assessed and identifying the most important adverse events to be included. The synthesis of outcomes is reported in order of importance assigned by the parent group. The parent group have also contributed to some concepts described in the report discussion, particularly relating to the challenges when reported. We have attempted to highlight the most important parent group contributions where these occur.

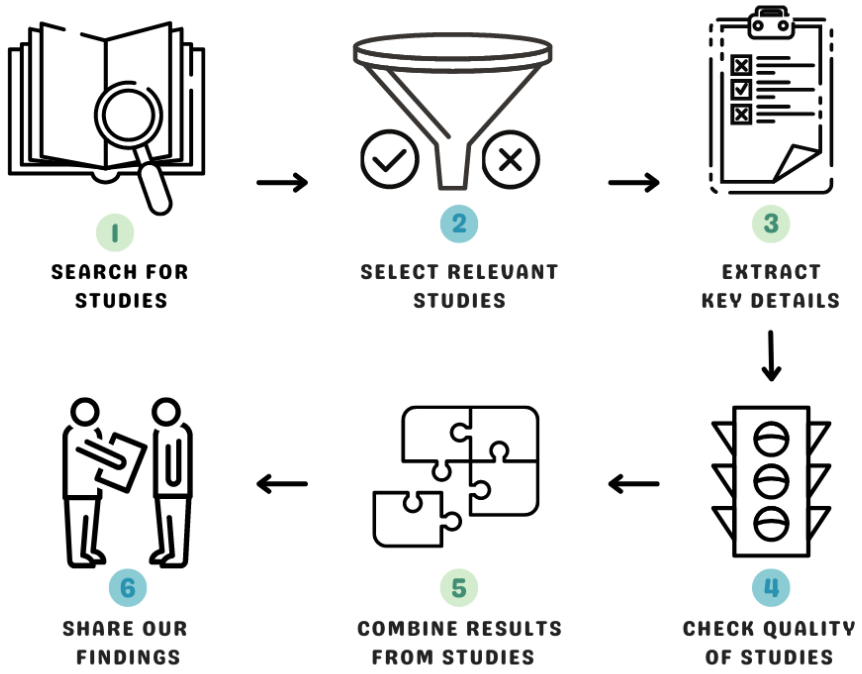
The REFoRMS research team were also supported through the work by a Clinical Advisory Group (CAG) which consisted of healthcare and research professionals with expertise in soft tissue sarcoma, who are also co-authors of this work. The CAG guided the design and conduct of the research to ensure it was best designed to meet the needs of the children and young people with rhabdomyosarcoma, their families, researchers and clinicians working in this field.

## Overview of process

This systematic review summarises the available evidence in accordance with standardised processes as depicted in Figure 2. An overview of each stage of the review is briefly explained below before we provide the detailed methods of this specific review and what has been found.

1. Firstly, we conducted a comprehensive online search to identify all research relevant to this project. This included identifying published research in academic journals, as well as clinical trial records.
2. The research identified was filtered based on pre-selected eligibility criteria to ensure that only the most relevant research was used within the review.
3. Once a final list of studies to be included in the review was identified, we extracted the data from each of these studies. This involved taking the data reported in the studies and collating it into large spreadsheets.
4. Alongside data extraction, each study was assessed to determine the quality of the research published. This is important for determining whether any bias has been introduced, and therefore helps us to evaluate the strength of the evidence.
5. The data was then combined to provide an overall picture of the evidence of the effectiveness of treatments for relapsed and refractory rhabdomyosarcoma.
6. Finally, the results of this systematic review will be published and made available to patients, parents, clinicians and researchers, in the form of this technical report, an executive summary, patient and parent-focused resources and an academic journal submission. Further dissemination resources may be created in the future where necessary.

**Figure 2.** Stages of a systematic review




## Search

A search strategy was developed in Ovid MEDLINE by an Information Specialist (HF) with input from the review team. The strategy included terms for the condition both precisely and with much broader terminology; terms to represent that the condition was relapsed or refractory; and terms for the population: children and young people. Each concept used a choice of subject headings and free-text terms as this reflects best practice in information retrieval. As a wide range of interventions and study types were of interest, structuring the search to identify papers based on the population and condition was considered the most effective and appropriate way to capture the evidence. No language or geographical restrictions were applied to the searches, but animal studies and irrelevant paper types (e.g. editorials and case reports) were removed where this was possible. A date limit of 2000 onwards was applied to the searches upon the advice of the study's Clinical Advisory Group.

The following sources were searched: Ovid MEDLINE(R) ALL <1946 to June 29, 2021> and Embase <1974 to 2021 June 29> were searched individually across the Ovid platform; Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR) were searched individually via Wiley; Science Citation Index via Web of Science; Database of Abstracts of Reviews of Effects (DARE) via the CRD; and the International HTA database. Details of the full search strategies are contained in Appendix 1.

In addition, the following resources were searched for any unpublished, ongoing, or completed studies: International Prospective Register of Systematic Reviews (PROSPERO) via the CRD; 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).

All of these above sources were searched on 30 June 2021. EndNote 20's default settings for deduplication was used to deduplicate the records, with those marked as duplicates checked by eye. Following this, various combinations of EndNote fields were compared against each other in a further manual process of deduplication, with records marked as duplicates checked by eye.

Owing to resource limitations, Conference Proceedings were not searched separately. However, we consider that the main databases that were searched would have captured the majority of conference abstracts (CAs) eligible for our review.

On 11 April 2022, reference lists of relevant systematic reviews and included articles were checked to identify any further relevant studies.

Forward citation searching of included articles was planned in the original protocol.[12] However, the research team have since received funding to convert the REFoRMS-SR to a living review and therefore, forward citation was not performed.

Although this had been planned in the initial protocol, due to limited resources and minimal responses to requests for additional data, authors of included studies were not contacted to seek further studies.

## Screening

The eligibility criteria used to determine whether studies should be included in the review are provided in Table 1. Study selection was conducted using Rayyan Software. Title and abstract and full-text screening was conducted independently and in duplicate by at least two researchers (LB, CE, JM and GB). Any conflicts or disagreements were resolved by a third reviewer or discussion within the review team. Foreign language studies that were included at the title and abstract stage were screened by a translator to determine eligibility based on the full-text. Data from the studies that were deemed eligible at this stage were extracted by the translator using the same data extraction form. Studies assessing an intervention in multiple tumour types were included if the outcomes for patients with rhabdomyosarcoma were reported separately.

The corresponding authors of studies were contacted to clarify whether studies should be included if the information provided was unclear, for example when tumour type was unclear or ages were not reported. Reminder emails were sent one to two weeks after the initial email, and studies were excluded if no response was received within two weeks from the reminder email.

Clinical trial registrations (CTRs) were screened in duplicate. For CTRs that were completed but where no corresponding publication could be identified, study authors were contacted by email and if no corresponding publication was provided, then only the CTR record was included in the review.

***Table 1.*** *Study Inclusion and Exclusion Criteria, based on the Population, Intervention, Comparator, Outcome and Study Design (PICOS) framework*

| PICOS | Inclusion and Exclusion Criteria |
|---|---|
| **Population** | *Inclusion Criteria*<br>● Patients with relapsed (recurrence of disease after scans demonstrating no evidence of active disease, or as defined in each study) and/or refractory (disease which has not shown sufficient radiological response or has clinically progressed, or as defined in each study) rhabdomyosarcoma.<br>● Patients 0-17 years old inclusive. Studies that had patients beyond this age range were included as long as 50% or more of the patients were in this age group.<br>● Studies including patients with other conditions were eligible for inclusion provided that greater than 50% of included patients had relapsed and/or refractory rhabdomyosarcoma or the data relating to this group could be extracted separately.<br><br>*Exclusion Criteria*<br>● Pre-clinical and animal studies of treatments for rhabdomyosarcoma were not eligible for inclusion. |
| **Intervention** | *Inclusion Criteria*<br>● Any treatment given with the intention of disease control, including with palliative or curative intent. This included traditional chemotherapeutic agents (for example, irinotecan), or novel agents (for example, bevacizumab), alone or in combination, including medications given in combination with surgical approaches and/or radiotherapy.<br><br>*Exclusion Criteria*<br>● Studies aimed to reduce the occurrence of or treat second primary malignancy in patients with rhabdomyosarcoma secondary to cancer predisposition syndromes.<br>● Studies which evaluated treatments for symptom management in patients with rhabdomyosarcoma. |
| **Comparator** | *Inclusion Criteria*<br>● Another intervention<br>● Placebo<br>● Standard of care<br><br>Studies didn't need to have a comparator group but were still eligible if reporting relevant outcomes. |
| **Outcomes** | *Inclusion Criteria*<br>● Primary Outcome: Survival (Event Free Survival, Overall Survival)<br>● Radiological response rates by RECIST criteria (Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD)).<br>● Quality of Life, measured by specific assessment tools (e.g. PedsQL), and also by experiential or qualitative data<br>● Side Effects/Adverse Events and tolerability<br>● Burden of therapy, including but not limited to inpatient stays, appointments, number of doses, supportive care burden, travel burden<br>● Costs/measures of cost-effectiveness<br><br>There were no restrictions on the time frame of measurement for which the data were sought. |
| **Study Design** | *Inclusion Criteria*<br>● Early phase studies, including single arms or randomised between two or more options.<br>● Early phase studies included:<br>  ● "First in child" studies (traditionally phase 1)<br>  ● Dose finding studies (traditionally phase 1b/2a)<br>  ● Proof of concept/efficacy studies (traditionally phase 2b)<br>  ● Early effectiveness studies (traditionally phase 2b/3).<br>● No language or geographical limitations were applied<br>● Published from 2000 onwards.<br><br>*Exclusion Criteria*<br>● Studies where enrolment ceased prior to 2000. |

## Data extraction and Quality Assessment

Prior to data extraction, the reviewers cross-checked any links between identified CTRs, CAs and full-text publications, as well as searching for additional reporting linked to each included record. As such, each study may include some, or all, of a CTR record, CAs and full text publications. Where multiple sources of data about a study were identified, data were extracted from the most helpful source: that is full text where available, if not, then conference abstract where data were available, and CTR record only where this was the single source of data for the study. If limited data was available (e.g. within a conference abstract) and other data sources were identified (e.g. CTR record), then data extraction was supplemented from the additional data source, and this has been reported within the results. In the cases where trials were registered to multiple CTRs, this was noted. This meant that the number of initial records, and number of unique studies was different, but unique studies are tracked.

Data extraction was conducted by one reviewer (LB, CE and JM). A second reviewer (LB, CE and JM) checked the data extraction for each study and disagreements were resolved by consensus or following discussion with the review team. Further details of the data extraction methods are described below.

### Full-Text Data Extraction

Full-text data extraction was conducted by one reviewer using forms in the Qualtrics Software (Provo, UT). The fields included in the full-text data extraction form were based on five clinical trials known to be eligible for inclusion prior to the commencement of the review.[13-17]

Data from each publication including study characteristics (e.g. phase, single/multicentre, enrolment dates and key eligibility criteria), details of the intervention and comparator (if applicable), patient's demographic and disease characteristics, adverse events and outcomes was extracted (see Appendix 2 for a full-text data extraction template). Where all authors of a manuscript were affiliated with institutions in the same country, the research reported was presumed to have been conducted within that country (unless stated otherwise). If authors came from institutions in multiple countries, and the location of the research was not directly described, then this was considered to be "not reported".

Given that some studies included patients with a range of tumour types, the following decisions were made about the granularity (i.e., rhabdomyosarcoma patients only or all participant data) of the data to be extracted:

Data on patient characteristics was extracted for all patients regardless of histology unless the data was reported separately for rhabdomyosarcoma patients.

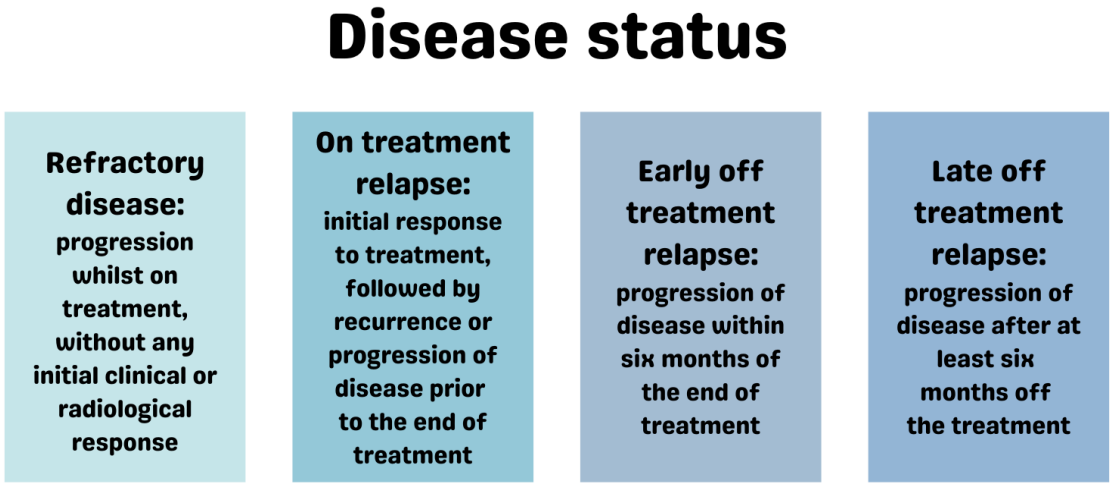
Data regarding the clinical outcomes was extracted for the rhabdomyosarcoma patients only. Pooled outcome data (such as an objective response rate [ORR] across all tumour types) was not extracted. Where outcome data for rhabdomyosarcoma patients could be calculated (e.g. ORR based on response rates), this was reported.

Data on the adverse event profile for the intervention of interest was extracted for all patients regardless of histology, based on the assumption that the safety profile of a drug is not dependent

on the disease characteristics of the individuals. Where toxicity-related death was not reported, it was assumed that none occurred.

Where available, we aimed to categorise patients according to relapsed/refractory status (see Figure 3). However, due to poor reporting quality, these data were rarely available and therefore have not been considered further.

***Figure 3.*** *Categories used to define disease status*




Conference abstracts without any clinical trial or full-text data were potentially eligible to be extracted. However, for CAs that did not provide separated data for rhabdomyosarcoma patients, they were not deemed eligible. The decision not to contact authors of CAs without separated data was based on two pragmatic reasons: 1) a balance between time spent contacting researchers for full data and the amount of eligible data we would receive; and 2) any fully available data published at a later point would be potentially available for extraction during the Living-REFoRMS review (discussed within Discussion section of this report).

Studies with multiple arms that only had rhabdomyosarcoma patients in one arm were handled as single arm studies. Similarly, studies with multiple arms that were non-comparable, were treated as single arm studies with each arm being extracted separately.

Studies extracted from CA and full-text publications were referred to as 'published studies' rather than 'completed studies'. A CA or full-text publication may not always represent a study that has completed, e.g. where the study is ongoing but data relating to a subset of patients have been published. In addition, some completed studies identified within clinical trial registries have not been published.

### Clinical Trial Registration Data Extraction

CTR data extraction was conducted by one reviewer (LB, CE and JM), and checked by another (LB, CE and JM), using Google Forms. The data extraction form was piloted based on trial registrations registered on a number of CTR sites (e.g. clinicaltrials.gov, WHO registry network and UMIN clinical trials registry). The data extracted included information such as registration number, recruitment status, eligibility criteria, study start and end dates, phase, estimated or actual enrolment, intervention of interest, and outcomes to be measured (see Appendix 2 for a full-text data extraction

template). For studies registered on multiple CTRs, data was initially extracted from clinicaltrials.gov and supplemented by additional information from other registries. Where clinical trials matched to a CA with no separable rhabdomyosarcoma data, the CTR record was extracted. CTR records identified through database searches were extracted and updated where necessary up to the date of 18 March 2022. CTRs identified from other sources were extracted according to the date of identification by the REFoRMS team. Additional updates to CTRs will be identified within the Living-REFoRMS project.

### Quality Assessment

Owing to the absence of any validated quality assessment tool for early phase studies, we decided to use an adapted version of the Downs and Black Checklist in this study.[18] This 27-item quality assessment tool was chosen as it allows for the assessment of the methodological quality of both randomised and non-randomised studies. In terms of adaptations, we considered the following:

- *Item 8: Have all important adverse events that may be a consequence of the intervention been reported?* This question could be answered as 'yes' if the study does not report G1-2 adverse events, as long as they reported G3-4 adverse events.
- *Item 19: Was compliance with the intervention/s reliable?* This question was answered 'yes' unless non-compliance was directly reported.
- *Item 27: Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a difference of x% and y%?* If the study provides a sample size calculation, this question was answered 'yes'. Owing to the large number of phase 1 dose finding studies, an additional category was created to capture sample size reported and used methods such as the 3x3 or rolling six design to determine the number of patients in each group. Studies which report these standard dose-finding methods were deemed to have provided a sample size calculation.

Quality assessment was performed for completed studies, reported in either full-text manuscripts or CAs. CTR records were not quality assessed. Quality assessment of each study was conducted by one reviewer (LB, CE and JM) and checked by another (LB, CE and JM). Disagreements were resolved by consensus.

## Analysis

Key study characteristics, quality assessment and outcome data were summarised in narrative and tabular forms. Outcome data are presented in order of importance to the parent group. Meta-analyses were planned within the protocol but ultimately not performed due to significant clinical heterogeneity of the interventions.[12] Nonetheless, the narrative synthesis focused on key groups determined to be of interest a priori:

- Relapsed vs refractory disease
- Histological and genetic risk strata (Embryonal vs alveolar rhabdomyosarcoma, FOX/PAX fusion status)
- Location of primary site (if known)
- Local vs metastatic relapse
- Any prognostic indices identified by the study (e.g., Oberlin score for metastatic disease[4])

- Relapse within prior radiotherapy field (or not)
- Timing of relapse (as per groupings described in population)
- Extent of prior therapy
- Targeted (based on a specific genetic mutation within the patient's rhabdomyosarcoma cells) vs traditional cytotoxic therapies
- Patient age (as reported most likely, but if possible, dichotomising at 10 years old at first presentation)

Furthermore, the study design, publication type (full text vs CA), language of publication, geographical location, and quality assessment were taken into consideration when synthesising the data.

Risk of publication bias could not be assessed with funnel plots or statistical analysis as insufficient comparative studies reported the same outcome. Nonetheless, we have considered the risk of publication bias in this literature within our analysis and discussion.

# Results

## Study selection

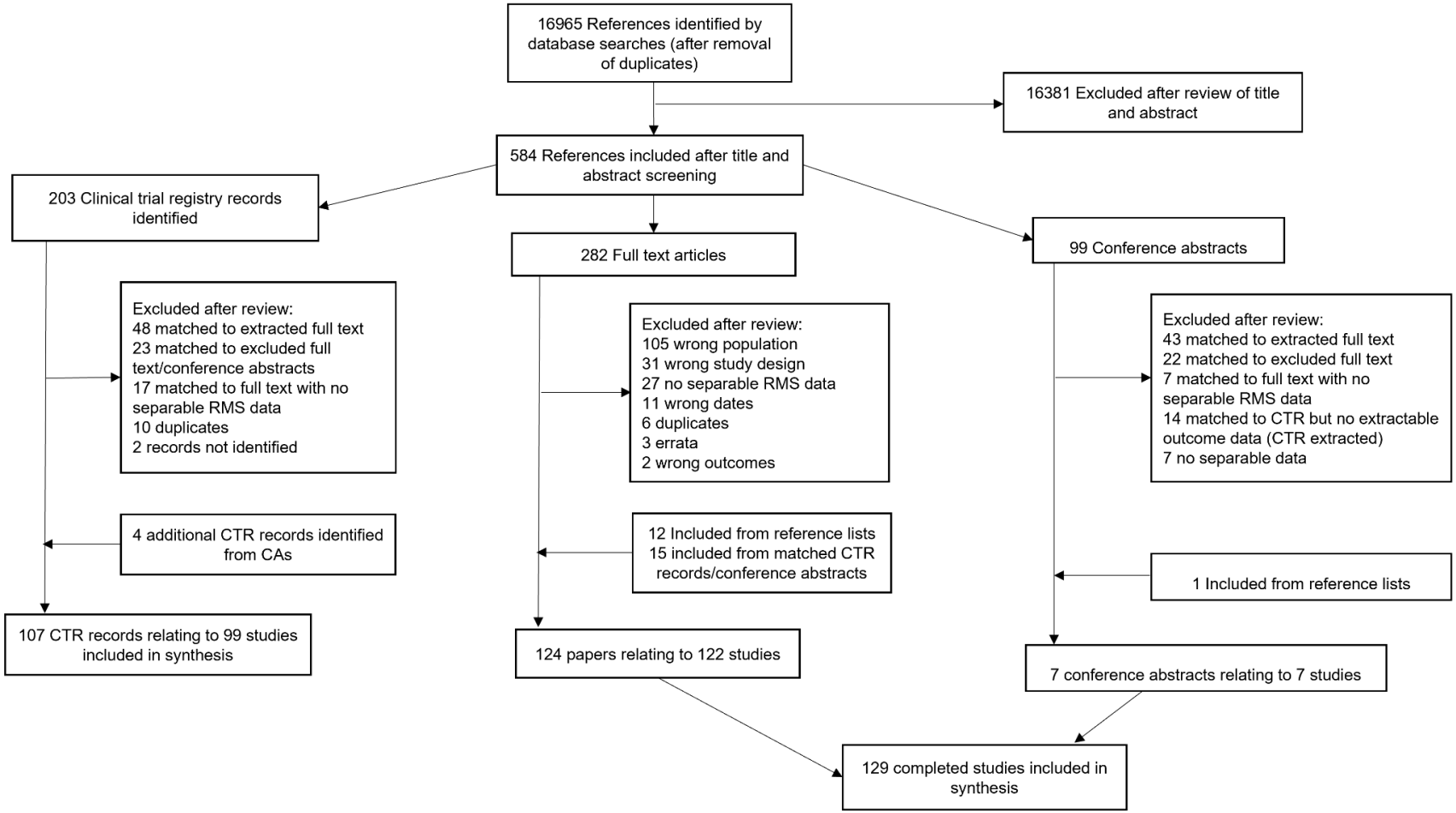
Overall, 16,965 records were identified by the database searches after the removal of duplicates. Following title and abstract screening, 16,381 studies were excluded (96.6%). There were 368 conflicts corresponding to 2.2% of the total records screened. Of these conflicts, 170 were eventually included (46.2%).

Five hundred and eighty-four studies were deemed eligible at title and abstract screening and were reviewed further. This included 203 CTR records, 99 CAs and 282 full-text publications. Further details on the study selection process are shown in the PRISMA flow chart (Figure 4) and details of studies excluded at full text stage are provided in Appendix 3.

Twenty additional potentially eligible full text papers were identified after matching to the included CAs and CTR records. Sixty-three potentially eligible papers were identified from reference lists.

Overall, 75 authors were contacted for further information, including 58 corresponding authors where we had queries about the full-text publications, and 17 authors where we had queries with the CTR record. We received replies from 32 authors (26 [45% response rate] from full-text publications and six [35% response rate] from the CTRs). Based on the responses to these emails, five studies were included (all full-text publications).

***Figure 4.*** *Flow diagram for study selection*



## Published Studies

### Studies with full text available

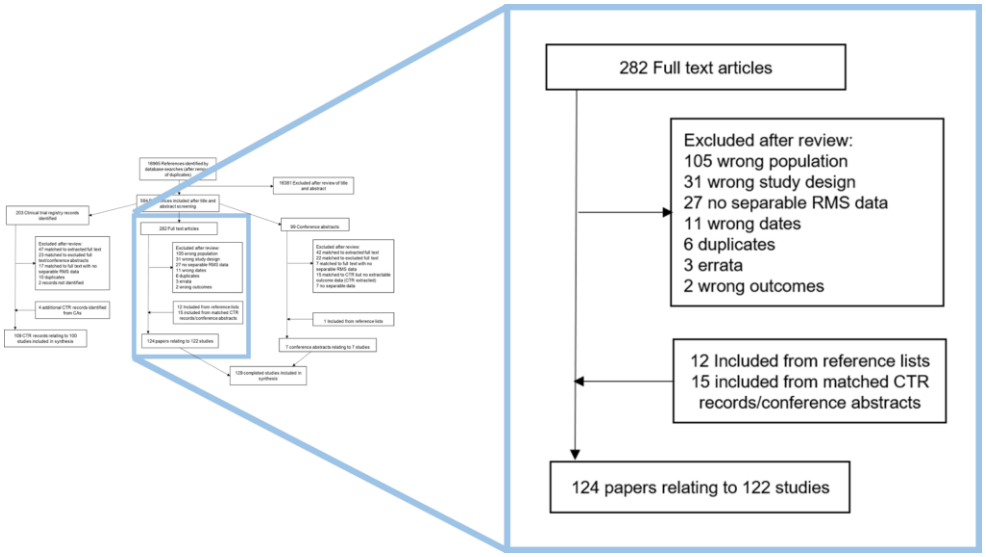



***Figure 5.*** *Breakdown of full-texts*

Two hundred and eighty-two full-text papers were screened for inclusion in the review, including 12 foreign language papers. Ninety-seven (95 individual studies)[1,13-17,19-108] of these were deemed eligible and 185 were excluded. There were conflicts on 31 full-text papers (11%); eight of which were eventually deemed eligible for inclusion. Reasons for exclusion include: 105 papers with the wrong population; 31 papers with the wrong study design, 27 papers with no separable rhabdomyosarcoma data, 11 papers that finished enrolment prior to 2000, six duplicates, three errata papers, and two papers with ineligible outcomes.

From the 12 non-English language papers included, there were two duplicates resulting in 10 unique publications for consideration: four published in Chinese, four in Russian, one in German, and one in French. Seven of these studies were excluded at the full-text screening stage. Of three potentially eligible studies, the authors of two Chinese papers were emailed for further information but we did not receive a response after four weeks, and therefore were also excluded. Only one eligible study was successfully translated (Russian).[57] The eligible paper and data extraction form were sent to the translator, and in response we received a translation of the paper in the form of a Word document. We used the Word document translation to fill in the data extraction and quality assessment forms from the data that was available. Any unclear or unavailable information from the translation was labelled as such in the appropriate forms.

Twenty-seven full text publications with extractable data were identified from additional searching (15 identified from included clinical trials/CAs[8,109-122] that were not identified in the original search, and 12 from reference lists[123-134]). In total, 124 papers, relating to 122 studies proceeded to data extraction.

### Studies with conference abstracts (+/- CTRs)

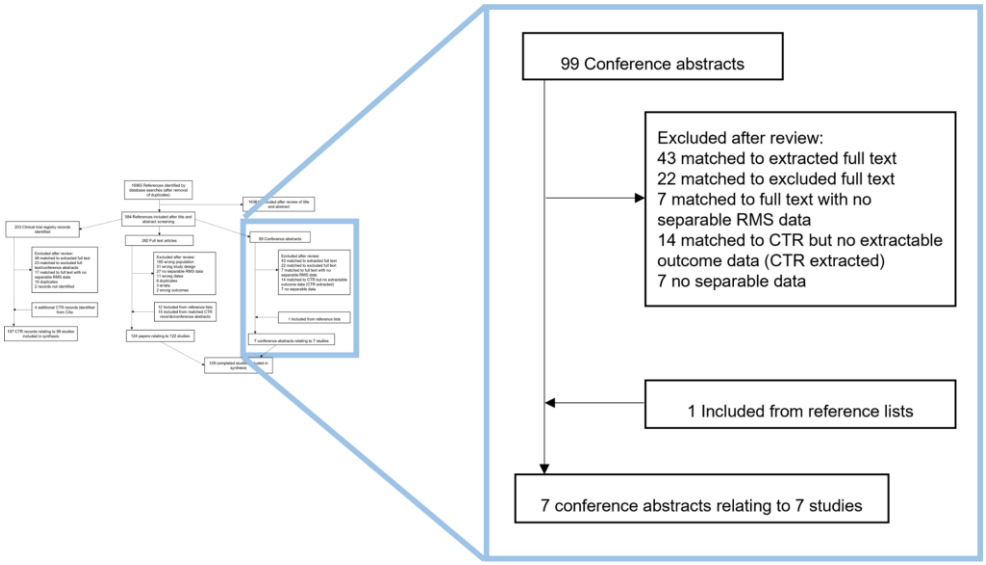



***Figure 6.*** *Breakdown of conference abstracts*

Ninety-nine CAs were identified after title and abstract screening.

Seventy-four of these abstracts were excluded because they matched to a full text publication/CTR with data, of which:

- 43 CAs matched to a full text publication that was extracted
- 22 CAs had a matched full text publication that was not deemed eligible for inclusion (and consequently the CA was also ineligible):
    - 10 excluded for wrong population
    - 10 excluded for wrong study design
    - 2 excluded for wrong outcomes
- 7 CAs had a matched full text publication with no separable rhabdomyosarcoma data, the authors of which were emailed for additional information and none replied.
- 2 CAs (without separable data) had a matched CTR record where outcome data was reported but was not separable for rhabdomyosarcoma patients

Fifteen CAs were matched to a CTR record but no full text. Three of these CAs provided separable data for rhabdomyosarcoma patients and were consequently extracted and are included in the synthesis of completed studies[135-137] (of these, one CA linked to a CTR record that provided the majority of data extracted for this study[137]). For 13 of the CAs (with a CTR record but no full text), neither the CA or CTR record provided extractable outcome data for rhabdomyosarcoma patients and therefore the CAs were not extracted and all information relating to these studies was collected from the CTR record.

There were 10 CAs that were not matched to a CTR record or full text publication. All of these abstracts were potentially eligible for extraction, however, only three provided separated data for rhabdomyosarcoma patients and were subsequently extracted.[138-140]

Following reference list searches, one additional CA with extractable data was identified. No matched CTR record or full text publication could be identified and therefore this CA was also extracted.[141]

In total, 93 CAs were not deemed eligible for extraction (94%), whilst seven CAs were included in the synthesis of published studies.[135-141]

The total number of studies included in the synthesis of published studies was 129 (see Figure 4). Three of the studies included seven non-comparative arms which have been extracted separately.[15,45,75] Thus, for the synthesis of published studies, there are 133 included cohorts.

***Figure 7.*** *Breakdown of published studies included in the synthesis*


## Clinical Trial Registrations

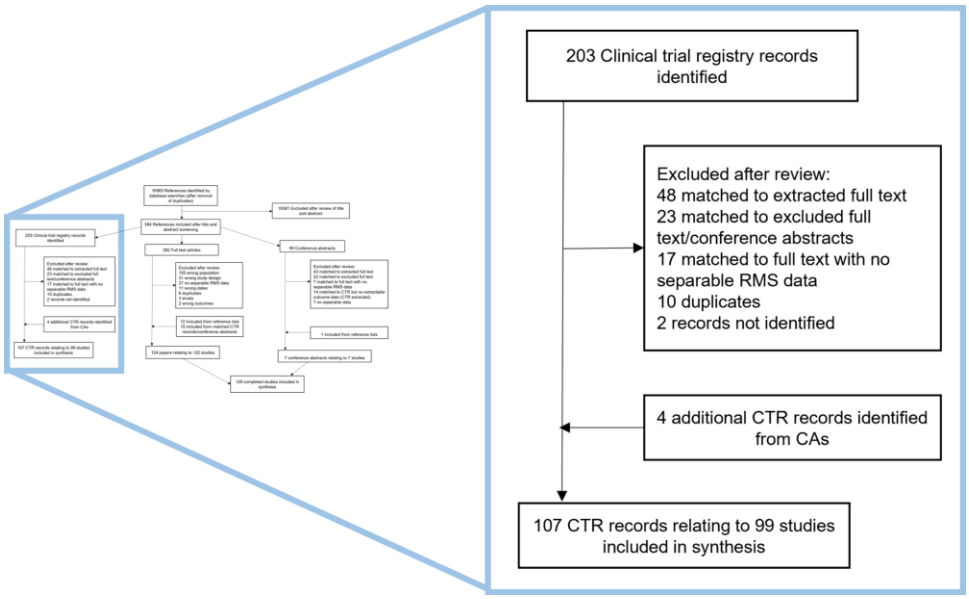



***Figure 8.*** *Breakdown of CTRs*

From 203 CTRs included at the title and abstract stage of screening, 12 registry records were initially removed (10 duplicates and two records not identified); therefore 191 records of 169 unique studies were deemed eligible.

Of the 191 CTRs, 88 records were matched to a CA and/or a full text paper and were not extracted. Reasons for not extracting these studies include:

- 48 records had a full-text publication with extractable data

- 23 records had associated CA/full text publications which were not deemed eligible for inclusion:
    - 21 excluded for wrong population
    - 1 excluded for being completed prior to 2000
    - 1 excluded for being a supportive care trial
- 17 records had associated full text publications with no separable rhabdomyosarcoma data and therefore the CTR record was not extracted.

The remaining 103 records were extracted.[142-244] Importantly, three of these CTR records link to another included publication:

- One study had an unknown status on the CTR, had an included CA, and no full text.[207]
- One active study was extracted as a full text[50] and a CA[135], as the full-text only provided data from the dose-escalation phase, and the CA only presented partial data - this has been labelled as appropriate in the relevant tables.
- One trial which is still recruiting links to a full text with only partial data so both records have been extracted.[71]

Four additional CTR records were identified from CAs (that did not have a full text) that were eventually extracted as the CAs did not have extractable data.[245-248] Therefore, in total, 107 CTR records relating to 99 studies were extracted and included in the synthesis of clinical trial registry data.

# Published studies

## Quality Assessment

Assessing the quality of the primary studies is an important step of conducting a systematic review. Evaluating how a study has been designed and reported helps to explore the effects chosen methods have on the results and determine whether the study findings are accurate (unbiased). Quality assessment provides an opportunity to gauge the strength of the included evidence, and also means recommendations can be made on how studies should be conducted or reported in the future.[249]

Overall, in the REFoRMS review, the study quality did not impact synthesis owing to minimal differences in the quality assessment between studies.

### Single Arm Studies

Single-arm studies are lower quality by their very nature because the lack of a comparator limits the ability to reliably estimate the effectiveness of an intervention.[250] Therefore, the quality assessment of a single-arm study should be viewed relatively to the other single-arm studies included in this review.

The 120 single-arm studies[13,15-17,19-72,74-85,87-91,93-140] were assessed based on the 17 Down's and Black Quality Assessment criteria relevant to single-arm studies.[18] In addition, the three studies which contributed non-comparative arms were assessed using this version of the tool.[15,45,75] Of these studies, one provided different levels of reporting for each arm of the studies, thus the arms have been quality assessed separately.[15] Therefore, 124 quality assessments were performed.

Overall, the studies included were reasonably well reported, with the majority reporting the aims/objectives, main outcomes, intervention of interest, and findings well. Several studies did not provide information about the trial's eligibility criteria and rather only provided details of the included participants. Adverse events were clearly reported in most studies. The random variation of the data was not reported in 20% of studies. See Figure 9 for a graphical representation of the quality assessments of single arm studies, and Appendix 4 for the full quality assessment table.

***Figure 9.*** *Graphical representation of the quality assessments of single arm studies*

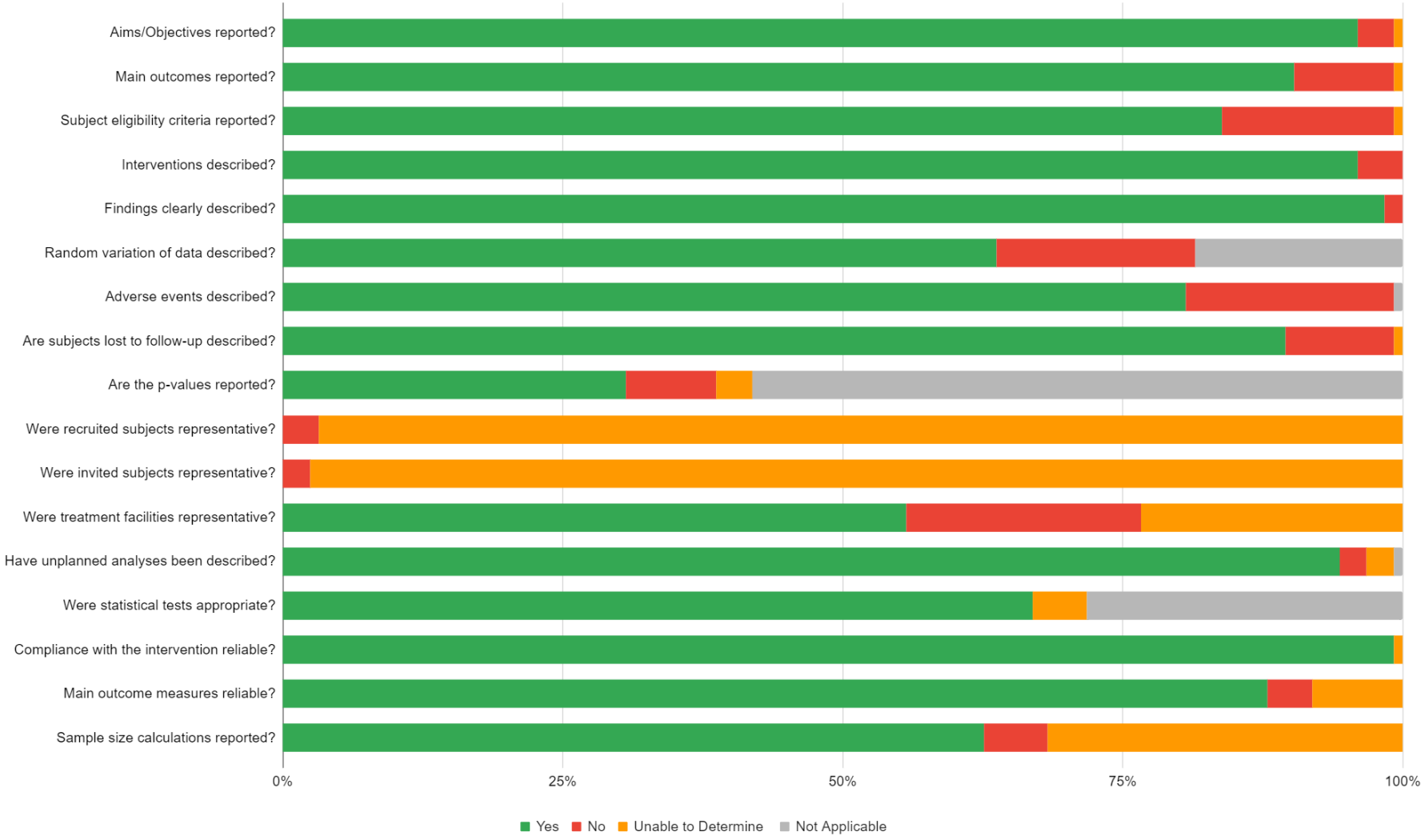


***Figure 10.*** *Graphical representation of the quality assessments of multi-arm studies*

### Multi-arm Studies

The six multiple-arm studies[8,14,73,86,92,141] were assessed on all 27 Down's and Black Quality Assessment criteria.[18] The majority of the studies provided reasonably comprehensive reporting of their trial. Five of the six multi-arm studies randomised patients into treatment arms, but only one study reported that randomisation was concealed or the study participants blinded to the intervention; and only two studies reported that they blinded the outcome assessors. Although most studies described the different baseline characteristics between the two arms of these studies, only half of the studies accounted for differences in populations or the lengths of follow-up in their analysis. It was unclear from the reports how generalisable the results were. As is common in many early phase trials, the wider potentially eligible population was not often described and some interventions would only be available in highly sub-specialised centres. The internal validity of the included studies were reasonable; most studies had used appropriate statistical tests (where applicable), used reliable outcome measures, and reported all analyses *a-priori*. See Figure 10 for a graphical representation of the quality assessments of multiple-arm studies, and Appendix 4 for the full quality assessment table.

## Synthesis

### Demographics of included studies

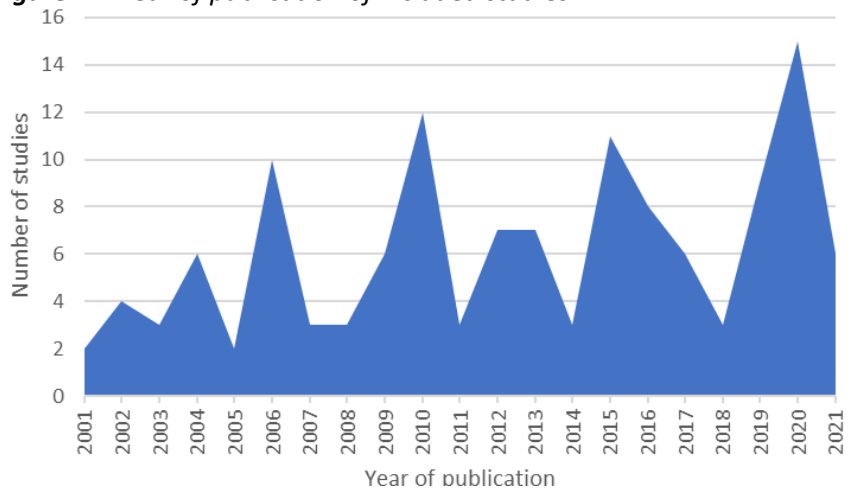
The majority of studies included the USA as a country of recruitment, where it was reported (n=71; 62%, (115 studies in total)) [14,15,22-24,28-30,36,40-45,47,49,51,53-56,58,59,63-68,71,73-75,77,80-84,87,88,90,92,94,95,97-100,102,103,105,108-113,115,116,120,124,126,127,131,133,137]. Other countries where patients were recruited to five or more studies include (number of studies): Italy (16),[8,25,26,31-33,37,38,48,69,78,79,110,112,113,140] France (13),[8,16,17,45,48,69,110,112,113,130,137], Canada (8),[82,90,110,112,124,128,134,137] Germany (8),[48,49,101,110,112,113,117,122] UK (8),[8,17,35,45,48,110,112,113], Japan (7),[19,91,114,119,121,132], Netherlands (6),[8,27,48,69,110,113] and Spain (6),[8,85,89,110,113,137]. Europe (countries not specified) was also reported in three studies,[50,82,111] whilst the country of recruitment was unreported in 14 studies[13,20,21,34,52,62,72,93,106,118,128,135,139,141]. Most studies were conducted in single countries (83%).[14-16,19,22,23,25-33,35,37-44,46,47,51,53-61,63-67,70,71,73,74,77-81,83-89,91,92,94-100,102,104,105,107,108,115-117,119-121,123,125-127,129-134,136,138,140]

Within the cohorts, the most common type of intervention was a standard single agent systemic therapies (n=29; 21.8%).[13,17,20,23,26,28,29,32,38,46,53,61,66,72,78,82,91,101,102,105,107,108,114,124-126,131,133] Of these, irinotecan was used in eight cohorts[17,26,28,29,46,91,114,124] (one study expressly stated irinotecan weekly[28]), oxaliplatin[23,125,133] and vinorelbine[32,66,126] was used in three cohorts each, high-dose ifosfamide[38,78,107], ixabepilone[58,105], nab-paclitaxel[20,82] and topotecan[53,131] was used in two cohorts each, and docetaxel[108], doxorubicin[72], etoposide[61], gemcitabine[101], pemetrexed[102], temozolomide[38] and trabectedin[13] were all used in one cohort each. Other interventions included (number of cohorts): standard multi-agent systemic therapies (24)[15,16,22,25,31,33,35,48,51,67,69,74,76,77,79,87,90,93,100,104,115,129,130,139], novel single agent systemic therapies (24)[36,37,42,45,47,49,50,52,62,63,68,70,81,84,94,95,103,106,111,116,118,128,136,137], novel multi-agent systemic therapies (22)[15,21,24,34,40,41,43-45,59,64,75,83,88,97,98,120,134,135], cellular therapies (6)[54,56,57,80,89,117], vaccine therapies (6)[19,30,65,119,121,132], haematopoietic stem cell transplantation (HSCT; 5)[71,85,109,138,140], biomarker driven therapies (4)[110,112,113,122], metronomic chemotherapy (3)[39,123,127] and other approaches (4)[27,55,60,96].

The six comparative studies explored a variety of interventions: two compared different standard chemotherapy regimens (carboplatin+irinotecan vs irinotecan alone[141]; vincristine + irinotecan vs vincristine, irinotecan and temozolomide[8]); one study compared different dosing schedules (combined with other chemotherapy agents)[73], one compared two different novel agents added to multiagent chemotherapy, (vinorelbine, cyclophosphamide and either bevacizumab or temsirolimus) [14], one compared metronomic chemotherapy with best supportive care[86,251], and one compared different donors (sibling vs matched unrelated donor) in allogeneic HSCT with minimal conditioning regimen[92]. These studies included, on average, more patients than the single arm studies (96 participants (not-rhabdomyosarcoma specific)) in each multi-arm study population vs 38 participants in each study population for the cohorts).

Whilst the number of included studies published varied from year to year, the trend progressively increased over the time period of the review (see Figure 11; note searches run to June 2021).

***Figure 11.*** *Year of publication of included studies*




## Demographics of included participants

Across the 129 studies (133 cohorts), at least 1,100 patients with relapsed and/or refractory rhabdomyosarcoma were included (see Table 2 for Demographic characteristics of included studies). Seven studies were specifically open to recruiting only rhabdomyosarcoma patients (6.2%),[8,14,17,27,33,79,138] three of which included newly diagnosed as well as relapsed and refractory rhabdomyosarcoma patients[27,79,138]. The majority of the studies were open to recruiting relapsed and refractory patients (n=94; 73%).[8,14-17,20,22-26,28,29,31,34-36,38-42,44,46-54,56,58,59,61-67,69,71,72,75,82-84,86-92,94-96,98,99,102,107,108,110-114,117,118,120-123,125-127,129-132,134-136,140]

The age of participants was extracted in 131 (98%) cohorts, either for the whole population (n=77),[13,14,16,21-23,28-32,34,36,39,40,42-48,50,53,59,60,62,64,66-68,72-78,81-84,88-90,93,94,97,100-105,108,110-113,115,116,120,123,124,126,128,130,133,135,136,140] a subgroup of the whole population (n=5)[41,52,69,106,134] or for rhabdomyosarcoma patients specifically (n=49)[8,14,17,19,20,24,25,27,33,35,37,38,49,51,54,55,58,61,63,65,70,71,79,80,85-87,91,92,95,96,98,99,107,109,114,117-119,121,122,127,129,131,132,137,138,251]. Of the cohorts reporting age specifically for rhabdomyosarcoma patients, 22 (65%; where 34 cohorts reported median age) included patients with a median age ≥10 years.[8,19,20,23,38,49,51,55,57,58,61-63,71,79,92,96,99,109,114,118,122] Where age range was reported, only eight cohorts (24%; 34 studies reporting range[8,19,20,23-25,27,33,35,37,38,49,51,55-58,61,63,71,79,80,86,91,92,96,98,109,114,118,122,127,129,132,251]) included any participants under the age of three

years.[8,23,27,33,38,49,99,132] Nine studies (26%; 34 studies reporting range[8,19,20,23-25,27,33,35,37,38,49,51,55-58,61,63,71,79,80,86,91,92,96,98,109,114,118,122,127,129,132,251]) included a minority of participants over the age of 18 years, whose data could not be separated from that of younger participants.[20,23,33,49,58,63,99,118]

Data on the sex/gender of participants was reported in 117 (88%) of cohorts, either for the whole population (n=79)[13,15,16,21-23,25,26,28-32,36,39,40,42-48,50,52,53,58-60,62,64,66-68,72-75,77,78,80-84,88,90,93,94,97,98,100-105,108,110-113,115,116,120,123-126,128-130,132,133,136], a subgroup of the whole population (n=4)[41,69,106,134], or for rhabdomyosarcoma patients specifically (n=34)[14,17,19,20,24,27,33,35,37,38,49,51,54,56,57,61,63,70,71,79,86,87,91,99,107,109,114,117-119,121,122,131,137,251]. Sex/gender was reported as a single binary characteristic in all cohorts included in the review. Sixty-five cohorts used sex as the descriptor,[13,15,17,19-22,24,25,27,29,30,33,35,38,40,41,45-47,52,56,59-62,64,67,70-73,75,79,81,83,84,86-88,90,91,98,100,103,105,106,109,112,113,115,116,120-122,126,128,137,251] 29 cohorts used gender,[23,26,31,32,37,39,48,51,53,57,58,63,66,68,69,74,78,99,101,102,104,107,108,110,114,117,119,130,131] and 15 simply stated male/female[28,42-44,54,77,80,93,94,97,123,124,132,134,136]. Six cohorts reported only the number of male participants, without reporting other gender(s).[16,82,111,125,129,133] Two cohorts reported only the number of female participants.[50,118] Where the number of both male and female participants with rhabdomyosarcoma were reported, the ratio was 161:133 (54.8% male). This is similar to the 55.9% male reported by SEER registry data for all rhabdomyosarcoma patients at first presentation.[252].

Only 41 (31%) cohorts reported any race/ethnicity data (32 for the whole population[13,21,23,30,32,36,44,47,58,59,62,64,66,67,75,84,88,90,94,100,102-104,108,110,113,115,120,128,133], one for a subgroup[41], one for an unclear group[27] and seven for rhabdomyosarcoma patients specifically[49,63,92,99,118,131,137]). Race and ethnicity were reported variably, and twelve cohorts reported both race and ethnicity.[30,36,44,47,59,64,84,88,94,115,118,120] Of those cohorts where data were reported specifically for rhabdomyosarcoma patients, 44 (70%) participants were white, 9 black, 0 Asian, 6 other, and 4 unknown (total 63 in these cohorts). Recent data from the USA demonstrated no difference in outcomes based on racial group for patients with rhabdomyosarcoma enrolled on clinical trials.[252,253] Nonetheless, it is essential to consider that access to clinical trials is affected by multiple factors, and that reporting of race/ethnicity stratified data is essential in continuing to understand the influences on outcomes.

Fusion status was reported in only two included cohorts, which may reflect that fusion testing only became available within the time frame of this review and, in Europe, has only become standard practice within the past five years (as reported by the REFoRMS CAG).[54,122] Considering this was identified as a variable of interest to our parent group, it would be important for future research to consider this in their publications where relevant, and this data will be collected and reported within the future Living-REFoRMS project. Similarly, data regarding the reporting of the site of primary rhabdomyosarcoma was also rarely identified (15 cohorts provide exact site [14,17,19,26,27,33,54,61,66,70,76,79,96,119,129], and an additional four cohorts provide favourable/unfavourable site information)[8,15,73].

### Disease response

One hundred and thirty-three cohorts (including six comparative studies) contributed data to the outcome synthesis (Table 3). The number of evaluable rhabdomyosarcoma patients was not clear for a number of studies (indicated within the table). However, all included studies report outcome data for at least one patient with relapsed and/or refractory rhabdomyosarcoma. The majority of cohorts

(n= 83; 62%) reported outcome data for five or fewer patients with relapsed and/or refractory rhabdomyosarcoma.[19,21,22,24,28,30,34,35,37,38,40-46,50-52,54-57,61,62,65,67,70-72,74-78,80,83-86,88,89,91-98,101,105-107,109,111,112,114-117,120-122,124-134,138,139] As such, response rates for these studies should be considered with caution. Studies 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.

### *Survival (Progression Free Survival/Overall Survival)*

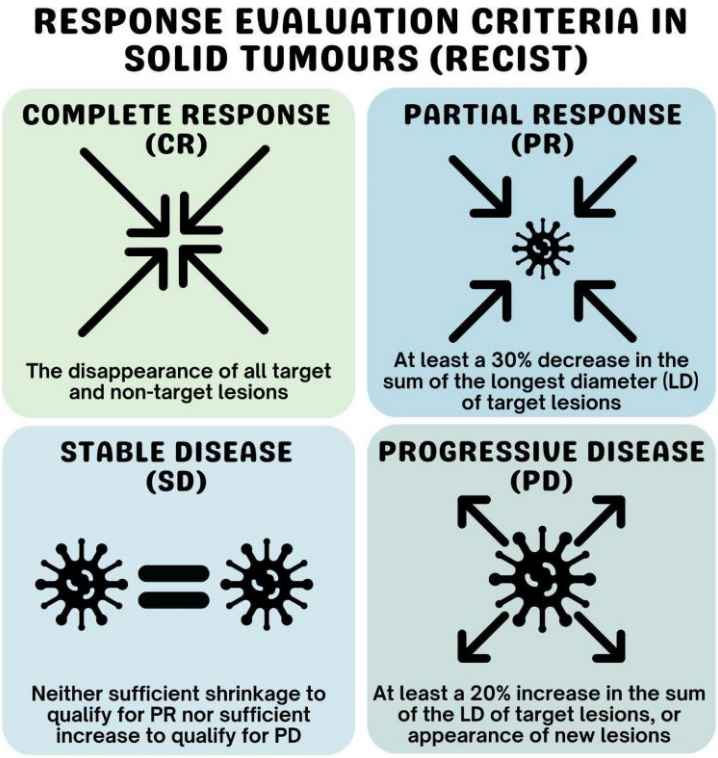
Progression Free Survival or Time to Progression was reported by a minority of studies (27 studies; 21%).[8,14,17,19,20,27,33,38,49,54,71,73,79,86,88,92,95,109,117,119,121,122,127,129,130,137,138] We acknowledge that these are technically different descriptors but, given that no study reported both measures and, in this population, the differences between the two are unlikely to be clinically significant, we have reported the results combined. Where reported, the median Progression Free Survival/Time to Progression was ≤6 months in 19 cohorts (70%), reflecting the challenging clinical situation for children and young people with relapsed and refractory rhabdomyosarcoma.[8,17,19,20,38,49,71,73,88,92,95,109,121,122,127,129,137] No single agent therapy (standard systemic therapies or novel agents) reported a Progression Free Survival/Time to Progression of >2 months.

Similarly, Overall Survival was reported by a minority of cohorts (26 studies; 20%)[8,16,17,19,20,38,55,60,61,71,73,85,86,95,96,107,109,119,121,123,137]; and only 15 (11.6%) cohorts reported both Progression Free Survival/Time to Progression and Overall Survival.[8,15,17,19,20,27,38,71,73,86,95,109,119,121,137]

### *Response rates*

The most commonly reported outcome of clinical effectiveness was response rate, primarily evaluated using the Response Evaluation Criteria in Solid Tumours (RECIST). The RECIST criteria assesses the change in tumour burden, including both tumour shrinkage or growth (also known as disease progression).[254] The RECIST criteria is based on measurements of lesions before and after the commencement of treatment via an image-based evaluation (e.g. X-ray, MRI or CT scan). The RECIST criteria categorises tumour burden into complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). The objective response rate (ORR) is a summary measure of the RECIST criteria, and describes the proportion of patients who achieved a complete or partial response. Figure 12 describes the RECIST criteria and its definitions.

***Figure 12.*** *RECIST criteria to assess tumour response*




In many studies, the timing of initial response assessment was after two courses (usually 6-8 weeks from study enrolment). Patients who progressed early after commencing treatment may not have been evaluable and thus in some studies were not reported. As such, disease response rates are likely to be lower than those reported within these studies.

Across all interventions, in total 59 out of 1151 evaluable children and young people showed a CR whilst an additional 190 patients had PR as best response. In the setting of early phase studies of relapsed and/or refractory rhabdomyosarcoma, on average 21.6% of people can expect an objective response, as defined by the RECIST criteria. We recognise that this is a very heterogenous group of populations and interventions, and that RECIST response does not necessarily correlate with duration or quality of survival, as such this should be interpreted carefully. However, we feel it is helpful for patients, families and clinicians to have an average across all studies to inform whether participating in early phase studies is something they wish to pursue.

Where it was possible to identify outcomes for patients experiencing their first relapse, the reported RECIST response rate for this group was 33.7% (29/86 participants, from seven cohorts).[15,25,35,56,87,92,119] Additional cohorts also included participants with first relapse but the outcomes for these were not separable from other relapsed and refractory patients.

Ten cohorts (8%) reported a 100% response rate (CR+PR) amongst rhabdomyosarcoma patients, and explored a wide range of interventions.[44,54,70,77,85,107,115,117,121,138] All 10 cohorts included fewer than five evaluable rhabdomyosarcoma patients, with eight cohorts including only one evaluable rhabdomyosarcoma patient. Due to these low participant numbers, response rates and subsequently, the effectiveness of such interventions for relapsed and refractory rhabdomyosarcoma, should be considered with caution.

### Quality of life

Two studies stated that they reported Quality of life (QoL) data, although this was not rhabdomyosarcoma-specific for either study.[39,86,251] In the study by Pramanik et al, self-report QoL scores were measured by child and parent up to four times.[251] There was no significant difference in health-related QoL between patients in the metronomic chemotherapy group vs placebo group at the second and later assessments. El Kababri et al reported Karnofsky/Lansky scores, with some improvement in these over time for 15% of patients.[39] Although this was reported as "quality of life" by the authors, Karnofsky/Lanksky scores are actually measures of performance status which evaluate ability to perform certain activities, rather than quality of life measures.

### Adverse events (AEs)

Following discussion with the REFoRMS parent group, only data for grade 3-5 adverse events were extracted for this review. The AEs felt to be particularly important for the parent group were neutropenia (and associated febrile neutropenia), thrombocytopenia, nausea, vomiting, diarrhoea, constipation, mucositis and weight loss. However, they also stressed the importance of reporting all significant AEs, to allow families and clinicians to be able to identify any AEs that were particularly important to the child or young person affected. For this reason, the above AEs are highlighted in bold in the AE table (Table 4), and all AEs reported by the studies are included. Notably, the parent group also felt hair loss to be an important AE, but this was not mentioned in any of the reported studies.

Our parent group also shared how the term "adverse event" sounds "very frightening", preferring the term side effects where this is relevant. Given the technical use of adverse events within early phase trials, we have used this within this report, and will do so within academic publications. However, we are working with the parent group to ensure that any patient/public facing materials are appropriately worded to facilitate understanding whilst maintaining accuracy, around this data.

Adverse event data were variably reported by studies included in the review (see Table 4). Some studies reported number of events, others reported the number of cycles or patients affected. Some disaggregated data based on which course of treatment the event occurred in, others reported summary information.

As per the Quality Assessment findings (see Figure 9 and 10, and Appendix 4), most studies used a standardised tool to assess for AEs; most commonly this was the Common Terminology Criteria for Adverse Events (CTCAE), or World Health Organization (WHO) classification.[255,256]

Three studies did not report any AE data[61,85,122] (and one regimen within a study had no AE data reported[15]), and eight who provided minimal data (e.g. "no severe treatment related AEs").[56,57,89,96,119,136,138,140]

Within the published studies included in the synthesis, over 4,500 participants were evaluable for toxicities (some studies did not report the number of patients evaluable).

As anticipated, the most common AEs were haematological, though these varied between interventions. A substantial number of laboratory test abnormalities were reported - the impact of these on patient symptoms and experience was generally unclear. Positively, in general, AEs relating

to nausea and vomiting were reported separately, which has previously been noted to be an important distinction for patients and families.[257]

Nineteen studies explicitly reported a total of 69 deaths, of which nine were reported to be treatment related or potentially treatment related, 32 determined not to be treatment related and were mostly due to progressive disease, and 28 not specified. [47-49,58,64,73,83,92,95,107,109,110,112,117,118,126,129,131,137] Thus, the majority of deaths within included studies related to disease progression rather than treatment-related mortality. Deaths due to disease progression were seen 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. This reflects the challenging situation of patients eligible for many of these early phase trials.

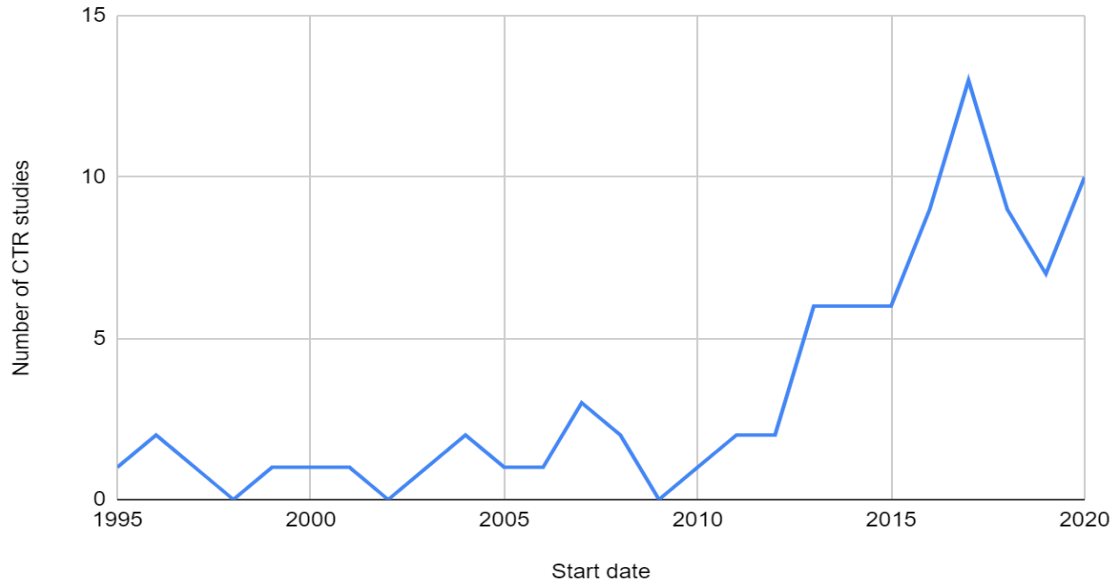
## Clinical trial registrations synthesis

Alongside published studies, the parent group felt that it was important to include CTRs in the review to get an overall picture of the trials currently open to children and young people with relapsed and refractory rhabdomyosarcoma. They felt that information about the availability of clinical trials was difficult to find online and a summary of this information was needed. The data from eligible CTRs is presented below.

Ninety-nine unique CTR studies were extracted (see Figure 8); 95 identified from the original systematic review search,[142-244] and four identified from matching CAs (that were included after title and abstract screening)[245-248]. We have used the word "studies" to refer to the research registered on these platforms, given that the majority do not meet the traditional definition of a trial. See Table 5 for details relating to included CTR records.

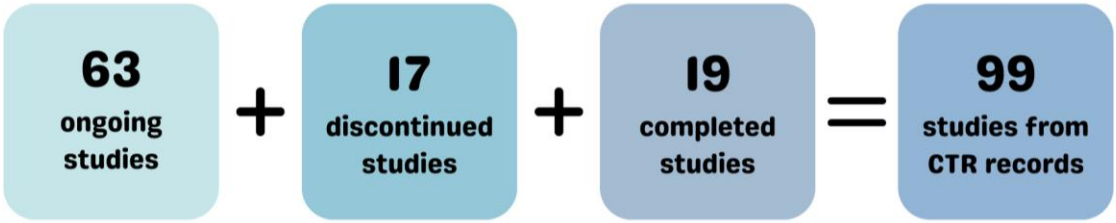
For the CTR studies where a start date was reported, the number of studies progressively increased over time (Figure 13). As only unpublished studies are included in this section of the synthesis, some increase would be expected over time as completed studies from previous years move into the synthesis of published studies.

***Figure 13.*** *Start date of included CTR studies*



Seventy studies were reported as being funded by an academic sponsor,[142,145,148,149,151,152,154,155,157-169,171-173,175-181,183-185,187,189-192,194,197-201,203-206,209,210,213,214,216-219,223,224,227,228,231,235,240,245-248] 17 by pharmaceutical companies,[144,146,147,153,156,174,182,193,195,202,211,212,215,226,232,239,243,244] six by both academic and pharmaceutical company sponsors,[150,170,174,208,230,242] and six by other funders (e.g. charities)[143,196,207,220,221,225].

***Figure 14.*** *Breakdown of the included CTR studies*




## Currently open

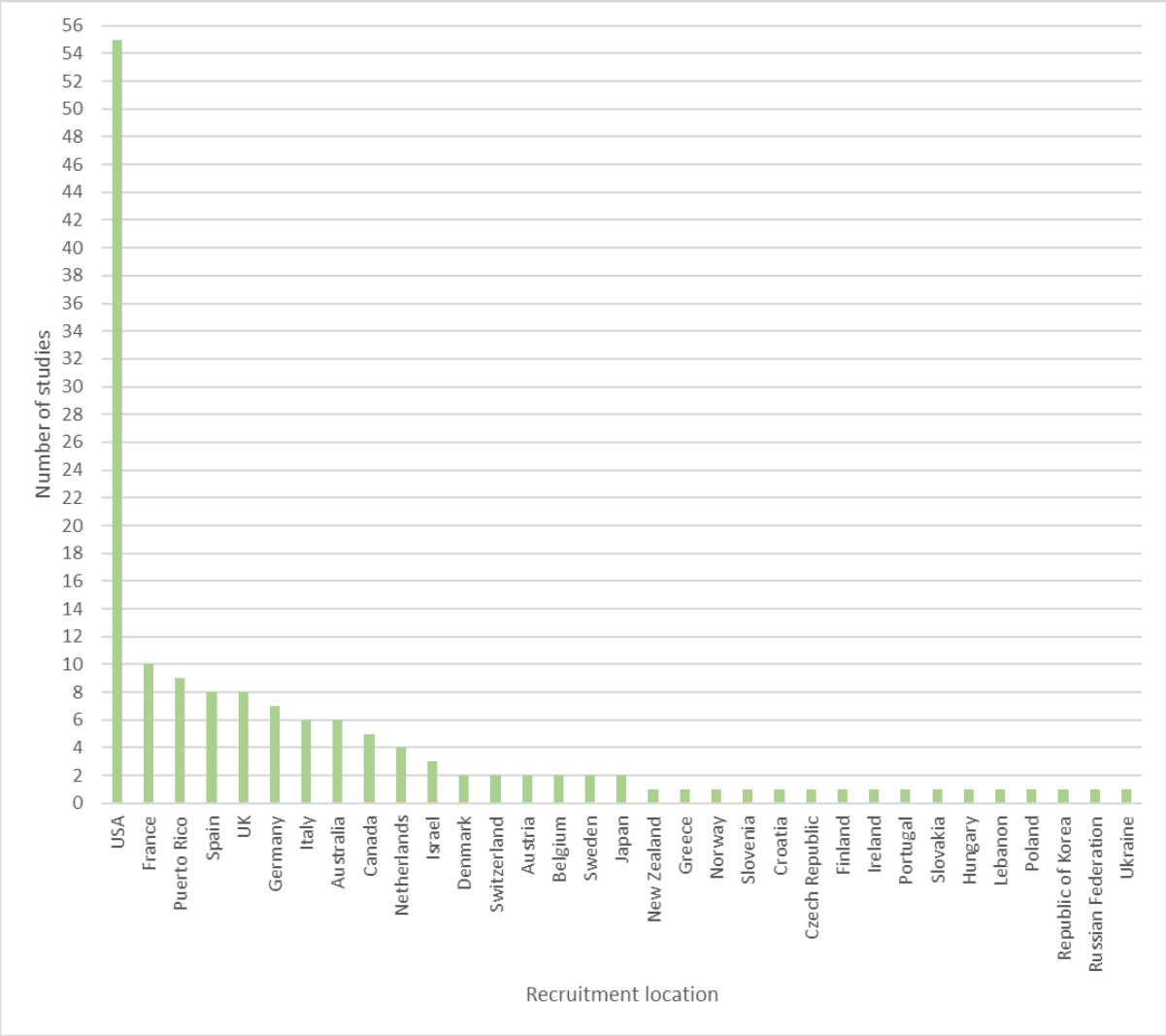
We identified 63 registered studies that are currently open, including 39 studies currently recruiting participants[142,143,145,146,156,157,161,165-169,174,177,180-183,185,186,188-190,195,196,199,200,209,210,226,228,230-232,240,242,244,245,248] (one study links to a full text that has also been extracted[71], representing a subset of patients), 18 studies that are active, not recruiting[144,147,149,153,154,159,163,164,176,178,184,192,198,212,216,221,239] (one study links to a full text publication[50] and conference abstract[135] that have also been extracted - the full text represents patients from the dose escalation stage of this study and the CA only presents a subset of patients from the full study), four studies not yet recruiting,[171,172,191,206] and two ongoing[235,243]. It is worth noting that the active, not yet recruiting studies may include studies that have finished recruiting but follow-up is ongoing.

Fifty-three of these studies aim to include relapsed and refractory patients,[143-147,149,153,156,157,159,161,163,164,166,168,169,171,172,174,177,178,180-186,188-192,198-200,206,209,210,212,213,216,221,226,228,230,232,239,240,242,244,245,248] whilst five include newly diagnosed and relapsed,[142,165,176,195,231] one includes newly diagnosed and refractory,[154] and four are unclear[167,196,235,243]. The majority of these studies are recruiting multiple tumour types (n=61; 96.8%),[142-229,232-248] whilst two studies are recruiting rhabdomyosarcoma patients only[230,231]. Fifteen of these studies focus on patients with a specific biomarker/mutation.[153,154,159,164,172,178,180,183-186,190,191,239] The ages eligible for recruitment across these studies varied widely. Most studies had a lower age range of one or two years old and therefore infants (0-1 years) were rarely eligible. Those with an upper age cut-off ranged from 17-80 years. Only seven studies were open to recruiting people of all ages.[153,154,165,198,213,235,245]

The most common intervention being studied is novel single agent systemic therapies (20 studies[153,154,156,157,159,164,177,178,180,183-186,192,196,212,226,228,232,239] including 9 pediatric MATCH trials[159,164,177,178,180,184-186]). Other treatment approaches include: novel multi-agent systemic therapies (15),[144,146,147,149,174,182,206,210,216,230,235,240,242,244,245] HSCT (7),[142,161,167,176,188,198] standard multi-agent systemic therapies (7),[145,189,195,199,200,221,231] cellular therapy (6),[166,168,172,190,191,213] biomarker driven studies (2),[163,177] standard single agent systemic therapies (1),[243] metronomic chemotherapy (1)[143] and other approaches (4)[169,171,181,209]. Seven trials include a comparison intervention.[166-168,210,221,231,242]

The country with the most currently open studies is the USA (55, includes one study where country is not reported but sponsor is USA[171]).[142-146,149,153,154,157,159,161,163,164,166,168,169,172,174,176-178,180-186,188-192,195,196,198-200,206,209,210,212,213,226,230,232,239,242,245,248] Eight countries have five or more currently open studies (France (10),[146,147,182,231,232,235,239,240,243,244] Puerto Rico (9),[159,164,177,178,180,184-186] Spain (8),[146,147,182,231,232,239,243,244] UK (8),[147,182,228,231,232,239,243,244] Germany (7),[146,182,231,232,239,240,243] Italy (6),[146,147,182,231,232,239] Australia (6),[182,226,228,231,232,240] Canada (5)[144,226,231,232,242]). Twenty-four countries had fewer than five currently open studies (See Figure 15). Most studies are being conducted in single countries (65%).[142,145,149,153,154,157,161,165-169,172,176,181,188-192,195,198-200,206,209,210,213,216,221,235,245,248] Of these 33 countries, 30 are high income countries, one upper-middle income country and two are low-middle income countries, which suggests a potential lack of access to these types of studies in low- and middle-income countries.

***Figure 15.*** *Recruitment locations for studies reported as currently open within CTRs*




## Discontinued studies

Seventeen studies were classified as discontinued. Twelve studies were identified as withdrawn (6),[170,173,194,214,215,223] suspended (4),[158,160,179,187] or terminated (2)[151,152]. Reasons for discontinuation included insufficient participant recruitment (4),[151,173,215,223] issues with the investigational drug (3),[160,170,194] amendments to trials (3),[158,179,187] being replaced by another study (1),[152] and due to investigator choice (1)[214]. An additional five studies were extracted with an unknown status where it

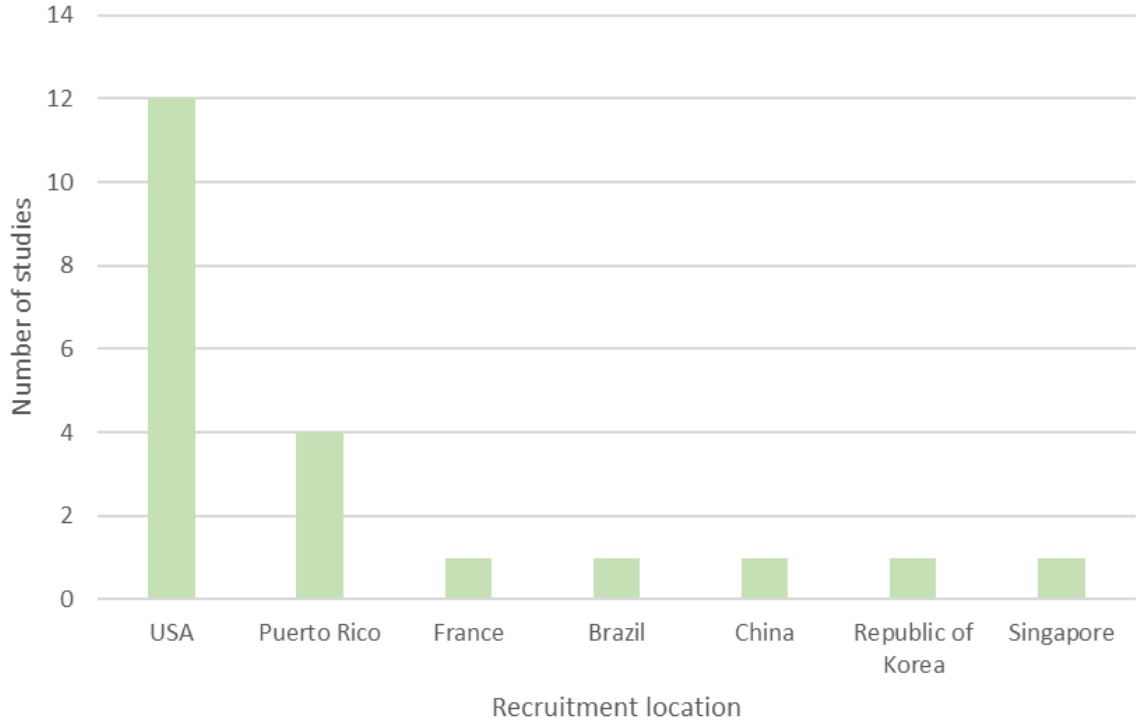
is unclear whether these were completed or not (one of these studies had an associated CA that has been extracted and is included in the main synthesis section[136]).[197,204,207,218,247]

Twelve of these studies include relapsed and refractory patients,[158,160,170,173,179,187,194,197,204,207,215,223] one includes newly diagnosed and relapsed patients,[152] one includes newly diagnosed and refractory patients,[214] and three are unclear[151,218,247]. Only one study was designed for rhabdomyosarcoma patients only.[218] Four of these studies are designed for patients with actionable mutations.[158,160,179,187] The age range of patients eligible for recruitment across these studies varied widely, with only six studies including infants (0-1 years) within their eligible age range (35%),[151,152,197,204,207,247] Six studies have an eligible age range of 1-21 years,[158,160,173,179,187,215] whilst three studies include patients of all ages.[151,152,204]

Both terminated studies aimed to investigate local therapy interventions.[151,152] All four suspended studies related to single novel agent arms of the pediatric MATCH trial.[158,160,179,187] Of the withdrawn studies, four related to single novel agents[170,173,194,215], one planned to evaluate HIFU hyperthermia with doxorubicin[223], and one to study doxorubicin with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and intraoperative brachytherapy for pelvic and abdominal disease[214]. Of the studies with unknown status, one related to single novel agents[207], one to a novel agent with radiotherapy[218], and three to studies involving HSCT[197,247] or cellular therapies[204].

The country with the most discontinued studies is the USA with 12 studies[151,152,158,160,170,173,179,187,194,214,215,223] (including three studies where country is not reported but sponsor is USA[173,194,214]), whilst six countries have fewer than five studies currently discontinued (see Figure 16). This is proportionate to the number of studies registered within the USA overall.

***Figure 16.*** *Recruitment locations for studies reported as discontinued within CTRs*



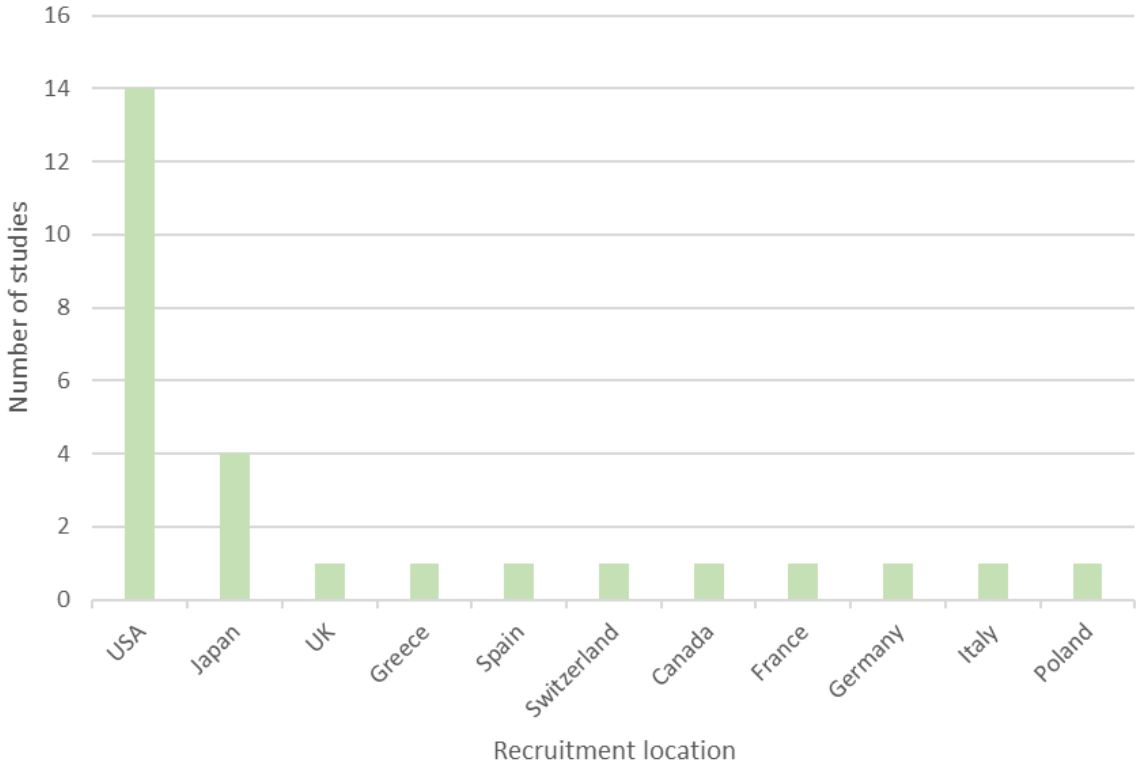
### Completed not yet reported

Nineteen completed studies with no identifiable publications of the full dataset were extracted.[148,150,155,162,175,193,201-203,205,208,211,217,219,220,224,225,227,246] The date range for completion of these studies is 2004-2021 with the majority being completed before 2019[148,150,155,175,201,203,205,211,219,220,224,227] (n=12, 63%, including two studies where the end date is not reported but the CTRs were last updated before 2019[155,220]).

Two studies recruited rhabdomyosarcoma patients only.[211,217] One study recruited patients of all ages.[211] Interventions studied included (number of studies): standard single agent systemic therapies (1),[155] standard multi-agent systemic therapies (5),[162,202,220,224,225] novel single agent systemic therapies (5),[193,201,208,211,219] novel multi-agent systemic therapies (2),[217,246] HSCT (3),[148,150,227] cellular therapy (1)[205] and other approaches (2)[175,203].

The country with the most completed studies without publication is the USA with 14 studies,[148,150,155,162,175,193,201,203,205,208,211,217,219,220,246] whilst an additional ten countries have fewer than five completed studies without publication (see Figure 17).

***Figure 17.*** *Recruitment locations for studies reported as completed within CTRs*




# Discussion

## Summary of findings:

We identified 129 published early phase studies including over 1,100 children and young people with relapsed and refractory rhabdomyosarcoma, along with 99 additional studies registered on CTRs. Most early phase research reported to date, and currently recruiting, is located in the USA. The

majority of studies focused on systemic treatments, with minimal early phase work related to local therapies. Overall, the quality of reporting was poor with multiple inconsistencies, making data extraction and synthesis challenging. Response rates to evaluated interventions within this population are generally poor, and reporting of more clinically meaningful outcomes is rare. A small, but not insignificant proportion, of registered early phase studies in this population are not publicly reported by two years after completion of the research.

## Broader discussion

Our broader discussion focuses on four main issues identified through the REFoRMS-SR project: 1) Quality assessment of early phase studies, 2) Definitions and reporting within studies of relapsed and refractory rhabdomyosarcoma, 3) Outcomes in early phase trials of relapsed and refractory childhood cancers, and 4) Reporting of completed studies.

### Quality assessment of early phase studies

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 trials. Indeed, many other systematic reviews of early phase trials have not included quality assessment.[258-260] All early phase trials, including single-/multiple-arm trials and randomised and non-randomised trials, were eligible for inclusion in the REFoRMS review, so the quality assessment tool had to be broad enough to capture all the different trial designs. The Down's and Black Quality Assessment Tool is a validated tool used to assess the quality of both randomised and non-randomised studies.[18] Given that the checklist was created to assess the quality of multiple-arm trials, some items on the checklist including randomisation, blinding and equal distribution of characteristics between groups, were not relevant for the single-arm studies. However, the utilisation of the same quality assessment tool allowed for a consistent approach to assessing the quality of the studies meaning there was greater comparability of the risk of bias across the included trials regardless of the study design, and a similar approach has been used in other studies before.[261]

Owing to the innovative nature of some of the interventions being studied, some of the items in the Downs and Black Quality Assessment Tool were not considered suitable for this review - specifically the items covering external validity of the studies. Items 11-13 aim to address whether the results are representative of the population to which the study findings will apply. More specifically, item 13 ("Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?") was not deemed appropriate to be assessed in the included studies, as by their very nature, early phase trials are often evaluating novel treatments not widely available for clinical use. Items 11 and 12 ("Were the subjects asked to participate in the study representative of the entire population from which they were recruited?" and "Were those subjects who were prepared to participate representative of the entire population from which they were recruited?") were also difficult to answer. Given the stringent eligibility criteria - which often require patients to be in a good physical condition - the trial's patients are unlikely to be truly representative of those who could receive the drug in a non-trial setting. However, given the unpredictable and uncertain side-effects of the treatments being investigated in early trials, stringent eligibility criteria are understandable.[262] Despite this, the early phase trials included in this

systematic review often failed to report the locations where patients were recruited, and the number of patients invited but who declined to participate, this has implications regarding the transferability and implementation of treatment strategies, and highlights the need for better reporting of early phase studies. Furthermore, some of the multi-arm comparative studies included in the review did not include a reliable control comparator and comparing with historical data in this population is unsatisfactory as there may be improvements in outcome for other reasons. We were unable to capture this, and other differences in randomisation techniques, when using the Down's and Black Quality Assessment Tool.

Quality assessment of phase 1 dose finding cancer trials was identified, but its scope was too narrow to be relevant to this systematic review, and the quality assessment checklist has not been widely validated or used.[263] Similarly, a quality assessment tool for phase 2 studies is available but only covers three domains (referencing of the primary endpoint, sample size calculation/justification and definition of rules to consider patients to be 'evaluable' in the analysis), so does not provide an exhaustive assessment of the quality of studies, and again, has not been widely validated or used.[264]

Finally, within this discussion, it is important to consider that the majority of included records within the REFoRMS-SR are of single arm studies. This is an appropriate study design for much early phase work, but these should be recognised as in their very nature at higher risk of bias compared to multi-arm studies. Thus, any interventions which indicate possible promise within single arm studies would be recommended to be further investigated using later stage, comparative designs.

### Definitions and reporting within studies of relapsed and refractory rhabdomyosarcoma

One challenge, which became apparent early in the process of conducting this review, was that the broad category of relapsed and refractory disease often does not adequately reflect the heterogeneity within this group where patients can have very different prognostic outlooks (e.g. first relapse at a single site of fusion-negative rhabdomyosarcoma three years after completing treatment, versus primary refractory metastatic fusion-positive disease). Few studies provided sufficient descriptions of the included populations to allow for the synthesis of data relevant to the four relapse/refractory categories which we had intended to study in our protocol.[12] Indeed, in many studies, the use of the word "refractory" was not always clear or consistent. Studies might report they included patients "refractory to conventional therapy" but then referred to patients with recurrent disease, implying the inclusion of patients with both relapsed and refractory disease. Within the review, this was handled by reporting studies as for patients with refractory disease where this word was used and there was no reference to any patient with relapse, but as including both groups of patients where there is reporting to suggest this. Similarly, some studies used the term 'progressive disease' interchangeably with refractory disease whilst some studies used this to refer to a broader group of patients. Work to improve the consistency of descriptive terminology across this population would support transparent reporting and enable systematic synthesis of data to inform clinical practice.

Additional challenges within the review occurred as many papers failed to report how many patients with rhabdomyosarcoma were evaluable for response. In some cases, the number who were non-evaluable for response was higher than the number of patients with rhabdomyosarcoma, and in this situation authors were contacted to ask them to confirm the evaluability of rhabdomyosarcoma

patients, as well as the outcomes for these individuals. Where it could not be confirmed that there were evaluable rhabdomyosarcoma patients within a study, this was excluded from the REFoRMS review. See the strengths/weaknesses section of this discussion for how we consider this has impacted on review outcomes.

Finally, there were often inconsistencies between reporting in the text of manuscripts, and reporting within associated tables and figures, making it difficult to extract data and impacting on the synthesis of findings. Authors, peer reviewers and editorial staff should check that the data provided in a study is consistent where it is reported in the scientific literature.

A particular challenge identified within the REFoRMS-SR was that of matching the included CTR records to CAs and full text publications, as trial registry numbers are not often reported in CAs or full text publications. Each CTR record is given an ID number which enables the trial to be found easily online and on the appropriate trial websites, but this is not consistently reported in outputs for studies that have been registered and completed. It is possible that for some CTR records, there may be published results but we have not managed to find them because of this lack of linking. However, extensive time and resources were used in tracking trials to published papers so this risk is minimal. It is certainly easier to match a published paper to a CTR record if the same CTR ID is cited in both publications. We therefore recommend that all researchers who publish the results of a registered study, provide the registry number or link in their outputs.

### Outcomes in early phase trials of relapsed and refractory childhood cancers

Whilst early phase trials predominantly focus on toxicities, and proxy measures of treatment effect (e.g., response according to RECIST criteria), our parent group were very clear that the outcomes they felt were more meaningful to them when considering these studies were those relating to duration of survival and quality of life. This makes clear the value of carefully selecting outcomes and defining them, as well as keeping in mind the differences between researcher-focus and PPI-focus. Incorporating PPI groups to understand their views so that treatments and analyses can be tailored with parents/patients views in mind, would strengthen this field of research.

Within the included studies, the benefits of a treatment were often limited to the reporting of response or survival and very few studies collected data on quality of life, the burden of therapy and the opportunity costs of treatment. Thus, this body of literature provides a limited perspective on the other outcomes of treatment, which was mentioned by the parent group as important to consider when looking at treatments. Given the late stage of disease for children and young people with relapsed/refractory rhabdomyosarcoma, limited treatment options and subsequent poor prognosis, information about the impact of a treatment on the quality of life is likely to be important for parents, children and young people, and clinicians so they have a better understanding of the impact of treatments that they could be offered, to aid decision making.[265]

Although disease response by RECIST was the most reported outcome in studies included in the review, for a number of studies this was simply reported as “no objective responses”. The lack of detail within this reporting meant it was unclear whether patients experienced stable disease or progressive disease, which may be clinically significant in this population. We would recommend

that future research report outcomes as per RECIST rather than using “no objective responses” to share their findings.

As demonstrated within Table 4, there was highly inconsistent reporting of AEs across studies. Some reported AEs by number of cycles, number of participants experiencing AEs, or the total number of AEs experienced. Other studies grouped Grade 3-4 AEs while others reported each grade separately. Some studies reported where AEs were deemed to be treatment-related, others did not. Very few studies explicitly reported the number of treatment-related deaths. This makes it difficult to compare across studies. Mackely et al (2021) consider that it is important that standard reporting guidelines for AEs should be followed, including reporting grade 3, 4 and 5 AEs separately, and reporting the number of patients experiencing an AE, rather than the total number of events.[265] By improving the reporting of AEs in primary studies, the subsequent evidence synthesis of AEs from clinical trials will be improved, and more meaningful results can be presented to patients, parents, clinicians and researchers.[266]

At this point, we feel it is important to report our discussions with our parent group, where the use of the phrase AEs was felt to be “very frightening” and that parents prefer for this term not to be used. We recognise that, within the early phase trial community, the term AE has a very precise meaning, and is relatively consistently applied, which provides significant scientific benefits. However, care should be taken in the dissemination of findings to those outside this specific community. We plan to work alongside our parent group to establish the best ways to communicate the REFoRMS-SR results with a broader audience, and will also be drawing on patient and parent experiences to design the Living-REFoRMS resource detailed below.

### Reporting of completed studies

The REFoRMS-SR reports a number of completed studies (n= 19) according to CTR records, without complete published results. Given the search for this review was conducted in April 2021 and knowing that publication processes may take some time, we might have reasonably expected any study that had completed before April 2019 to have published results by the time our search was conducted. However, only six of these studies had been completed after April 2019. Thus we were unable to identify published findings for 13 trials for which this could have been reasonably expected (includes two trials with no identifiable end date despite the trial registry record stating trial completion). The reason for this could be due to our search strategy, though this was extensive and sought studies through multiple routes, or due to the researchers not publishing the results. The failure to publish easily identifiable results, preferably linked to the relevant CTR record, has been highlighted as of particular concern within academic practice.[267] If their data is unpublished, then participants have taken part in research which does not benefit the wider community and funders have used resources which might reasonably have been used elsewhere. Furthermore, there is a risk of publication bias, and thus compromise within systematic reviews given that unpublished studies are more likely to be those with negative findings.[268] It is the responsibility of all those involved in childhood cancer research, including patients, families, clinicians, researchers and funders, to hold researchers to account for publishing the findings of their early phase studies.

## Strengths/weaknesses of the review

The REFoRMS-SR represents a comprehensive synthesis of early phase studies in relapsed and refractory rhabdomyosarcoma from 2000-2021. The review follows standard SR methodologies to provide systematic searching, quality assessment, data extraction and synthesis. Furthermore, the engagement with key stakeholders throughout the project means that there has been input from patients, families and clinicians to shape the research, and the ongoing dissemination of findings, including through non-standard routes such as social media (@REFoRMS_Rhabdo), has ensured that this project will have significant impact on the community.

In our design, we specifically chose a search strategy focused on soft tissue sarcoma. This allowed for screening of broader studies than a pure rhabdomyosarcoma search, but may potentially have missed a small number of studies which included "all relapsed/refractory paediatric malignancies". Testing of the search strategies in advance, including screening of samples of broader searches, suggest that this number is likely to be minimal and is unlikely to have included data which would substantially impact on the review conclusions. The significant resource required for such a broad approach was not available to the project team.

As in many evidence syntheses, some of the most significant challenges to the project relate to the poor reporting of data within the included studies. In particular, extracting data relating to the outcomes of rhabdomyosarcoma patients was frequently challenging. This resulted in 46 studies being excluded from our analysis as it was not possible to identify this data, and responses to contact with authors were minimal. Whilst we understand the necessity to conduct trials which include a range of tumour types, we encourage researchers to report patient demographics and outcome data by tumour type as this would be more clinically meaningful and would facilitate future syntheses of these kinds of studies.

## Future research plans/implications

Future research opportunities identified by this review can best be grouped into three main categories: those relating to methodology, those relating to relapsed and refractory rhabdomyosarcoma specifically, and those that apply to the wider field of paediatric oncology.

Further work is needed into the most appropriate tools for quality assessment within systematic reviews of early phase studies, either through the development of new tools or assessment of currently available tools. 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 these evidence syntheses.[265,269] Reporting guidelines for phase 2 trials have been developed, but as yet, seem to be poorly implemented.[264] In addition, methodologies for the synthesis of early phase data, including both efficacy and toxicity data, are relatively novel and require further attention to facilitate the appropriate methods and tools for communication of findings to researchers, clinicians, patients and their families.

Within the field of relapsed and refractory rhabdomyosarcoma, the greatest future research challenge, posed to the REFoRMS team by our parent group, is the speed at which early phase studies are conducted, and thus the risk of any evidence synthesis becoming rapidly out of date. Patients, families and clinicians require innovative solutions to provide high quality data in a form that is continually updated. As such, the REFoRMS-SR will now become the first living systematic review in childhood cancer – "Living-REFoRMS".

Within the Living-REFoRMS work, funded by CCLG and Alice's Arc, the research team will perform regular updates of the evidence synthesis, whilst also working on the methodological challenges of living reviews, including testing different methods for searching, screening, assessment, and synthesis. For example, Living-REFoRMS will actively identify biomarker driven therapies at data extraction phase. The first update review is in progress and will explore the potential role of automated search strategies within the living systematic review. In addition to this, an interactive and user-friendly online resource will be developed to facilitate access to the Living-REFoRMS data for patients, families, clinicians and researchers.

In addition to the continuation of this overarching work, a number of smaller projects have been identified, including further work around synthesis of local therapy data. Many of these manuscripts do not meet the inclusion criteria of the REFoRMS-SR as they are not early phase studies, nonetheless we feel they provide important information for the management of relapsed and refractory rhabdomyosarcoma and thus we will work to establish how best these can be evaluated and synthesised in the future.

We have identified two key future research needs within the wider childhood cancer community. The first is a need for a core outcome set for early phase studies in relapsed and refractory paediatric 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. The second area of broader childhood cancer research is 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 relating to early phase options.

## Acknowledgements

We appreciate the contributions of the contacted authors who supplied additional information relating to their included studies (n=32). We also acknowledge the foreign language translation skills of Olga Bridges.

## Contributions

The overarching project was developed and designed by JCC, JEM, and BP. Search strategies were designed and implemented by HF in collaboration with the rest of the research team. JEM, CE, LB and GB screened titles and abstracts as well as full texts for study selection. JEM, CE and LB performed data extraction and quality assessment, as well as all analyses as part of the review. CE and LB created all infographics. CE led the social media activity with collaboration from the research team. LB managed the emailing of authors for additional information. BP provided a supervisory role throughout the project supporting each stage of the review where necessary, e.g., conflict resolution.

The parent and CAG groups provided key insights and discussions throughout the project that influenced the production and presentation of this review.

All authors have read and approved the final report.

## Funding

The systematic review is part of the overarching REFoRMS project funded by CCLG [Grant Number: CCLGA 2020 06].

JCC is supported by the Giant Pledge through the Royal Marsden Cancer Charity and this independent research is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

## Appendices

- Search Strategy
- Data extraction templates
- Table of studies excluded at full text stage and reason for exclusion
- Quality assessment tables

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## **Table 2.** Demographic characteristics of included studies

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| **Standard systemic therapies- single agent** | | | | | | | | | | | | |
| Marina, 2002[72] | NR | NR | Multi | January 1997 to June 2000 | Relapsed; refractory; all solid tumours | ⩽ 21 years | No standard therapy available | Pegylated Liposomal Doxorubicin (Doxil) *40-70mg/m² IV every 4 weeks for at least 2 cycles* | 2 (22) | WP: 9.3 years (4-21 years) | NR | |
| Kebudi, 2004[61] | Turkey | NR | Single | December 1993 to August 2001 | Relapsed; refractory | ⩽ 16 years | Progressive or recurrent/refractory malignant sarcoma who had been previously treated | Etoposide *50mg/m² po od on days 1-20 of 30-day cycle* | 4 (21) | RMS: 10.5 years* (8-14 years) | RMS: 3.5* (2-4) | 2 relapsed, 2 refractory RMS. 2 parameningeal, 1 perineum (with metastasis to breast) and 1 orbital RMS |
| Wagner-Bohn, 2006[101] | Germany, Austria | II | Multi | May 2003 to September 2004 | Relapsed | No age limit | ESFT, OS, RMS, NBL, HBL and nephroblastoma. With first or additional recurrence of a solid tumour of embryonic or mesenchymal origin | Gemcitabine *1200mg/m² IV on days 1, 8, and 15 of 28-day cycle. For at least 6 months or until tumour progression* | 8 (20) | WP: 15.8 years (2-23 years) | NR | All relapsed RMS |
| Meazza, 2010[78] | Italy | NR | Single | June 2005 to January 2010 | Relapsed; refractory | NR | STS or bone sarcoma. No limit on the number of prior chemotherapy lines | High-dose Ifosfamide *14g/m² IV as 14-day continuous infusion via ambulatory pump, with mesna. New cycle every 21 days* | 5 (14) | WP: 6 years (1-16 years) | NR | |
| Yalcin, 2004[107] | Turkey | NR | Single | September 1996 to June 2002 | Relapsed; refractory; all solid tumours | 10-65 years | Recurrent or locally advanced or metastatic high-grade sarcomas. Includes chemotherapy naive or previously treated. | High-dose Ifosfamide *2g/m² up to 20g/m² in total as continuous infusion over 24 hours from days 1-9 (with loading dose on first day), with mesna* | 1 (39) | RMS was 17 years | NR | |
| De Sio, 2006[38] | Italy | NR | Single | April 1998 to April 2004 | Relapsed; refractory; all solid tumours | NR | Excludes brain stem tumours | Temozolomide *215mg/m² (180mg/m² for those with prior CSI), po od on days 1-5, repeated every 21-28 days (max 24 cycles)* | 2 (52) | RMS: 177.5 months* (144-211 months) | NR | 2 Embryonal RMS |
| Vassal, 2007[17] | UK, France | II | Multi | November 1999 to June 2002 | Relapsed; refractory, RMS only | 6 months to 20 years | Patients could not have received more than one previous salvage therapy for relapse | Irinotecan *600mg/m² (20mg/kg if weight <10kg), IV every 21 days (max 16 courses)* | 35 (35) | RMS: 12 years (2-19 years) | RMS: 1 (1-2) | 17 embryonal RMS, 17 alveolar RMS, 1 not classified. 20 first relapse, 10 second relapse, 5 refractory |
| Makimoto, 2019[114] | Japan | I/II | Multi | January 2006 to March 2008 | Relapsed; refractory | 2-18 years | NBL, RMS, ESFT, retinoblastoma, nephroblastoma, HBL, OS, synovial sarcoma, leiomyosarcoma or any other | Irinotecan *40mg/m² escalating to 60mg/m², IV on days 1,2,3,8,9 and 10 of 21 day cycle (max* | 4 (17) | RMS: 9 years* (4-15 years) | NR | |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | | solid tumour of non-epithelial origin were eligible. Patients on standard chemotherapy without relapse or refractory tumour were considered for enrolment if they were unable to continue chemotherapy due to adverse reactions. Patients were excluded if they had concurrent active malignancy in a different site, symptomatic metastasis to the CNS or primary CNS tumour | *8 cycles)* | | | | |
| Shitara, 2006[91] | Japan | NR | Multi | June 2001 to November 2004 | Relapsed; refractory; all solid tumours | NR | Solid tumours deemed to be treatment failures on conventional treatment | Irinotecan<br>*180mg/m² IV on days 1,2,3 of 28-day cycle* | 3 (16) | RMS: 6 years* (3-6 years) | NR | |
| Bomgaars, 2007[29] | USA | II | Multi | NR | Relapsed; refractory | 1-22 years at the time of initial diagnosis | Solid or CNS tumours. Excluded if they had received more than two prior chemotherapy regimens, had previously received irinotecan, or were receiving anticonvulsants. | Irinotecan<br>*50mg/m² IV on days 1-5 of 21-day cycle* | 19 (171) | WP: 9 years (1-23 years) | NR | |
| Bisogno, 2005[26] | Italy | II | Multi | July 2002 to September 2004 | Relapsed; refractory; soft-tissue sarcomas only | NR | Surgically unresectable and malignant disease | Irinotecan<br>*20mg/m² IV on days 1-5 and 8-12 of 28-day cycle* | 13 (32) | WP: 10.6 years (1-18.5 years) | WP: 2 (1-3) | 7 Alveolar RMS, 6 embryonal RMS |
| Furman, 2006[46] | USA | I | NR | NR | Relapsed; refractory; all solid tumours | <21 years | | Irinotecan<br>*Cohort 1: 15-45mg/m² po on days 1-5 and 8-12 of 21-day cycle*<br>*Cohort 2: 45-75mg/m² po on days 1-5 and 8-12 of 21-day cycle, with cefixime support* | 4 (39) | WP: 10 years (3-19 years) | WP: 6 (1-11) | |
| Blaney, 2001[124] | USA, Canada | I | Multi | NR | Refractory; all solid tumours | 1-21 years (inclusive) | Whole trial excludes patients who received prior extensive radiotherapy or BM transplantation with total body irradiation. Stratum 2 (less-heavily pretreated) excluded patients who received more than 2 prior lines of chemotherapy as well as patients who received prior central axis radiation or a BM transplant | Irinotecan<br>*30-65mg/m² IV on days 1-5 of 21-day cycle* | 2 (30 evaluable) | WP: 9 years (1-20 years) | Stratum 1: 3 (1-8) | 2 refractory RMS |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| Bomgaars, 2006[28] | USA | I | Multi | NR | Relapsed; refractory; all solid tumours | 1-21 years | Patients where no effective therapy were known were eligible for this study. Excluded if they previously received irinotecan. For stratum 1 the number of prior chemo regimens was not restricted but after MTD determined in stratum 1, eligibility was restricted to less heavily pre-treated patients - excluded if they had more than 2 prior lines of chemo or prior BM transplant | Irinotecan *125-200mg/m² IV on days 1,8,15,22 of 42-day cycle* | 2 (23 entered, 18 evaluable) | WP: stratum 1 was 11 years (4-17 years); stratum 2 was 6 years (2-15 years) | WP in stratum 1: 3 (1-6) | Included 1 alveolar RMS |
| Hawkins, 2006[53] | USA | II | Multi | May 1999 to March 2003 | Relapsed; refractory | ⩽ 21 years at initial diagnosis | Strata included: ESFT, OS, STS, NBL, MB/PNET, astrocytoma. Excluded patients who had been previously treated with topotecan or other camptothecins | Topotecan *0.3mg/m² IV on days 1-21 of 28-day cycle* | 9 (53) | WP: 12.9 years (2-13 years) | NR | 2 alveolar RMS, 4 embryonal RMS, 3 NOS |
| Santana, 2003[131] | USA | NR | NR | NR | Relapsed; refractory; all solid tumours | <21 years | | Topotecan *AUC target dosing - Cohort 1: 120-180ng/ml x hr, Cohort 2: 80-120ng/ml x hr, IV on days 1-5 and 8-12 of 24-28 day cycle* | 1 (15) | RMS was 13.8 years | NR | |
| Zwerdling, 2006[108] | USA | II | Multi | January 1997 to November 2001 | Relapsed; refractory; all solid tumours | ⩽ 21 years | Excluded patients who received more than two previous therapies, and patients who had received paclitaxel or docetaxel | Docetaxel *125mg/m² IV every 21 days, with GCSF support* | 10 (173) | WP: 13 years (1-27 years) | NR | |
| Widemann, 2009[105] | USA | I | Single | NR | Refractory; all solid tumours | 2-18 years (inclusive) | Patients were excluded for myeloablative therapy requiring BM or stem-cell rescue or extensive radiotherapy within the previous 6 months | Ixabepilone *3-10mg/m² IV on days 1-5 of 21 day cycle* | 3 (19 enrolled, 18 assessable) | WP: 10.5 years (2-18 years) | WP: 3 (1-10) | |
| Jacobs, 2010[58] | USA | II | Multi | 5th May 2006 to 17th April 2007 | Relapsed; refractory | 12 months to 35 years at original diagnosis (inclusive) | No known curative treatment options. Histologies: RMS, ESFT, OS, synovial sarcoma, or MPNST, NBL, WT | Ixabepilone *8mg/m² (to 16mg per dose) IV on days 1-5 of 21 day cycle* | 10 (61) | RMS: 13 years (4-25 years) | WP: 2 (1-7) | |
| Amoroso, 2020[20] | NR | II | Multi | NR | Relapsed; refractory | 6 months | Treatment failure with ≤ 3 prior lines of therapy. RMS, ESFT and NBL. Excluded | Nab-Paclitaxel *240mg/m² (11.5mg/kg if weight ≤10kg) IV* | 14 (42) | RMS: 14 years (3-24 years) | RMS: 2 (1-3) | |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | to 24 years (inclusive) | primary brain tumours or brain metastasis | *on days 1,8 and 15 of 28-day cycle* | | | | |
| Moreno, 2018[82] | USA, Canada, Europe | I | Multi | December 2013 and ongoing as of paper being published in 2018 | Relapsed; refractory | ⩾ 6 months to < 18 years | Patients with primary brain tumours, active/untreated brain metastasis or baseline peripheral neuropathy grade >/= 2 were excluded | Nab-paclitaxel *120-270mg/m² IV on days 1,8 and 15 of 28-day cycle* | 14 (65 enrolled, 64 treated) | WP: 12 years (2-17 years) | WP: 3 (1-10) | |
| Beaty, 2010[23] | USA | II | NR | 18th October 2004 to 1st September 2006 | Relapsed; refractory | ⩽ 21 years | ESFT/peripheral PNET, OS, RMS, NBL, high grade astrocytoma, low grade astrocytoma, brain stem glioma, ependymoma, malignant germ cell tumour, HBL, and selected rare tumours of interest (NRSTS, hepatocellular carcinoma, renal cell carcinoma, childhood and adolescent colorectal carcinoma, nasopharyngeal carcinoma and adrenocortical carcinoma). No limit to the number of prior chemo regimens or prior platinum exposures | Oxaliplatin *130mg/m² (4.3mg/kg if ≤12 months old) IV every 21 days (max 17 courses or one year of therapy)* | 10 (124) | WP: 9 years at diagnosis (0-21 years); 11 years at study entry (1-22 years) | WP: 2 (1-6) | |
| Geoerger, 2008[125] | France | I | Multi | NR | Relapsed; refractory; all solid tumours | 6 months to 21 years | Two or more prior lines of chemo and/or no effective treatment available | Oxaliplatin *40-110mg/m² IV on days 1,8 and 15 of 28 day cycle* | 2 (29 from dose escalation stage only) | Dose-escalation group: 9 years (2-19 years) | Dose-escalation group: 2 (1-10) | |
| Spunt, 2007[133] | USA | I | NR | September 2000 to April 2003 | Refractory; all solid tumours | <21 years | | Oxaliplatin *100-160mg/m² IV every 21 days (max 6 cycles)* | 1 (11) | WP: 11 years (5-21 years) | WP: 2 (0-9) | 1 refractory |
| Warwick, 2013[102] | USA | II | Multi | September 2007 to October 2009 | Relapsed; refractory | 6 months to 21 years at time of diagnosis | Included OS, ESFT/peripheral PNET, RMS, NBL, ependymoma, MB/supratentorial PNET, or non-brainstem high-grade glioma. Excluded patients if they had prior treatment with pemetrexed | Pemetrexed *1,910mg/m² (max dose 3,820mg; 60mg/kg if <12 months old) IV every 21 days* | 9 (72) | WP: 11 years (3-23 years) | NR | |
| Baruchel, 2012[13] | NR | I/II | Multi | January 2008 to April | Relapsed | 12 months | RMS, ESFT or NRSTS; Weight had to be greater than or equal to 15 kgs. Excluded | Trabectedin *1.3-1.5mg/m IV over 24 hours every 21* | 23 (50) | WP: 15.5 years (4-21 years) | NR | |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | 2010 | | to 21 years (inclusive) at initial diagnosis | patients with prior history of Allogeneic SCT | *days* | | | | |
| Kuttesch, 2009[66] | USA | II | Multi | May 1998 to May 2002 | Relapsed; refractory | ⩽ 21 years at initial diagnosis | Three strata: STS, CNS tumours and NBL. No more than two prior chemotherapy regimens | Vinorelbine *30-33.75mg/m² IV on days 1,8,15,22,29,and 36 of 56 day cycle (max 10 cycles)* | 11 (50) | WP: 8.5 years at diagnosis (0-20 years); 10 years at study entry (1-25 years) | NR | 5 alveolar RMS, 3 embryonal RMS, 1 NOS, 2 NR |
| Casanova, 2002[32] | Italy | NR | Single | September 1998 to August 2001 | | NR | Sarcomas: advanced progressive measurable disease where there is no known cure | Vinorelbine *30mg/m² IV on days 1 and 8 of 21-day cycle* | 13 (33) | WP: 16 years (2-29 years) | WP: 2 (1-4) | 7 alveolar, 6 embryonal RMS |
| Johansen, 2006[126] | USA | I | Multi | NR | Relapsed; refractory | ⩽ 21 years | Previous treatment with vincristine or vinblastine was allowed. Includes brain-stem tumours not refractory to conventional therapy | Vinorelbine *24-37.5mg/m² IV (first dose given orally as 3x IV dose, rounded to nearest 10mg, max 200mg) every 7 days (max 6 cycles)* | At least 1 (46 enrolled, 29 evaluable) | WP: 12 years (2-17 years) | WP: 24 received 1-3; 4 received 4-6; 1 received 8 prior lines | 7 STS<br>1 relapsed RMS |
| **Standard systemic therapies- multiple agents** | | | | | | | | | | | | |
| Souid, 2003[93] | NR | I | Multi | December 1999 to June 2001 | Refractory; all solid tumours | 1-22 years | Confirmed malignant solid tumours. For the less heavily pretreated cohort, patients were excluded if they had more than two previous chemotherapy regimens, central axis radiation, BM involvement with cancer, and previous BM transplantation | Cisplatin *30mg/m² IV on days 1,8,15 and 22 of 42 day cycle*<br>and Irinotecan *40-65mg/m² IV on days 1,8,15 and 22 of 42 day cycle*<br>+ Amifostine (added after MTD of irinotecan determined) *825mg/m² IV immediately prior to cisplatin* | 3 (24) | WP: 15 years (4-21 years) | NR | 3 refractory |
| Wells, 2002[104] | USA | I | Multi | NR | Refractory; all solid tumours | Children (ages not specified) | Patients can have previously received either topotecan or cisplatin but not in combination. Patients were stratified based on the presence of BM metastases and/or previous history of extensive radiation therapy to the BM (cranio-spinal or pelvic) | Topotecan *0.75-1mg/m²/day IV over 72 hours* and Cisplatin *45-75mg/m² IV on days 1-3 (duration of cycle not specified)* | 6 (36) | WP: 12 years at study entry (2-21 years) and 10.5 years at diagnosis (0-19 years) | NR | |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| McCowage, 2011[76] | Australia, New Zealand | NR | Single | November 1995 to April 2001 | Relapsed; refractory; all solid tumours | Up to 22 years | Included patients with newly diagnosed disease who were considered at high risk of treatment failure. Patients with BM involvement were ineligible | Escalation of cyclophosphamide in VETOPEC regimen<br>*Standard VETOPEC regimen with cyclophosphamide increased from 40mg/kg to 60-90mg/kg IV on days 1-3 with PBSC support. Cycles repeated every 21-28 days (max 4 cycles)* | 4 (48 from recurrent/ refractory group) | WP: 91 months at diagnosis (3-260 months); 124.5 months at mobilisation (10-270 months) | NR | 2 embryonal, 2 NR |
| Saylors, 2001[90] | USA, Canada | II | Multi | NR | Relapsed; refractory; all solid tumours | NR | Prior therapy with cyclophosphamide was allowed but patients must not have been previously treated with topotecan. Had to have evidence of BM recovery from prior chemotherapy. Patients were eligible if they had received ≤ two prior chemotherapy regimens, except if the patients had been previously enrolled on a phase I or single-agent phase II study, in which case ≤ two prior chemotherapy regimens in addition to the phase I or single-agent phase II study were allowed | Cyclophosphamide<br>*250mg/m$^2$ IV on days 1-5 of 21 day cycle*<br>and Topotecan<br>*0.75mg/m$^2$ IV on days 1-5 of 21-day cycle* | 15 (91) | WP: 13.8 years (1-21 years) | NR | 9 embryonal RMS, 4 alveolar RMS, 1 mixed, 1 unknown |
| George, 2010[51] | USA | I | Multi | March 2004 to May 2006 | Relapsed; refractory | > 12 months to ⩽ 21 years | Extracranial solid tumours. Stratum A only related to RMS. Excluded prior cumulative anthracycline dose of ≥450 mg/m2 | Decitabine<br>*5mg/m$^2$ IV on days 0-6 of 28-day cycle*<br>Doxorubicin<br>*45mg/m$^2$ IV on day 7 of 28-day cycle*<br>& Cyclophosphamide<br>*1g/m$^2$ IV on day 7 of 28-day cycle (max 12 cycles)* | 2 < 18 years (23) | RMS: 11.7 years* (8.5-14.9 years) | RMS: 2.5* (2-3) | |
| Davidson, 2002[35] | UK | NR | Multi | NR | Relapsed; refractory | 6 months to 20 years | Primary or metastatic malignancy | (EVE/cyclosporin)<br>Etoposide<br>*75mg/m$^2$ IV on days 1-3 of 21-day cycle*<br>Vincristine<br>*0.25mg/m$^2$ IV on days 1-3 of 21-day cycle*<br>Epirubicin<br>*12.5mg/m$^2$ IV on days 1-3 of 21 day cycle*<br>High dose Cyclosporin<br>*30mg/kg IV on days 1-3 of 21-day cycle* | 4 (16) | RMS: 8 years 9 months* (6-16 years 6 months) | NR | 2 Alveolar RMS, 2 Embryonal RMS. 2 first relapse, 1 second relapse, 1 7th local relapse |
| Geoerger, 2011[48] | UK, France, Germany, Italy, Netherlands | II | Multi | February 2007 to July 2008 | Relapsed; refractory | 6 months to 21 years | Not more than 1 salvage therapy for relapse. Excluded diffuse infiltrative pontine glioma | Gemcitabine<br>*1000mg/m$^2$ IV on day 1 of 14 day cycle*<br>and Oxaliplatin<br>*100mg/m$^2$ on day 1 of 14 day cycle* | 12 (95 enrolled, 93 treated) | WP: 11.7 years (1.3-20.8 years) | WP: 2 | |
| Loss, 2004[129] | Brazil | II | Single | July 1996 to | Relapsed; | <18 | No evidence of brain involvement or | Ifosfamide | 2 (21) | RMS: 6 years* (4- | RMS: 1.5* (1- | 1 first relapse, 1 |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | November 2000 | refractory; all solid tumours | years | leptomeningeal disease | *3g/m² IV on days 1-3 of 21-28 day cycle*<br>Carboplatin<br>*400mg/m² IV on days 1-2 of 21-28 day cycle*<br>Etoposide<br>*160mg/m² IV on days 1-3 of 21-28 day cycle (max 8 cycles)* | | 8 years) | 2) | refractory RMS. 1 head & neck RMS, 1 prostate/ bladder RMS |
| Lam, 2015[67] | USA | I | NR | March 2009 to September 2011 | Relapsed; refractory; all solid tumours | ⩽ 21 years | Includes patients without known effective therapy. Excluded if previously received oxaliplatin | Ifosfamide<br>*1200-1500mg/m² IV on days 1-3 of 21-day cycle*<br>Oxaliplatin<br>*130mg/m² IV on day 1 of 21-day cycle*<br>Etoposide<br>*75-100mg/m² IV on days 1-3 of 21-day cycle*<br>*With mesna and GCSF support* | 3 (19 enrolled, 17 treated) | WP: 4 years at diagnosis (1-19 years); 7 years at enrolment (2-21 years) | WP: 3 (1-7) | |
| Bisogno, 2021[25] | Italy | NR | NR | November 2013 to January 2020 | Relapsed; refractory | >6 month to ⩽ 25 years | Metastatic at diagnosis or relapsed /refractory disease. RMS, ES and DSRCT | Irinotecan<br>*20mg/m² IV on days 8-12 of 21-day cycle*<br>+ Standard VAC | 7 (10) | RMS: 7.3 years* (4.10-15 years) | RMS: 1 (1-1) | 5 alveolar, 2 embryonal RMS. All 7 first relapse |
| Mascarenhas, 2013[74] | USA | I | Single | August 2006 to October 2009 | Refractory | ⩽ 21 years | Includes extra-cranial solid tumours. Must not have previously received oxaliplatin or cumulative anthracycline (doxorubicin equivalent) dose of >450 mg/m2 | Oxaliplatin<br>*105-130mg/m² IV on day 1 of 21 day cycle*<br>and Doxorubicin<br>*20-25mg/m² IV on days 1-3 of 21 day cycle (max 8 cycles)* | 2 (17) | WP: 13.8 years (2.9-20.4 years) | WP: 2 (0-6) | |
| McGregor, 2009[115] | USA | I | Multi | April 2005 to February 2006 | Refractory; all solid tumours | 1-22 years | Weigh >10kg. No previous oxaliplatin exposure was allowed | Oxaliplatin<br>*40-60mg/m² IV on days 1 and 8 of 21 day cycle*<br>and Irinotecan<br>*15-20mg/m² IV on days 1-5 and 8-12 of 21 day cycle (max 17 cycles)* | 2 (14 enrolled, 13 eligible) | WP: 16 years (5-21 years) | WP: 1 (1-3) | 1 metastatic recurrent alveolar RMS |
| Le Teuff, 2020[69] | France, Netherlands, Italy | II | Multi | June 2009 to October 2013 | Relapsed; refractory; all solid tumours | 6 months to ⩽ 20 years | Maximum 2 lines of previous chemotherapy. Histological or cytological diagnosis of extracranial solid or CNS malignancy | Topotecan<br>*0.75mg/m² IV on days 1-5 of 28-day cycle*<br>and Temozolomide<br>*150mg/m² on days 1-5 of 28-day cycle* | 9 (91 in total, 32 in the extracranial tumours group) | Extracranial tumours group: 13.4 years (1.6-20.9 years) | NR | |
| Rubie, 2010[130] | France | I | Multi | February to October | Relapsed; refractory; | 6 months | ≥ 2 previous lines of chemotherapy or no effective treatment available | Topotecan<br>*0.75-1.5mg/m² IV on days 1-5 of 28-day* | 1 (16) | WP: 8.5 years (3-19 years) | NR | |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | 2007 | all solid tumours | to 21 years | | *cycle*<br>and Temozolomide<br>*100-200mg/m² po on days 1-5 of 28-day cycle* | | | | |
| Bagatell, 2014[22] | USA | I | Multi | July 2010 to February 2013 | Relapsed; refractory; all solid tumours | >12 months to <22 years | No prior treatment with the combination of the three anticancer agents comprising this regimen | Temsirolimus<br>*15-35mg/m² IV on days 1 and 8 of 21-day cycle (and day 15 in final cohort)*<br>Irinotecan<br>*50-90mg/m² po on days 1-5 of 21-day cycle*<br>and Temozolomide<br>*100-150mg/m² po on days 1-5 of 21-day cycle* | 4 (71 eligible, 62 evaluable) | WP: 10.9 years for eligible patients (1-21.5 years); 10.8 years for evaluable patients (1-21.5 years) | WP: 2 (0-8) for eligible patients; 2 (0-7) for evaluable patients | |
| Compostella, 2019[33] | Italy | NR | Multi | 2002 to 2011 | Relapsed; refractory; RMS only | NR | Progressive or relapsed after inclusion in one of the protocols coordinated by The Italian Soft Tissue Sarcoma Committee | Topotecan<br>*2mg/m² IV on days 1-3 of weeks 1,4,7 and 13*<br>Carboplatin<br>*250mg/m² IV on days 4 and 5 of weeks 1,4,10, and 16* Cyclophosphamide<br>*1500mg/m² on days 1 and 2 of weeks 7 and 13*<br>& Etoposide<br>*100mg/m² on days 1-3 of weeks 10 and 16* | 38 (38) | RMS: 6.7 years (0.8-20.7 years) | NR | 18 Alveolar RMS, 18 Embryonal RMS, 1 spindle cell RMS, 1 NOS. 30 relapsed, 8 refractory. |
| Kawamoto, 2010[139] | NR | I/II | NR | NR | Relapsed; all solid tumours | NR | No more than 20 cycles of previous chemotherapy | Topotecan<br>*0.6-0.75mg/m² on days 1-5 of 21 day cycle*<br>and Ifosfamide<br>*1.2g/m² on days 1-5 of 21 day cycle* | 4 (11) | NR | NR | |
| Radhakrishnan, 2015[87] | USA | NR | Multi | NR | Relapsed; refractory; all solid tumours | ⩽ 22 years | Solid tumour or lymphoma and had failed initial therapy - those with failure to previous therapy had to have radiographic or biopsy proof that they had evidence of disease prior to study entry | Topotecan<br>*0.5mg/m² IV on days 1-3 of 21 day cycle*<br>Ifosfamide<br>*Initially 3000mg/m² IV on days 1-3, then 1800mg/m² IV on days 1-5 of 21 day cycle*<br>Carboplatin<br>*3mg/ml/min IV on days 1-3 of 21 day cycle*<br>*(max 3 cycles)* | 1 (15 enrolled, 14 evaluable) | RMS patient was 16 years | NR | 1 first relapse RMS |
| Meazza, 2009[79] | Italy | NR | Single | July 2003 to January | Relapsed; RMS only | NR | ECOG performance score of 2 or less | Topotecan<br>*1.5mg/m² IV on days 1-5 of 21-day cycle* | 8 < 18 years (9) | RMS: 10.5 years* at relapse (3-17 | RMS: 1* (1-2) | 4 embryonal RMS, 4 alveolar |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | 2007 | | | | Vincristine<br>*2mg/m² (max 2mg/m²) IV on days 5-6 of 21-day cycle*<br>and Doxorubicin<br>*45mg/m² IV on days 5-6 of 21-day cycle. When cumulative doxorubicin exceeded 375mg/m², continued with topotecan based regimen described in manuscript (max 6 cycles)* | | years) | | RMS. 5 first relapse, 2 second relapse, 1 refractory RMS. 3 parameningeal, 3 pelvis, 1 trunk, 1 paratesticular |
| McNall-Knapp, 2010[77] | USA | I | Multi | October 2004 to October 2006 | Relapsed; refractory; all solid tumours | <22 years | Malignant solid tumours, including CNS tumours and lymphoma. Patients with leukaemia, uncontrolled infection, or those that had received more than four prior chemotherapy regimens were not eligible | Vincristine<br>*1.5mg/m² (max 2mg) IV on days 1 and 8 of 28-day cycle*<br>Irinotecan<br>*15-20mg/m² (max 40mg) IV on days 1-5 and 8-12 of 28-day cycle*<br>& Temozolomide<br>*100mg/m² (max 200mg) po on days 1-5 of 28-day cycle*<br>*(Max 12 cycles)* | 1 (26) | WP: 9.6 years (2-20 years) | WP: 2 (up to 4) | |
| Wagner, 2010[100] | USA | I | Multi | NR | Refractory; all solid tumours | >12 months to ⩽ 21 years | Patients were excluded if they had previous treatment with temozolomide and irinotecan, or prior progression with either agent | Vincristine<br>*1.5mg/m² IV on days 1 (and day 8 in Schedule A) of 21 day cycle*<br>oral Irinotecan<br>*35-90mg/m² po on days 1-5 (and days 8-12 in Schedule A) of 21 day cycle*<br>& Temozolomide (VOIT)<br>*100-150mg/m² po on days 1-5 of 21-day cycle* | 6 (42) | WP: 9.7 years (1-21 years) | WP: 2 (0-8) | |
| Casanova, 2004[31] | Italy | NR | NR | April 2022 to November 2003 | Relapsed; refractory | ⩽ 21 years | Sarcoma, not amenable to surgical treatment with curative intent following conventional chemotherapy | Vinorelbine<br>*15-30mg/m² IV on days 1,8 and 15 of 28-day cycle*<br>+ low dose cyclophosphamide<br>*25mg/m² po od on days 1-28 of 28 day cycle* | 9 (18) | WP: 12 years (2-13 years) | WP: 2 (1-4) | 1 Alveolar RMS, 7 Embryonal RMS, 1 NOS. 1 RMS with parameningeal disease |
| Minard-Colin, 2012[16] | France | II | Multi | October 2003 to December 2008 | Relapsed; refractory | 12 months to 25 years | RMS, other STS (NRSTS), NBL, OS, ESFT and MB | Vinorelbine<br>*25-30mg/m² IV on days 1,8 and 15 of 28-day cycle*<br>and low-dose Cyclophosphamide<br>*25mg/m² po on days 1-28 of 28 day cycle* | 50 (117) | WP: 12 years (1-24 years) | NR | 25 alveolar, 23 embryonal, 2 NOS |
| **Novel agents - single agent** | | | | | | | | | | | | |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| Epelman, 2015[136] **(This conference abstract represents data from a study with an unknown trial status, and so the trial registry record has also been extracted - NCT01216839)** | Brazil | II | NR | NR | Relapsed; refractory | NR | OS, RMS and other STS. Children and adolescents | Everolimus *5mg/m² po on days 1-30 of 30-day cycle* | 6 (17) | WP: 13 years (4-21 years) | WP: 3 (1-6) | |
| Geoerger, 2012[49] | USA, France, Germany, Poland, Russia | II | Multi | March 2006 to May 2008 | Relapsed; refractory | 1-21 years | HGG, NBL or RMS. Histologic confirmation at initial diagnosis (except for patients with diffuse pontine gliomas) and not at the time of relapse. | Temsirolimus *75mg/m² IV on days 1,8 and 15 of 21-day cycle* | 16 (52) | RMS: 11 years (1-21 years) | NR | 1 Alveolar RMS, 1 Embryonal RMS, 13 NR. 14 refractory RMS, 2 relapse RMS (relapsed from CR on their last line of therapy prior to enrolment) |
| Mossé, 2019[118] | NR | II | Multi | NR | Relapsed; refractory | >12 months to <22 years | Solid and hematologic malignancies (including NBL, RMS, NRSTS, OS, ESFT/peripheral PNET, WT, HBL, malignant germ cell tumours and rhabdoid tumours, AML and ALL). Patients excluded if they had concurrent administration of selected P-glycoprotein substrates (digoxin, cyclosporine, tacrolimus or sirolimus); or use of daily benzodiazepines | Alisertib *80mg/m² (max 160mg) po od on days 1-7 of 21 day cycle (max 35 cycles, 2 years)* | 10 (139) | RMS: 12 years (4-21 years) | NR | |
| Liu, 2020[70] | China | II | NR | September 2015 to February 2018 | Relapsed; soft-tissue sarcomas only | NR | | Apatinib *500mg/day (reduced to 375mg and 250mg if necessary) po od on days 1-28 of 28-day cycle* | 1 (42) | RMS was 14 years | | Metastatic Alveolar RMS |
| Gaspar, 2021[111] | USA, Europe (13 sites) | I/II | Multi | 29 December 2014 to 31 October 2018 | Relapsed; refractory; all solid tumours | Phase 1 (includes RMS): 2 to <18 years | Excluded patients who had previously been treated with lenvatinib outside of the current study, had received ≥2 previous VEGF/VEGF receptor-targeted therapies | Lenvatinib *9-17mg/m² (max 24mg) po od on days 1-28 of 28 day cycle (Patients <6 years old had run-in period during which they received 5mg/m² for 21 days and were assessed for DLTs)* | Phase 1: 5 (23) | WP: 12 years (3-17 years) | WP: 3 (0-9) | |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| Geoerger, 2021[50] **(This full-text represents data from the dose escalation stage of a trial. As trial is still active, not recruiting, the trial registry record has also been extracted - NCT02085148)** | Europe (5 sites) | I | Multi | April 2014 to October 2015 | Relapsed; refractory; all solid tumours | 6 months to <18 years | Includes CNS tumours. Excluded patients with prior exposure to regorafenib | Regorafenib *60-93mg/m² po od on days 1-21 of 28-day cycle* | 3 (41) | WP: 13 years (3-17 years) | NR | 1 alveolar, 1 embryonal RMS, 1 NR |
| Lee 2015/ clinical trial 2020[137] | USA, Canada, France, Czech Republic, Hungary, Slovakia, Spain | II | Multi | NR | Relapsed; refractory | 1-18 years | RMS, NRSTS (including DSRCT), ESFT/PNET, OS, NBL (measurable), NBL (evaluable), HBL. Subjects may have received bevacizumab, VEGF-Trap, or other VEGF blocking tyrosine kinase inhibitors, provided that they did not progress while receiving one of these agents. Patients with known involvement of the CNS by malignancy will be excluded | Pazopanib *Tablets: 450mg/m² (max 800mg) or suspension: 225mg/m² (max 400mg) po od on days 1-28 of 28 day cycle* | 12 (57) | RMS: ^9.8 years (SD=3.82 years) | NR | Conference abstract and clinical trial registry record used for data extraction |
| Glade Bender, 2013[52] | NR | I | Multi | July 2009 to May 2011 | Relapsed; refractory; all solid tumours | ⩾ 2 years to 22 years | Part 1 and 2A: included patients with solid tumours (including CNS tumours). Part 2B: only STS included and patients had to be under 25 years | Pazopanib *Part 1: 275-600mg/m² po od on days 1-28 of 28 day cycle*<br>*Part 2a: 160-225mg/m² po od on days 1-28 of 28 day cycle*<br>*Part 2b: 450mg/m² po od on days 1-28 of 28 day cycle*<br>*(max 24 cycles)* | 5 (51) | Part 1: 13.4 years (5-21.7 years); part 2A: 10.5 years (3.8-19.2 years); Part 2B: 17.2 years (8.3-23.9 years) | WP: 2 (0-15) | Includes 1 alveolar RMS, 4 NR |
| Kim, 2015[63] | USA | II | Multi | January 2012 to August 2013 | Relapsed; refractory | 24 months to 30 years (inclusive) for RMS patients | | Sorafenib *200mg/m² po bd on days 1-28 of 28-day cycle (max 24 cycles)* | 10 (20) | RMS: 12 years (5-21 years) | NR | |
| Widemann, 2012[106] | NR | I | Multi | August 2006 to February 2010 | Refractory | 24 months to 21 | Solid extracranial tumours (part A) or with refractory leukemias with >25% leukemic blasts in the BM (part B) | Sorafenib *150-325mg/m² po bd on days 1-28 of 28 day cycle* | 4 (49 from solid tumours | Solid tumours cohort: 14 years (4-21 years) | Solid tumours cohort: 2 (0-7) | 4 refractory alveolar RMS |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | years (inclusive) | | | group) | | | |
| Souid, 2010[94] | USA | I | Multi | September 2006 to January 2008 | Relapsed; refractory; all solid tumours | >12 months and ⩽ 21 years | Included CNS tumours and lymphoma. Patients with brainstem gliomas were excluded. The use of enzyme-inducing anticonvulsants (e.g., phenytoin, phenobarbital, felbamate, primidone, oxcarbazepine, or carbamazepine) or agents known to inhibit CYP3A4 (e.g., itraconazole, ketoconazole, and voriconazole) were prohibited | Ispinesib *5-12mg/m² IV on days 1,8 and 15 of 28 day cycle* | 2 (24) | WP: 10 years (1-19 years) | WP: 1 (0-6) | |
| Kieran, 2017[62] | NR | I/II (RMS only in stage I) | Multi | NR | Relapsed; refractory | 1-18 years | MB, RMS, NBL, HBL, HGG, OS. Treatment with strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 or drugs metabolised by CYP2B6 or CYP2C9, which have a narrow therapeutic index, was prohibited during the study | Sonidegib *372-680mg/m² po od on days 1-28 of 28 day cycle* | 4 (60) | WP: 12 years (2-17 years) | NR | |
| De Pasquale, 2011[37] | Italy | NR | NR | June 2006 to December 2009 | Relapsed | NR | Poor prognosis tumours | Bevacizumab *5-10mg/kg IV every 14 or 28 days* | 2 (17) | RMS: 70.5 months* (30-111 months) | NR | Both relapsed RMS |
| Weigel, 2014[103] | USA | II | Multi | January 2009 to March 2012 | Relapsed; refractory; all solid tumours | 1-31 years | | Cixutumumab *9mg/kg IV on days 1,8,15 and 22 of 28-day cycle* | 20 (116 in total but 102 analysed; 14 previously reported) | WP: 12 years (2-30 years)) | NR | |
| Fouladi, 2006[42] | USA | I | Multi | NR | Relapsed; refractory; all solid tumours | <22 years | | Depsipeptide *10mg/m² (escalated in 30% increments) IV on days 1,8 and 15 of 28-day cycle* | 4 (23) | WP: 13 years (2-21 years) | | 1 embryonal RMS |
| Merchant, 2016b[81] | USA | I | Multi | NR | Relapsed; refractory; all solid tumours | 2-21 years | Patients with primary brain malignancies were excluded from the trial but asymptomatic patients with subcentimetric or treated brain metastases were eligible for enrolment | Ipilimumab *1-10mg/kg IV every 21 days for 4 cycles. If no evidence of PD or DLT, maintenance therapy initiated 3 weeks after induction with infusion of same dose every 12 weeks* | 2 (33) | WP: 13.4 years (2-21 years) | NR | |
| Merchant, 2012[116] | USA | I | Multi | NR | Relapsed; refractory | 2-21 years | Patients with hepatic metastases were excluded, as well as patients with primary | Lexatumumab *3-10mg/kg IV on days 1 and 15 of 28-day* | 3 (24) | WP: 16 years (2-21 years) | WP: (2-6) | All RMS were relapsed patients |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | | CNS malignancies or active brain metastases | *cycle* | | | | |
| Geller, 2020[47] | USA | II | Multi | NR | Relapsed; refractory | 12 months to 30 years | WT, RMS NBL, pleuropulmonary blastoma, MPNST, or synovial sarcoma were eligible. Exclusion criteria included active CNS metastases, grade 2 or higher CNS or peripheral neuropathies. Patients taking agents to treat or prevent GVHD or organ rejection after transplantation were not eligible | Lorvotuzumab Mertansine *110mg/m$^2$ IV on day 1 and 8 of 21-day cycle (max 17 cycles)* | 16 (62 enrolled, 61 treated) | WP: 13.9 years (2.8-26.3 years) | NR | |
| Davis, 2020[36] | USA | I/II | Multi | February 2015 to July 2018 | Relapsed; refractory; all solid tumours | Part A: 1- 18 years, Part B: 1-30 years | Part A was solid tumours. Part B was specific cohorts: RMS, ESFT, OS, NBL, HL, NHL and melanoma. Patients with known CNS metastases or CNS tumour excluded | Nivolumab *Part A 1-3mg/kg IV on day 1 and 15 of 28 day cycle Part B 3mg/kg IV on day 1 and 15 of 28 day cycle (Max 2 years of treatment)* | 12 (85; 13 in part A and 72 in part B) | WP: 14 years (IQR 8-17 years)) | WP: 3 (IQR 1-4) | 1 embryonal, 11 NOS |
| Norris, 2018[84] | USA | I | Multi | August 2013 to November 2014 | Relapsed; refractory; all solid tumours | 12 months to 22 years | Excluded patients with primary CNS tumours or prior history of metastatic CNS disease | Ontuxizumab *4-12mg/kg IV on days 1,8,15 and 22 of 28-day cycle* | 5 (27) | WP: 15 years for all eligible and 16.5 years for all evaluable (3-21 years) | WP: 3 (1-6) | |
| Langevin, 2008[68] | USA, Canada | II | Multi | NR | Refractory | < 22 years at diagnosis | Extracranial solid tumours (NBL, ESFT/PNET, OS, RMS, NHL, other) or CNS tumours (MB/PNET, ependymoma, brainstem glioma, other) | Rebeccamycin Analogue (NSC #655649) *650mg/m$^2$ IV every 21 days (max 16 cycles)* | 21 (133) | WP: 11 years at study entry (0-26 years); 9 years at diagnosis (0-21 years) | NR | |
| Langevin, 2003[128] | NR | I | NR | NR | Refractory; all solid tumours | ⩽ 21 years | Included lymphomas and CNS tumours. Includes patients for which no effective therapy was known. Stratum 2 restricted patients to those with no more than 2 prior chemotherapy regimens, no prior central axis radiation or BM transplantation, and no BM involvement | Rebeccamycin Analog (NSC #655649) *450-760mg/m$^2$ IV every 21 days* | 1 (16) | WP: 13.5 years (1-17 years) | NR | Refractory RMS |
| Streby, 2019[95] | USA | I | Single | NR | Relapsed; refractory | 7-30 years (inclusive) at time of virus | Focus on non-CNS solid tumours | Sephrevir *Level 1: 5x10$^4$ iu/kg (max 2x10$^6$ iu) Level 2: 2.5x10$^5$ iu/kg (max 1x10$^7$ iu) IV (max 4 cycles)* | 1 (9) | RMS was 11 years | RMS received 2 lines | RMS patient with metastatic disease |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | injection | | | | | | |
| **Novel agents - multiple agents** | | | | | | | | | | | | |
| Morgenstern, 2014[34] | NR | I | Multi | April 2010 to February 2012 | Relapsed; refractory; all solid tumours | ⩽ 21 years at the time of diagnosis | Solid tumour including CNS malignancies and lymphomas, with histological verification at diagnosis or relapse and radiographically measurable disease. Excluded patients with brain stem gliomas. Exclude patients who were previously treated with the combination of vinblastine and mTOR | Vinblastine<br>*4-6mg/m² IV on days 1,8,15 and 22 of 28 day cycle*<br>and Sirolimus<br>*0.42mg/m² (max 15mg) loading dose then 0.14mg/kg (max 8mg) po od on days 1-28 of 28 day cycle* | 2 (14) | WP: 8.7 years at trial entry (2.3-19 years) | | 1 Alveolar RMS, 1 NR |
| Vo, 2017[97] | USA | I | NR | NR | All solid tumours | 12 months to 30 years | No known curative options. Patients previously treated with all three drugs of investigation were excluded | Sirolimus<br>*3-7.9ng/ml (up to 8-12ng/ml) po on days 1-21 of 28 day cycle*<br>Cyclophosphamide<br>*25-50mg/m² po on days 1-21 of 28 day cycle*<br>Topotecan<br>*0.8mg/m² po od on days 1-14 od 28-day cycle (max 2 years)* | 3 (21) | WP: 18 years (9-30 years) | NR | |
| Stempak, 2006[134] | Canada | NR | Multi | August 2000 to October 2003 | Relapsed; refractory; all solid tumours | <21 years | | Celecoxib<br>*250mg/m² po bd*<br>+ Vinblastine (CV group)<br>*1mg/m² IV three times weekly* | 3 (17 from the only group including RMS patients) | CV group: 11.9 years (3.7-17.5 years) | NR | All 3 alveolar RMS |
| Jakacki, 2008[59] | USA | I | Multi | March 2004 to December 2005 | Relapsed; refractory | Younger than 22 years | CNS tumour, osteogenic sarcoma, RMS, STS, NBL, or germ cell tumour. No previous exposure to erlotinib | Erlotinib<br>*35-110mg/m² po od on days 1-28 of 28-day cycle*<br>and Temozolomide<br>*180-200mg/m² po on days 1-5 of 28-day cycle* | 8 (46) | WP: 11.5 years (3-20 years) | NR | |
| Casanova, 2020[135] **(This conference abstract represents a subset of patients. As trial is still active, not recruiting, the trial registry record has** | NR | I | NR | NR | Relapsed; refractory; all solid tumours | NR | At least 50% of patients had to have RMS | Regorafenib<br>*6-24months - 60-65mg/m²*<br>*2-18yrs - 72-82mg/m²*<br>*Po od on days 1-14 (concomitant dosing) or days 8-21 (sequential dosing) of 21-day cycle*<br>Vincristine<br>*1.5mg/m² IV on days 1 and 8 of 21-day* | 12 (21) | WP: 10 years (1.5-17 years) | NR | At least 4 alveolar RMS |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| **also been extracted - NCT02085148)** | | | | | | | | *cycle*<br>Irinotecan<br>*50mg/m² IV on days 1-5 of 21-day cycle* | | | | |
| Reed, 2016[88] | USA | I | Multi | October 2013 to December 2014 | Relapsed; refractory; all solid tumours | 3-18 years | CNS tumours and fibromatosis included, no known curative therapy available. Patients with known BM metastatic disease were eligible but could not be refractory to red blood cell or platelet transfusion | Sorafenib<br>*150-200mg/m² po bd on days 1-28 of 28 day cycle*<br>and Topotecan<br>*1.0-1.4mg/m² po on days 1-5 and 8-12 of 28-day cycle* | 1 (12) | WP: 13 years (8-18 years) | RMS received 2 | 1 embryonal |
| Federico, 2020b[41] | USA | I | Single | March 2015 to January 2019 | Relapsed; refractory; all solid tumours | 12 months to 25 years (inclusive) | | Talazoparib<br>*400-600mcg/m² po bd on day 1 then od on days 2-6 of 21 day cycle*<br>and Irinotecan<br>*20-50mg/m² IV od on days 2-6 of 21 day cycle* | 3 (29 from Stratum A) | Stratum A: 14.2 years (4.7-23 years) | Stratum A: 3 (1-7) | 2 alveolar, 1 embryonal RMS |
| Schafer, 2020[120] | USA | I/II | NR | April 2014 to January 2018 | Phase I: Relapsed; refractory; all solid tumours | 1-21 years | Patients excluded if they had a history of total body or craniospinal irradiation or radiation to ≥50% of the pelvis, or uncontrolled infection. Phase I component, a history of disease progression after exposure to a PARPi plus temozolomide was excluded | Talazoparib<br>*400ug/m² (max 1000ug/day) po on day 1-6 of 28 day cycle*<br>and Temozolomide<br>*20-55mg/m² po od on days 2-6 of 28 day cycle* | 1 (40) | WP: 15.5 years (4-25 years) | WP: 3 (1-7) | |
| Federico, 2020a[40] | USA | I | NR | NR | Relapsed; refractory; all solid tumours | ⩽ 21 years at initial diagnosis | | Bevacizumab<br>*15mg/kg IV on day 1 of 21-day cycle*<br>Cyclophosphamide<br>*50mg/m² po od on days 1-21 of 21-day cycle*<br>Sorafenib<br>*90mg/m² po bd on days 1-21 of 21-day cycle*<br>*(max 24 cycles)* | 1 (25) | WP: 14.5 years (1.1 to 22.4 years) | WP: 3 (1-10) | 1 alveolar RMS |
| Navid, 2013[83] | USA | I | Single | NR | Relapsed; refractory; all solid tumours | ⩽ 21 years at initial diagnosis | Patients with solid tumours metastatic to BM were eligible for study but not evaluable for hematologic toxicity | Bevacizumab<br>*5-15mg/kg IV on day 1 of 21-day cycle*<br>Cyclophosphamide<br>*50mg/m² po od on days 1-21 of 21-day cycle*<br>Sorafenib<br>*90-180mg/m² po bd on days 1-21 of 21-day cycle*<br>*(Max 24 cycles)* | 2 (19) | WP: 9.2 years (1.2-24.5 years) | WP: 3 (1-6) | |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| Wagner, 2013[98] | USA | NR | Single | NR | Relapsed; refractory; all solid tumours | 1-30 years | Includes brain tumours. Prior therapy with vincristine, temozolomide or irinotecan was allowed but patients' disease mustn't have progressed while receiving these agents | Vincristine<br>*1.5mg/m² (max 2mg) IV on day 1 of 21 day cycle*<br>+ Irinotecan<br>*90mg/m² po on days 1-5 of 21-day cycle*<br>+ Temozolomide (VOIT)<br>*100-150mg/m² po od on days 1-5 of 21-day cycle*<br>and Bevacizumab<br>*15mg/kg (max 800mg) IV on day 1 of 21-day cycle*<br>*(max 6 cycles)* | 1 (13) | RMS patient was 12 years | WP: 2 (1-7) | |
| Fouladi, 2015[43] | USA | I | Multi | NR | Refractory; all solid tumours | >12 months to <22 years | Excluded if they had known BM involvement, or had received prior temsirolimus or monoclonal antibody therapy targeting IGFIR | Cixutumumab<br>*6-9mg/kg IV on days 1,8,15 and 22 of 28 day cycle*<br>and Temsirolimus<br>*8-35mg/m² IV on days 1,8,15 and 22 of 28 day cycle*<br>*(max 25 cycles)* | 9 (39) | WP: 11.8 years (1-21.5 years) | WP: 2 (0-7) | |
| Wagner, 2015[99] | USA | II | Multi | June 2012 to June 2013 | Relapsed; refractory | 1-30 years | Divided in 4 cohorts: OS, ESFT, RMS and NRSTS | Cixutumumab<br>*6mg/kg IV on days 1,8,15 and 22 of 28 day cycle*<br>and Temsirolimus<br>*8-20mg/m² (max 16-20mg) IV on days 1,8,15 and 22 of 28 day cycle* | 11 (46 enrolled/ 45 eligible) | RMS: 14 years (1-23 years) | NR | |
| Becher, 2017[24] | USA | I | NR | 10th February 2010 to 21st August 2012 | Relapsed; refractory; all solid tumours | ⩽ 21 years | Patients who failed standard therapy | Perifosine<br>*25-75mg/m² po loading dose on day 1, maintenance dose every 1-4 days, in 28-day cycles*<br>and Temsirolimus<br>*25-75mg/m² IV on days 1,8,15 and 22 of 28 day cycle* | 2 (22) | RMS: 7.5 years* (5-10 years) | NR | |
| Kolb, 2015[64] | USA | I | Multi | April 2011 to August 2013 | Relapsed; refractory; all solid tumours | 3-21 years (inclusive) | Excluding tumours originating in or metastatic to the CNS or lymphoma | Reovirus (Reolysin)<br>*3-5x10e8 TCID50/kg IV on days 1-5 of 28-day cycle*<br>Cyclophosphamide<br>*50mg/m² po on days 1-21 of 28-day cycle* | 6 (29 enrolled, 28 treated) | WP: 12.5 years (3-20.2 years) | WP: 3 (1-8) | 2 alveolar RMS, 3 embryonal RMS, 1 NR |
| Fox, 2015[44] | USA | I | NR | NR | Relapsed; refractory; all solid | >2 years to <19 years | | Tariquidar<br>*2mg/kg IV on days 1,3 and 10 of 21 day cycles* | 1 (29) | WP: 13 years (2-18 years) | WP: 3 (1-6) | 1 Metastatic RMS |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | tumours | | | & Doxorubicin (RMS specific)<br>*50mg/m² IV on day 3 of 21 day cycle* | | | | |
| Aquino, 2004[21] | NR | I | Multi | NR | Refractory; all solid tumours | ⩽ 21 years | Following the established MTD in stratum 1, stratum 2 was revised to exclude those who received more than two chemo regimens, any central axis radiation (skull, spine, pelvis, ribs), previous BM or HSCT, or those with BM involvement | Tirapazamine<br>*250-420mg/m² IV on day 1 of 21 day cycle*<br>& Cyclophosphamide<br>*1500mg/m² IV on day 1 of 21 day cycle* | 3 (23) | WP: 10 years (4-19 years) | NR | |
| **Biomarker driven studies** | | | | | | | | | | | | |
| Geoerger, 2020b[113] | UK, USA, France, Germany, Italy, Spain, Netherlands, Denmark, Israel, Switzerland | I/II | Multi | 5th November 2015 to 2nd April 2018 | Relapsed; refractory | <30 years | Solid tumours, HL or NHL. Known or expected PD-L1 involvement, previous treatment has proven ineffective or for whom no curative standard-of care options existed. Excluded patients with primary CNS tumours or CNS metastases, with the exception of atypical teratoid rhabdoid tumour without brain stem involvement. Previous allogeneic HSCT or previous solid-organ transplantation was also not permitted | Atezolizumab (Known or expected PDL1 involvement)<br>*15mg/kg (max 1200mg) IV on day 1 of 21 day cycle* | 10 (90) | WP: 14 years (IQR 10-17 years) | WP: 6 (3-10) | |
| Geoerger, 2020a[112] | UK, USA, Canada, France, Germany, Australia, Brazil, Israel, Italy, South Korea, Sweden | I/II | Multi | 23rd March 2015 to 3rd September 2018 | Relapsed; refractory | 6 months to 17 years | Advanced melanoma or a PD-L1-positive, solid tumour or lymphoma. Patients with active brain metastases and those who had received previous therapy with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 drug were excluded. Also excluded patients with prior solid organ transplant at any time or patients with prior allogeneic SCT within the last 5 years | Pembrolizumab (PDL1 positive only)<br>*1-10mg/kg (phase 2 dose 2mg/kg) IV on day 1 of 21 day cycle (max 24 months)* | 7 (154) | WP: 13 years (8-15 years) | NR | 2 alveolar, 4 embryonal RMS, 1 NOS. All required PD-L1 expression |
| Fischer, 2021[110] | UK, USA, Canada, France, Germany, Spain, Australia, Netherlands, Italy, Korea | I | Multi | 28th August 2013 to 17th October 2017 | Relapsed; refractory | ⩾ 12 months to < 18 years | Advanced or metastatic malignancy. Patients had to have ALK-positive tumours (i.e., ALK expression in the case of RMS) | Ceritinib (ALK positive tumours)<br>*Fasted state: 300-560mg/m²*<br>*Fed state 320-500mg/m²*<br>*po od on days 1-21 of 21-day cycle (max 52 cycles)* | 12 (83) | WP: 8 years (4-13 years) | NR | All ALK-positive tumours |
| Worst, 2016[122] | Germany | NA | Multi | NR | Relapsed; refractory | 1-40 years | Includes progressive disease. No established curative treatment options. | Personalised therapy - crizotinib for RMS patients | 2 (57 enrolled, | RMS: 11.5 years* (11-12 years) | NR | Study of feasibility of |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | | First-line treatment with one of the therapies approved by the Society for Pediatric Oncology and Hematology (excluding cases of primary RMS) | *Dosage information not reported* | 10 receiving matched therapy) | | | personalised medicine. 2 relapsed alveolar RMS with PAX3:FOXO1 status |
| **Metronomic chemotherapy** | | | | | | | | | | | | |
| Kieran, 2005[127] | USA | NR | NR | June 2001 to July 2002 | Relapsed; refractory | <22 years | Includes progressive poor prognosis tumours for which no curative therapy remained. Brain tumour patients receiving steroids and/or anticonvulsants were eligible for study. Patients could not have received prior oral low dose etoposide or cyclophosphamide but could have received prior IV etoposide/cyclophosphamide | Metronomic chemotherapy: thalidomide *3-24mg/kg (max 100mg) po on days 1-21 of 21 day cycle* celecoxib *100mg for patients <20kg; 200mg for patients 20-50kg; 400mg for patients >50kg; po bd on days 1-21 of 21 day cycle* and alternating etoposide *50mg/m² po on days 1-21 of alternating 21 day cycles* / Cyclophosphamide *2.5mg/kg (max 100mg) po od on days 1-21 of alternating 21-day cycles* | 2 (20) | RMS: 10.5 years* (7-14 years) | NR | |
| Ali, 2016[123] | Egypt | Nr | Single | January 2013 to January 2015 | Relapsed; refractory; all solid tumours | ⩽ 18 years | | Metronomic chemotherapy: Celecoxib *100mg for patients <20kg; 200mg for patients 20-50kg; 400mg for patients >50kg; po bd on days 1-42 of 42-day cycle* Vinblastine *3mg/m² IV on days 1,8,15,22,29 and 36 of 42-day cycle* Cyclophosphamide *2.5mg/kg po od on days 1-21 of 42-day cycle* Methotrexate *15mg/m² po twice weekly on days 21-42 of 42-day cycle* + radiotherapy *According to tumour type and size (details in manuscript). Each 42-day cycle followed by 7 days rest* | 14 (64) | WP: 7 years (3-17 years) | NR | |
| El Kababri, 2020[39] | Morocco | II | Multi | July 2014 to January | Relapsed; refractory | <18 years | Very advanced disease. Solid Tumours | Metronomic - Cyclophosphamide *30mg/m² po on days 1-21 of 28-day cycle* | 14 (98) | WP: 8 years (2-18 years) | RMS: 1 (1-3) | |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | 2018 | | | | Etoposide *25mg/m² po on days 1-21 of 28-day cycle* and valproic acid *20mg/kg po on days 1-28 of 28-day cycle* | | | | |
| **HSCT** | | | | | | | | | | | | |
| Shiriaev, 2013[138] | Russia | NR | NR | NR | RMS only | NR | | High dose chemotherapy + *Autologous HSCT* *Single HDCT: Busulfan: 16mg/kg. Melphalan: 140mg/m².* *Tandem HDCT: as above, then carboplatin 500mg/m² with etoposide 300mg/m² and 900mg/m² (etoposide 45mg/m² and cyclophosphamide 120mg/m² cycles also conducted) Note: not clearly reported within CA* | 3 R+R (of 8 RMS in total) | RMS: ^8 years | NR | 3 embryonal |
| Prete, 2010[140] | Italy | NR | NR | NR | Relapsed; refractory | NR | RMS or ESFT. Patients who had 1 year probability of survival less than 5% | Allogeneic HSCT *Conditioning: thiotepa, melphalan, and fludarabine or cyclophosphamide* *Donor: identical sibling or unrelated* | 11 (20) | WP: 16 years (6-22 years) | NR | 8 relapsed, 3 refractory RMS |
| Perez-Martinez, 2012[85] | Spain | NR | Single | October 2005 to October 2009 | NR | NR | | Haplo-SCT with non-myeloablative conditioning *Conditioning: Fludarabine (130mg/m²), Busulfan (3.2-4.8mg/kg for 2 days), Thiotepa (10mg/kg), Methylprednisolone (5mg/kg for 5 days)* *Graft: CD3/CD19 depleted, mean CD34+ 5.71 x10⁶/kg* | 1 (6) | RMS was 5 years | NR | 1 metastatic Embryonal RMS |
| Llosa, 2017[71] **(This full-text represents a subset of patients. The trial is still recruiting so the trial registry has also been extracted - NCT01804634)** | USA | II | NR | March 2013 to December 2016 | Relapsed; refractory; all solid tumours | ⩽ 40 years | High risk features defined by having an expected survival of <10% | Haplo-identical bone marrow transplant + reduced intensity conditioning *Conditioning: fludarabine (30mg/m² on days -7 to -3), cyclophosphamide (14.5mg/kg on days -7 and -6), melphalan (100mg/m² on day -2), TBI (200cGy on day -1)* | 2 (16) | RMS: 15.5 years* (15-16 years) | RMS: 5.5* (4-7) | 2 alveolar RMS |
| Baird, 2012[109] | USA | II | NR | September 2002 to | Relapsed | NR | ESFT or alveolar RMS, initial diagnosis with BM metastases, enrolled after | Reduced intensity Allogeneic HSCT *Conditioning: cyclophosphamide* | 2 < 18 years (30) | RMS: 14 years* (12-16 years) | NR | 2 alveolar RMS |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | November 2008 | | | standard front-line therapy, PD after front line therapy, tumour recurrence within 1 year after completing standard front-line therapy, and enrolled at the time of recurrence; second or subsequent recurrence. Patients with DSRCT were eligible if they had unresectable or metastatic disease (extra-abdominal and abdominal), progressive or persistent disease with standard front-line therapy, or recurrence within 1 year of completing standard front-line therapy | *(1200mg/m$^2$ on days -6 to -3), fludarabine (30mg/m$^2$ on days -6 to -3), melphalan (100mg/m$^2$ on day -2)*<br>*(Patients received 3 cycles of EPOCH-F induction prior to conditioning)* | | | | |
| **Cellular therapies** | | | | | | | | | | | | |
| Ruano, 2020[89] | Spain | I | Single | January 2013 to May 2015 | Relapsed; refractory; all solid tumours | 6 months to 18 years | Recurrent/refractory to at least 2 lines of conventional treatment. Excluded patients with symptomatic, uncontrolled CNS metastases | Autologous MSCs with oncolytic virus Icovir-5 (Celyvir)<br>*2x10$^6$ cells/kg IV every week for 6 weeks* | 1 (9) | WP: 7.5 years (3.5-17.3 years) | NR | First in human |
| Merchant, 2016a[80] | USA | NR | NR | September 2007 to March 2011 | Relapsed | <35 years at initial diagnosis | Newly diagnosed metastatic or relapsed sarcoma (ES, RMS, DSRCT, synovial sarcoma, undifferentiated sarcoma). Those who had recurrent disease had to have a prolonged disease-free interval (>1 year for patients 5 years and older and >6 months for patients <5 years) | Autologous lymphocyte infusion<br>*Dose not reported, given on Day 2*<br>and dendritic cell vaccines (cohort 1)<br>*3 at 1x 10e7 cells per site (subcutaneous), 1x 10e6 cells per site (intradermal) on days 2,16,30,44,58,and 72*<br>plus CYT107 (recombinant human IL7) in cohort 2<br>*20mcg/kg subcutaneous on day 0,14,28, and 42* | 4 < 18 years (29) | RMS: 9 years* (7-14 years) | RMS: 1* (1-2) | 2 alveolar, 2 embryonal RMS. 3 first relapse, 1 second relapse |
| Merker, 2019[117] | Germany | NR | Single | 1st October 2003 to 1st January 2014 | Relapsed; refractory; all solid tumours | NR | | Consecutive donor-derived adoptive cellular immunotherapy after allogeneic HSCT<br>*Conditioning: Fludarabine- 30mg/m$^2$ for 5 days, Thiotepa - 5mg/kg for 2 days, Melphalan - 70mg/m$^2$ for 2 days*<br>*Graft: Haploidentical graft with CD3/CD19 depletion. 7 x10$^6$ CD34+ cells/kg*<br>*Adoptive cellular immunotherapy: CIK cells: 5 x 10$^6$ T cells/kg* | 1 < 18 years (18) | RMS was 12.5 years at diagnosis | | Relapsed RMS |
| Hegde, 2020[54 270] **(This trial is still recruiting so total** | USA | I | NR | NR | Relapsed; refractory | NR | HER2 positive sarcoma (at least grade 1 (1-25% positive) and intensity score 1+ for HER2 staining | HER2 CAR-T cells<br>*Lymphodepletion: Fludarabine: 25 mg/m$^2$ for 5 days. Cyclophosphamide: 30 mg/kg* | 1 (6) | RMS was 7 years | RMS received 2 | 1 refractory Alveolar RMS with a somatic |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| **population number is up to date of current publication)** | | | | | | | | *for 2 days.*<br>*CAR-T cells: 1 x $10^8$ cells/$m^2$* | | | | variant of PIK3CA Q546R, and had to have HER2 positive variant |
| Ismail-zade, 2010[57] | Belarus (Russian) | Not extractable | Not extractable | Not extractable | Refractory | Not extractable | | LAK cell therapy and whole body hyperthermia<br>*Chemo: doxorubicin 40-50mg/$m^2$, carboplatin 400mg/$m^2$, etoposide 100-150mg/$m^2$, ifosfamide 3mg/$m^2$, topotecan 0.75-1.0mg/$m^2$, cyclophosphamide 0.25-1.0g/$m^2$.*<br>*LAK cell dose 0.5-1.5 x$10^9$* | 4 (19) | RMS: 15 years* (7-16 years) | All RMS had >4 | All 4 embryonal RMS |
| Hont, 2019[56] | USA | I | Single | 5th May 2016 to 1st December 2018 | Relapsed; refractory | 6 months to 60 years | ESFT, WT, NBL, RMS, STS, OS, adenocarcinoma and esophageal carcinoma; express 1+ of the target tumour antigens: WT1, PRAME and/or survivin. High risk solid tumours | TAA cytotoxic T cells (TAA-Ts)<br>*3 dose levels: 1, 2 and 4 x 10e7 cells/$m^2$. IV. 1st and 2nd dose given 45 days apart then every 28 days. (max 8 doses)* | 3 (15) | RMS: 9 years* (3-10 years) | NR | First in human.<br>3 alveolar. 1 first relapse, 2 second relapse RMS |
| **Other approaches** | | | | | | | | | | | | |
| Blank, 2009[27] | Netherlands | NR | Single | 1993-2007 | RMS only | NR | Non orbital non metastatic head and neck RMS. Group B: salvage treatment: local recurrence or unresectable residual parameningeal and non parameningeal disease after first line chemo and EBRT. Patients with inoperable intracranial tumour growth after chemotherapy and M1 disease were not eligible. | AMORE<br>*consecutive Ablative surgery, MOld technique with after loading brachytherapy (dose to CTV 40-50Gy, full radiotherapy details in manuscript) and surgical REconstruction after induction chemotherapy* | 9 (11 in group B with relapsed disease) | RMS: 7.9 years* (2.4-16.9 years) | RMS: 1* (1-2) | 3 alveolar, 6 embryonal RMS. 6 first relapse, 3 second relapse. 3 parameningeal, 6 non-parameningeal |
| Streby, 2017[96] | USA | I | Multi | NR | Relapsed; refractory | 7-30 years at the time of virus injection (inclusive) | Incurable non-CNS tumours. Asymptomatic patients with treated brain metastases were eligible for enrolment. Patients needed to have at least one cancer lesion amenable to HSV1716 administration by needle via imaging guidance without undue risk. The lesion(s) had to be at least 3 times greater than the volume of HSV1716 to be injected (based on available lots, the volumes were 1 mL of HSV1716 injected for dose levels 1 and 2, 5 mL for dose level 3). History of allogeneic SCT excluded. Excluded | Intratumoral injection of HSV1716 (oncolytic herpes virus)<br>*1.0 x 10(e5) infectious units (dose level one), 2.0 x 10(e6) infectious units (dose levels 2 (1 vial) and 3 (5 vials)), and 1 x 10(e7) infectious units. Every 28 days (max 4 cycles)* | 2 (9) | RMS: 10.5 years* (8-13 years) | RMS: 3.5* (3-4) | First in child study<br>2 Relapsed RMS; 1 parameningeal and 1 retroperitoneal |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | | patients who planned use of antiviral therapy between 2 days prior to HSV1716 administration up to 28 days after HSV1716 administration | | | | | |
| Hoffer, 2009[55] | USA | I | NR | January 2003 to September 2006 | Relapsed | <21 years | Recurrent or progressive disease in the lung, liver or musculoskeletal system. Patients with uncorrectable coagulopathy or thrombocytopenia were not eligible. Pulmonary radiofrequency ablation candidates must have had prior pulmonary nodule resection, not require supplemental oxygen, and be expected to be free of dyspnea at rest in room air at 1 month after the ablation | Radiofrequency Ablation + chemotherapy *Target temperature 50°C. (max 2 sessions 2 days to 2 weeks apart)* | 2 (16) | RMS: 14.5 years* (13-16 years)) | NR | |
| Jiang, 2016[60] | China | NR | Multi | 2010 to 2014 | Relapsed; soft-tissue sarcomas only | <80 years | Previous failure in all standard therapies including surgery, chemotherapy, radiotherapy or combined therapy, target lesions based on patients' symptoms. Advanced STS (CT/MRI proven metastasis or recurrence), moderate to high sensitivity to chemotherapeutic drugs (e.g., OS and alveolar STS) | Transarterial Chemoembolization (TACE) *5-fluorouracil (5-FU), oxaliplatin (L-OHP), epirubicin (EADM). Injected into feed artery at flow rate of <0.1ml/s followed by infusion under angiographic monitoring. TACE ended when either feeding vessel showed complete stasis or angiographic tumour stain disappeared* | 6 (39) | WP: 38^ years (10-59 years) | NR | |
| **Non-comparative multi-arm cohorts** | | | | | | | | | | | | |
| Frappaz, 2016[45] | UK, USA, France | I | Multi | NR | All solid tumours | 3-17 years | Excluded patients who previously received dalotuzumab or other IGF-1R inhibitors | Dalotuzumab **(monotherapy arm of study)** *900-1500mg/m² IV on day 1 of 21-day cycle* | 3 (20) | WP: Median NR (3-17 years) | NR | |
| | | | | | | 6-17 years | | Dalotuzumab *900mg/m² IV on day 1 of 21-day cycle* and Ridaforolimus *28mg/m² po on days 1-5, 8-12 and 15-19 of 21-day cycle* **(combination arm of study)** | 1 (4) | WP: 13.5 years (7-15 years) | NR | |
| Mascarenhas, 2019b[15] | USA | II | NR | June 2002 to October 2006 | First relapsed or refractory | ⩽ 21 years at the time of initial diagnosis | Biopsy-proven RMS, undifferentiated sarcoma or ectomesenchymoma. Patients with unfavourable risk features (stage 2-4, clinical group II-IV ERMS at the initial diagnosis; stage I or clinical group I ERMS at the initial diagnosis with distant | Doxorubicin *75mg/m² IV on weeks 1,4,10,19 and 28* Cyclophosphamide *1.2g/m² IV on weeks 1,4,10,19 and 28* Etoposide *100mg/m² on days 1-5 of weeks* | 91 (91) | WP: 14 <10 years; 16 >/=10 years | WP: 1 (1-1) | 19 alveolar, 6 embryonal RMS; 5 'other'. (30 who were ineligible for |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | | recurrence after vincristine and dactinomycin or recurrence after VAC; and alveolar RMS at the initial diagnosis) who did not respond, or were ineligible (prior irinotecan, who declined randomisation or who did not have measurable disease) for the VI phase 2 study (Mascarenhas, 2010) were included in REGIMEN 2. Patients who had received more than one prior chemotherapy treatment regimen, or those with prior exposure to anthracyclines, those with myeloablative chemotherapy followed by hematopoietic stem cell rescue, or disease impinging on or within the brain and spinal cord were excluded | *7,13,16,22 and 25*<br>Ifosfamide<br>*1.8g/m$^2$ on days 1-5 of weeks 7,13,16,22 and 25*<br>& Tirapazamine<br>*330mg/m$^2$ IV on weeks 1,4,10,19 and 28*<br><br>**(Regimen 2 of study)** | | | | window trial **[demographic data is only provided for this subgroup in this paper]**, 61 who did not respond to window trial) |
| | | | | | | | First relapse or disease progression; biopsy-proven RMS, undifferentiated sarcoma or ectomesenchymoma. Patients with favourable risk features (botryoid histology at the initial diagnosis or stage 1 or clinical group I ERMS at the initial diagnosis not treated with cyclophosphamide, and who recurred locally or regionally) at the time of first relapse or disease progression received multi-agent chemotherapy without VI or TPZ starting at week 1. REGIMEN 3. Patients who had received more than one prior chemotherapy treatment regimen, or those with prior exposure to anthracyclines, those with myeloablative chemotherapy followed by hematopoietic stem cell rescue, or disease impinging on or within the brain and spinal cord were excluded | Doxorubicin, Cyclophosphamide, Etoposide & Ifosfamide<br>*All doses as per Regimen 2 above*<br><br>**(Regimen 3 of study)** | 14 (14) | WP: 8 <10 years; 6 >/=10 years | WP: 1 (1-1) | 10 embryonal RMS; 4 'other' |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| Mascarenhas, 2021[75] | USA, Japan | I | Multi | NR | Relapsed; refractory; all solid tumours | <18 years | Not amenable to curative treatment and for which chemotherapy with doxorubicin, vincristine/irinotecan, or high-dose ifosfamide was deemed appropriate by the treating investigator. Patients were excluded if they had undergone a BM or solid organ transplant (prior autologous stem cell infusion was allowed) | Olaratumab<br>*Part A: 15mg/kg, Part B&C: 20mg/kg IV on days 1 and 8 of 21 day cycle*<br>+ Doxorubicin<br>*37.5mg/m² IV on days 1 and 2 of 21-day cycle (to 6 cycles or cumulative dose of 450mg/m²)*<br><br>**(specific combination therapy)** | 11 (16) | WP: 5 years (2-15) in part A; 10 years in part B; 12 years (5-15 years) in part C | NR | |
| | | | | | | | | Olaratumab<br>*As per above arm*<br>+ Irinotecan<br>*50mg/m² IV on days 1-5 of 21-day cycle*<br>/Vincristine<br>*1.5mg/m² (0.05mg/kg if <10kg) on days 1 and 8 of 21 day cycle*<br><br>**(specific combination therapy)** | 7 (26) | WP: 10 years (2-17 years) in part A; 12 years (3-16 years) in part B; 10 years (2-16 years) in part C | NR | |
| | | | | | | | | Olaratumab<br>*As per above arm*<br>+ Ifosfamide<br>*2.8g/m² IV on days 1-5 of 21-day cycle (to 6 cycles or cumulative dose of 84g/m²)*<br><br>**(specific combination therapy)** | 1 (26) | WP: 12 years (4-16 years) in part A; 13 years (4-17 years) in part B; 8 years (2-15 years) in part C | NR | |
| **Comparative studies** | | | | | | | | | | | | |
| Petrilli, 2004[141] | NR | II | NR; RCT | NR | Refractory; all solid tumours | 1-21 years (based on title) | Includes CNS tumours | Carboplatin<br>*4mg/m*min on day 1 of 21-day cycle*<br>+ Irinotecan<br>*12mg/m² od on days 1-10 of 21-day cycle* | NR (74) | NR | NR | Non-comparative trial |
| | | | | | | | | Irinotecan<br>*20mg/m² od on days 1-10 of 21 day cycle* | At least 2 (74) | NR | NR | |
| Shook, 2013[92] | USA | I | Single | March 2001 to July 2008 | Relapsed; refractory; all solid tumours | 21 years and younger | Standard therapy unavailable or failed. Solid malignancy including lymphoma. All patients required either an available human leukocyte antigen (HLA) identical sibling or a 6/6 HLA-matched unrelated donor. Primary brain tumours excluded | Allogeneic HSCT: sibling donor. Conditioning: fludarabine *30mg/m² on days -4 and -2* and total body irradiation *2Gy*. | 2 (12) | RMS: 16.9 years* (16.2-17.6 years) | NR | 1 second relapse, 1 refractory RMS |
| | | | | | | | | Matched unrelated donor. All other therapeutics the same | 1 (12) | RMS patient was 3.2 years | NR | 1 first relapse |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| Mascarenhas, 2019a[14] | USA | II, RCT | Multi | October 2010 to July 2013 | Relapsed; refractory; RMS only | < 30 years | Biopsy-proven RMS - either embryonal, alveolar or NOS. Patients with primary refractory disease, defined as first progression after at least one cycle of cyclophosphamide or ifosfamide-containing chemotherapy without a prior response to chemotherapy were also eligible. Botryoid RMS, patients with Stage 1 disease at original diagnosis that presented with local/regional recurrence were excluded. Prior therapy with vinorelbine, bevacizumab, temsirolimus, other mTOR or VEGF/VEGF receptor targeting agents was excluded | Bevacizumab<br>*15mg/kg IV on day 1 of 21 day cycle*<br>Vinorelbine<br>*25mg/m² IV on day 1 and 8 of 21-day cycle*<br>Cyclophosphamide<br>*1200mg/m² IV on day 1 of 21-day cycle (max 12 cycles)* | 44 (44) | RMS: 19 patients <10 years; 20 patients 10-19 years; 5 patients >19 years | | 27 alveolar RMS, 15 embryonal RMS, 2 'other' |
| | | | | | | | | Temsirolimus<br>*15mg/m² (max 30mg) on days 1,8 and 15 of 21 day cycle*<br>Vinorelbine<br>*As per above arm*<br>Cyclophosphamide<br>*As per above arm* | 42 (42) | RMS: 13 patients <10 years; 24 patients 10-19 years; 5 patients >19 years | | 25 alveolar RMS, 17 embryonal RMS |
| Mascarenhas, 2010[73] | USA | II, RCT | NR | June 2002 to October 2006 | Relapsed | < 21 years | First relapse or disease progression, RMS/undifferentiated sarcoma or ectomesenchymoma. Patients who had received more than one prior chemotherapy treatment regimen were excluded | Irinotecan<br>*20mg/m² IV on days 1-5 of weeks 1,2,4,5,13,14,25,26,34,35,46,47,49 and 50*<br>Vincristine<br>*1.5mg/m² (max 2mg) IV on day 1 of weeks 1,2,4,5,13,14,25,26,34,35,46,47,49 and 50*<br>Doxorubicin<br>*75mg/m² IV on weeks 7,16,28,37 and 40*<br>Cyclophosphamide<br>*1.2g/m² IV on weeks 7,16,28,37 and 40*<br>Etoposide<br>*100mg/m² IV on days 1-5 of weeks 10,19,22,31 and 43*<br>and Ifosfamide<br>*1.8g/m² IV on days 1-5 of weeks 10,19,22,31 and 43* | 45 (45) | WP: 24 patients <10 years; 21 patients >= 10 years | NR | 22 alveolar RMS, 15 embryonal RMS, 8 'other'. 6 favourable site, 39 unfavourable site |
| | | | | | | | | Irinotecan, Vincristine, Doxorubicin, Cyclophosphamide, Etoposide and Ifosfamide (different dosage of Irinotecan)<br>*All dosages and timings as per above arm except irinotecan:*<br>*50mg/m² on days 1-5 of weeks 1, 4, 13,* | 47 (47) | WP: 24 patients <10 years; 23 patients >= 10 years | NR | 27 alveolar RMS, 16 embryonal RMS, 4 'other'. 6 favourable site, 41 unfavourable site |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | | | *25, 34, 46 and 49* | | | | |
| Defachelles, 2021[8] | UK, France, Italy, Netherlands, Spain | II, RCT | Multi | March 2012 to April 2018 | Relapsed; refractory, RMS only | 6 months to 50 years | Includes progressive disease. Patients with previous exposure to irinotecan or temozolomide were excluded | Vincristine *1.5mg/m$^2$ (max 2mg; 0.05mg/kg if <10kg) IV on day 1 and 8 of 21 day cycle* and Irinotecan (VI) *50mg/m$^2$ IV on day 1-5 of 21 day cycle (max 12 cycles)* | 60 (60) | RMS: 10.5 years (3-45 years) | | 34 alveolar RMS, 26 non-alveolar. 14 undifferentiated relapse, 41 first relapse, 5 refractory. 13 favourable site, 47 unfavourable site |
| | | | | | | | | Vincristine *As per above arm* Irinotecan *As per above arm* and Temozolomide (VIT) *125-150mg/m$^2$ po od on days 1-5 of 21 day cycle (max 12 cycles)* | 60 (60) | RMS: 12 years (9.1 months to 45 years) | | 34 alveolar RMS, 26 non-alveolar. 12 undifferentiated relapse, 40 first relapse, 8 refractory. 8 favourable site, 52 unfavourable site |
| Pramanik, 2017[86,251] | India | III | Single, RCT | 1st October 2013 to 31st December 2015 | Relapsed; refractory | 5-15 years | Non-hematopoietic primarily extracranial solid tumours that had progressed after treatment with at least 2 lines of chemotherapy and had no curative treatment options | Metronomic chemotherapy Alternating three weekly cycles of: Cycle A: *thalidomide (3mg/kg po od), celecoxib (100mg for patients <20kg; 200mg for 20-50kg; 400mg for > 50kg; po bd) & etoposide (50mg/m$^2$ po od)* Cycle B: *thalidomide (as above), celecoxib (as above) and cyclophosphamide (2.5mg/kg (max 100mg) po od))* and best supportive care | 3 (56) | RMS: 7 years* (6-16 years) | RMS: 2 (2-2) | |
| | | | | | | | | No metronomic chemotherapy - placebo (same size and colour as metronomic chemo) and best supportive care | 5 (52) | RMS: 10 years* (6-15 years) | RMS: 2 (2-2) | |
| **Vaccines** | | | | | | | | | | | | |
| Krishnadas, 2015[65] | USA | I | Multi | February 2011 to July 2013 | Relapsed; refractory | 12 months to 18 | NBL, RMS, ESFT or OS. Patients were required to have received treatment with standard therapy for their disease. | Dendritic Cell Vaccine *Once per week for two weeks* and Decitabine. | 1 (15 enrolled, 10 treated) | RMS was 14 years | NR | The RMS patient had 3 pulmonary relapses |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | years | Patients were excluded if they had autoimmune disease, hypersensitivity to decitabine, imiquimod or any vaccine component or were receiving concurrent systemic steroid therapy | *10mg/m² IV on days 1-5*<br>Imiquimod was used as an adjuvant at the site of vaccination<br>*(max 4 cycles)* | | | | |
| Tsuchiya, 2018[121] | Japan | I | NR | September 2011 to June 2016 | Relapsed; refractory | 1-40 years | All tumours except leukaemia. Patients with histo-logical confirmation of GPC3 expression in tumour cells, HLA-A24- or HLA-A2-positive status as determined using commercially available genomic DNA typing tests. Excluded patients: 1) pleural effusion or ascites requiring removal by puncture; 2) active concurrent cancer or secondary cancer within 5 disease-free years of primary cancer; 3) currently taking systemic steroids or immunosuppressant medication | Glypican-3-derived peptide vaccine therapy<br>*<20kg: 1.5mg; >20kg 3.0mg. Intradermal injection every 2 weeks* | 1 (18) | RMS was 3 years | NR | |
| Akazawa, 2019[19] | Japan | I | NR | March 2013 to December 2014 | Refractory | 1-40 years | Diagnosis of NBL, ESFT, RMS or OS | NCCV Cocktail-1 Vaccine<br>*Two incremental doses of the peptide given. Less than 20kg: total 6mg - every 2mg of every 3 peptides. More than 20kg: 3mg - every 1mg of the 3 peptide. Intradermal injection, weekly.* | 3 (12) | RMS: 14 years* (7-15 years) | NR | All refractory. 2 patients KOC1 positive, FOXM1 and KIF20A. 1 patient KIF20A positive only. All HLA class I negative |
| Oda, 2020[119] | Japan | II | NR | October 2016 to March 2017 | Refractory; all solid tumours | NR | | Personalised Peptide Vaccine<br>*Dosing information not reported* | 1 (4) | RMS patient was 3 years at onset, 5 years at study entry | RMS: 2 | RMS patient had relapsed alveolar RMS |
| Burke, 2015[30] | USA | I | Multi | September 2009 to February 2013 | Refractory | 3-21 years (inclusive) | Incurable disease, NBL, RMS, retinoblastoma, WT, adrenocortical carcinoma, or carcinoid tumour. Patients with a primary CNS tumour or known metastatic CNS disease; known pulmonary tumours or metastases >5 cm, as evaluated by chest CT were excluded | Part A: NTX-010 (Seneca Valley virus) alone.<br>*1 x 10e9 vp/kg up to 1 x 10e12 vp/kg. IV*<br>Part B: NTX plus cyclophosphamide<br>*NTX-010: 1 x1 10e11 vp/kg [max dose 12 x 10e12] on day 8 of 21 day cycle*<br>*Cyclophosphamide 25mg/m² (max 50mg) po on days 1-14 and 750mg/m² IV (max 1000mg) on day 8. (max 2 cycles)* | 3 (22) | WP: 8.8 years (4.8-18.3 years) | WP: 3 (1-6) | 2 alveolar RMS, 1 embryonal RMS |
| Sawada, 2016[132] | Japan | I/II | Single | August 2005 to July 2011 | Relapsed; refractory | <20 years | Solid and haematological malignancies. Patients have to have HLA-A*24:02, | WT1 Peptide Vaccine<br>*0.5mg for patients <10kg; 1mg for 10-* | 3 (26) | RMS: 4 years* (2-8 years) | NR | 1 patient with overt disease |

| Author, date (Ref) | Countries performed (language if not English) | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range), ^mean) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | | tumour cells or leukemic cells expressing WT1 mRNA or protein. Excluded patients with myelodysplastic syndrome, myelodysplastic/myeloproliferative neoplasms and myeloproliferative neoplasms before allogeneic HSCT | *20kg; 2mg for 20-40kg; 3mg for >40kg. Intradermal injection once weekly for 12 weeks* | | | | and 2 were in CR prior to vaccine treatment. 2 alveolar, 1 'RMS Mixed'. 2 relapsed, 1 refractory (primary induction failure) |

* data has been calculated for RMS patients specifically

AMORE = Ablative surgery, Moulage technique brachytherapy & surgical Reconstruction; ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; ALK = anaplastic lymphoma kinase; bd = twice daily; BM = bone marrow; CNS = central nervous system; CAR-T = chimeric antigen receptor T-cells; CR = complete response; CT - computerised tomography; DLT = dose limiting toxicity; DSRCT = desmoplastic small round cell tumours; ECOG = Eastern Cooperative Oncology Group; ERMS = embryonal rhabdomyosarcoma; EVE = etoposide, vincristine, epirubicin; ESFT = Ewing's sarcoma family of tumours; EBRT = external beam radiation therapy; GCSF = granulocyte colony stimulating factor; GVHD = graft-versus-host disease; HSCT = haematopoietic stem cell transplant; HBL = hepatoblastoma; HDCT = high-dose chemotherapy; HGG = high grade glioma; HL = Hodgkin lymphoma; HER2 = human epidermal growth factor receptor 2; HLA = human leukocyte antigen; IQR = interquartile range; IV = intravenous; MRI = magnetic resonance imaging; MPNST = malignant peripheral nerve sheath tumour; MTD = maximum tolerated dose; mTOR = mechanistic target of rapamycin; MB = medulloblastoma; MSC = mesenchymal stem cells; NBL = neuroblastoma; NHL - non-Hodgkin lymphoma; NRSTS = non-rhabdomyosarcoma soft tissue sarcoma; NOS = not otherwise specified; NR = not reported; od = once daily; OS = osteosarcoma; PD = progressive disease; PNET = primitive neuroectodermal tumour; po = orally; RCT = randomised control trial; R+R = relapsed and refractory; RMS = rhabdomyosarcoma; STS = soft tissue sarcoma; SD = standard deviation; SCT = stem cell transplant; TACE = transarterial chemoembolization; UK = United Kingdom; USA = United States of America; VEGF = vascular endothelial growth factor; VETOPEC = vincristine, etoposide & dose-escalated cyclophosphamide; VIT = vincristine, irinotecan & temozolomide; VOIT = vincristine, oral irinotecan & temozolomide; VAC = vincristine-actinomycin D-cyclophosphamide; WP = whole population; WT = Wilm's tumours

**Table 3.** Outcome Data

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | 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[102] | *2nd R+R RMS* | 0 | 0 | | | 0%* | NR | NR | No objective responses. 2 RMS patients either SD, PD, or non-evaluable (at least one evaluable). |
| Etoposide | Kebudi, 2004[92] | 2 relapsed, 2 refractory RMS | 1 | 1 | 0 | 2 | 50%* | NR | 8.5 (2- >94) | 3 of 4 patients had previously received etoposide. Response duration: 10 months for patient with PR, 87 months for patient with CR. |
| Gemcitabine | Wagner-Bohn, 2006[135] | 3 relapsed RMS | 0 | 0 | 0 | 3 | 0%* | NR | NR | |
| High-dose Ifosfamide | Meazza, 2010[110] | 5 R+R RMS | 0 | 1 | 1 | 3 | 20%* | NR | NR | |
| High dose Ifosfamide | Yalcin, 2004[141] | 1 R+R RMS | 1 | 0 | 0 | 0 | 100%* | NR | 97.5 | |
| Temozolomide | De Sio, 2006[69] | 2 R+R RMS | 0 | 0 | 0 | 2 | 0%* | 1 (range N/A) | 2.5* (2-3) | |
| Irinotecan | Vassal, 2007[130] | 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 & 6.4 months for patients with PR. |
| Irinotecan | Makimoto, 2019[20] | 4 R+R RMS | 0 | 0 | 3 | 1 | 0%* | NR | NR | SD lasted > 8 weeks for 1 patient with RMS, and >24 weeks for a second patient with RMS. |
| Irinotecan | Shitara, 2006[124] | 3 R+R RMS | 0 | 1 | 0 | 2 | 33.3%* | NR | NR | |
| Irinotecan | Bomgaars, 2007[59] | 18 R+R RMS | 0 | 1 | | | 5.6%* | NR | NR | 17 other evaluable RMS patients not clearly reported. |
| Irinotecan | Bisogno, 2005[56] | 12 R+R RMS | | 2 | | 6 | 16%* | NR | NR | 3 minor responses, 1 no response. RESPONSE OUTCOMES INCONSISTENT WITH DEMOGRAPHIC DATA. |
| Irinotecan | Furman, 2006[77] | *4th R+R RMS* | 0 | 0 | 0 | | 0%* | NR | NR | No complete or partial responses. Between 0-3 patients with RMS had PD (based on number evaluable) |
| Irinotecan | Blaney, 2001[30] | *2nd Refractory RMS* | 0 | 0 | 0 | At least 1 | 0%* | NR | NR | At least 1 patient had PD. One patient unclear if PD or non-evaluable. |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| Irinotecan (weekly) | Bomgaars, 2006[58] | 2 R+R RMS | 0 | 0 | 1 | | 0%* | NR | NR | 1 pt NR but assumed PD.<br>One patient in each stratum (where stratified by previous treatment) |
| Topotecan | Hawkins, 2006[84] | 9 R+R RMS | 0 | 0 | | | 0%* | 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[37] | 1 R+R RMS | 0 | 0 | 0 | 1 | 0%* | NR | NR | Response data provided via email communication with authors |
| Docetaxel | Zwerdling, 2006[142] | 8 R+R RMS | 1 | 0 | 1 | 6 | 12.5%* | NR | NR | |
| Ixabepilone | Widemann, 2009[139] | 3 R+R RMS | 0 | 0 | 0 | | 0%* | NR | NR | 3 evaluable RMS, assumed PD but not explicitly reported |
| Ixabepilone | Jacobs, 2010[89] | 10 R+R RMS | 0 | 0 | | | 0%* | NR | NR | No partial or complete responses were observed |
| Nab-paclitaxel | Amoroso, 2020[49] | 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[115] | 12 R+R RMS | 0 | 1 | 1 | 9 | 8.3%* | NR | NR | |
| Oxaliplatin | Beaty, 2010[53] | 10 R+R RMS | 0 | 0 | 0 | 10 | 0%* | NR | NR | |
| Oxaliplatin | Geoerger, 2008[31] | *2nd R+R RMS* | 0 | 0 | | | 0%* | NR | NR | At least one PD or SD, and one unclear if PD/SD or non-evaluable |
| Oxaliplatin | Spunt, 2007[39] | 1 Refractory RMS | 0 | 0 | 0 | 1 | 0%* | NR | NR | |
| Pemetrexed | Warwick, 2013[136] | 8 R+R RMS | 0 | 0 | 0 | 8 | 0%* | NR | NR | |
| Trabectedin | Baruchel, 2012[52] | 20 R+R RMS | 0 | 1 | 1 | 18 | 5%* | NR | NR | |
| Vinorelbine | Kuttesch, 2009[97] | 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[63] | 12 R+R RMS | 0 | 6 | 1 | 4 | 50% (21-79%) | NR | NR | Response rate for alveolar RMS 83% (95% CI 36-99%)<br>1 patient had minor response<br>DOR for patients with PR: median 10 months (range 3.5+ - 15months) |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| Vinorelbine | Johansen, 2006[32] | 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. |
| **Standard systemic therapy - multiple agents** | | | | | | | | | | |
| Cisplatin, Irinotecan, Amifostine | Souid, 2003[126] | 3 Refractory RMS | 0 | 0 | 3 | 0 | 0%* | NR | NR | Median number of course (1.5). 1 patient with RMS received at least 3 course (~18 weeks) |
| Cisplatin + topotecan | Wells, 2002[138] | 6 R+R RMS | | 1 | | | NR | NR | NR | 5 other RMS pts, unclear if all evaluable or their response |
| Escalation of cyclophosphamide in VETOPEC regimen | McCowage, 2011[108] | 4 R+R RMS | 1 | 3 | 0 | 0 | 100%* | NR | NR | One RMS patient with PR still alive after 48 months from study entry |
| Cyclophosphamide + topotecan | Saylors, 2001[123] | 15 R+R RMS | 0 | 10 | | 2 | 67% | NR | NR | 3 had mixed response or SD. Outcomes for each RMS subgroup also reported. |
| Decitabine, Doxorubicin, Cyclophosphamide | George, 2010[82] | 1 R+R RMS | 0 | 0 | 1 | 0 | 0%* | NR | NR | |
| Etoposide, Vincristine, Epirubicin, High dose cyclosporin (EVE/cyclosporin) | Davidson, 2002[66] | 2 1st relapse, 1 2nd relapse, 1 7th relapse | 0 | 1 | 2 | 1 | 25%* | NR | NR | 2 RMS patients had vincristine only, 1 doxorubicin/vincristine/ etoposide, and 1 etoposide/vincristine. |
| Gemcitabine + oxaliplatin | Geoerger, 2011[79] | 12 R+R RMS | 0 | 1 | 0 | 11 | 8.3%* | NR | NR | |
| Ifosfamide, Carboplatin, Etoposide | Loss, 2004[35] | 1 relapsed, 1 refractory RMS | 0 | 1 | 1 | 0 | 50%* | 6* (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[98] | 3 R+R RMS | 0 | 0 | 2 | 1 | 0%* | NR | NR | |
| Irinotecan + VAC | Bisogno, 2021[55] | 7 1st Relapse RMS | 2 | 3 | 2 | 0 | 71.4%* | NR | NR | Response after 3 cycles.<br>RMS patients with CR alive with NED at 48 months and 3 months. All other patients DOD. |
| Oxaliplatin + Doxorubicin | Mascarenhas, 2013[106] | 2 R+R RMS | 0 | 0 | 0 | 2 | 0%* | NR | NR | |
| Oxaliplatin + Irinotecan | McGregor, 2009[21] | *2ª R+R RMS* | 1 | 0 | 0 | | NR | NR | NR | 1 RMS patient not clearly reported - PD or not evaluable |
| Topotecan + Temozolomide | Le Teuff, 2020[100] | 8 R+R RMS | 0 | 0 | 3 | 5 | 0%* | NR | NR | |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| Topotecan + temozolomide | Rubie, 2010[36] | 1 R+R RMS | 0 | 0 | 1 | 0 | 0%* | 7 | NR | |
| Temsirolimus, Irinotecan, Temozolomide | Bagatell, 2014[51] | *4# R+R RMS* | 0 | 0 | 1 | | 0%* | NR | NR | 3 RMS patients NR, may not be evaluable for response.<br>SD lasted at least 9 cycles for this RMS patient. |
| Topotecan, carboplatin, Cyclophosphamide, Etoposide | Compostella, 2019[64] | 32 R+R RMS | 2 | 7 | 9 | 11 | 28% | 14% at 5years | NR | 3 had minor response.<br>Response rate by histology:<br>35% (6/17) for alveolar RMS<br>20% (3/15) for non-alveolar RMS<br>Response did not significant differ between patients with an early vs late relapse (33% vs 26%) |
| Topotecan + ifosfamide | Kawamoto, 2010[146] | 4 R+R RMS | 0 | 1 | | | 25%* | NR | NR | 3/4 RMS did not respond but not sure of their exact outcome. |
| Topotecan, Ifosfamide, Carboplatin | Radhakrishnan, 2015[121] | 1 1st relapsed RMS | | | 1 | | 0%* | NR | NR | RMS patient received only 1 cycle |
| Topotecan, Vincristine, Doxorubicin | Meazza, 2009[111] | 6 R+R RMS (most relapsed) | 1 | 4 | | | 83%* | 7 (3-15) | NR | 1 RMS patient had minor response.<br>5/6 evaluable patients later relapsed. |
| Vincristine, Irinotecan, Temozolomide | McNall-Knapp, 2010[109] | 1 R+R RMS | 1 | 0 | 0 | 0 | 100%* | 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[134] | *6# R+R RMS* | 0 | 0 | 0 | | 0%* | NR | NR | All RMS patients (between 3-6 evaluable) had PD but unclear how many were evaluable |
| Vinorelbine + low-dose cyclophosphamide | Casanova, 2004[62] | 8 R+R RMS | 1 | 2 | 2 | 3 | 37.5%* | NR | NR | DOR: Embryonal RMS Male (9yr) SD alive at 14mo; Embryonal RMS Female (18yr) PR DOR = 8 mo, DOD 12 mo; Embryonal RMS Female (12yr) PR, DOR=5 mo, DOD 10 mo; Embryonal RMS Female (13yr) SD, DOR = 8+mo, receiving treatment; Alveolar RMS Male (16yr), CR, DOR= 10+ mo, receiving treatment. |
| Vinorelbine + low-dose cyclophosphamide | Minard-Colin, 2012[114] | 50 R+R RMS<br>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 is still alive with no evidence of recurrence of disease, 3.6 years after achieving a CR.<br>Median DOR for 14 PR patients = 7 months (range 0.5-35 months). |
| | | Results over whole duration of treatment: | 4 | 14 | 11 | 21 | 36% (95% CI 23-49%) | | | |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| | | | | | | | | | | 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= 0.04). None of the five patients with primary refractory RMS achieved a CR or a PR |
| **Novel agents - single agent** | | | | | | | | | | |
| Everolimus (MoA: mTORs) **(This conference abstract represents data from a study with an unknown trial status, and so the trial registry record has also been extracted - NCT01216839)** | Epelman, 2015[145] | *6# 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[80] | 13 R+R RMS (most refractory) | 0 | 0 | 4 | 9 | 0%* | 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% CIs, 56-256). |
| Alisertib (MoA: AKI) | Mosse, 2019[24] | 10 R+R RMS | 0 | 0 | 1 | 7 | 0%* | NR | NR | 2 Non-responders (unclear if these are SD). Patient with SD had 15 cycles. |
| Apatinib (MoA: VEGFR-2 TKI) | Liu, 2020[46] | 1 R+R RMS | 0 | 1 | 0 | 0 | 100%* | NR | NR | RMS patient followed-up for 48 days. |
| Lenvatinib (MoA: multi-TKI) | Gaspar, 2021[17] | *5# R+R RMS* | 0 | 0 | | | 0%* | NR | NR | Unclear whether RMS patients had SD, PD, or not evaluable (at least 4 were evaluable). |
| Regorafenib (MoA: multi-TKI) **(This full-text represents data from the dose escalation stage of a trial. As trial is still active, not recruiting, the trial registry record has also been extracted - NCT02085148)** | Geoerger, 2021[81] | *3# R+R RMS* | 0 | 1 | 1 | | NR | NR | NR | 1 PR reported as unconfirmed (tumour 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[147] | 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 |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| Pazopanib (MoA: multi-TKI) | Glade Bender, 2013[83] | *5# R+R RMS* | 0 | 0 | 1 | | 0%* | NR | NR | 4 RMS patients either PD or not evaluable. RMS patient with SD had SD for ≥6 months |
| Sorafenib (MoA: multi-TKI) | Kim, 2015[94] | 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[140] | *4# Refractory RMS* | 0 | 0 | | | 0%* | NR | NR | No confirmed objective response but the number of RMS evaluable is unclear |
| Ispinesib (MoA: kinesin spindle protein inhibitor) | Souid, 2010[127] | 2 R+R RMS | 0 | 0 | | | 0%* | NR | NR | 2 RMS patients evaluable but not clearly reported and assumed PD |
| Sonidegib (LDE225) (MoA: hedgehog pathway inhibitor) | Kieran, 2017[93] | *4# R+R RMS* | 0 | 0 | 0 | | 0%* | NR | NR | 3-4 patients with PD |
| Bevacizumab (MoA: Anti-VEGF mab) | De Pasquale, 2011[68] | 2 Relapsed RMS | 1 | | | | NR | NR | NR | 1 RMS response NR.<br>Duration on treatment: 1 month and 5 months. |
| Cixutumumab (MoA: insulin like growth factor mab) | Weigel, 2014[137] | 20 R+R RMS | 0 | 1 | 3 | 16 | 5%* | 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[73] | 4 R+R RMS | 0 | 0 | 1 | | NR | NR | NR | 3 patients could have had PD or not evaluable. SD was for 7 courses |
| Ipilimumab (MoA: CTLA-4 mab) | Merchant 2016b[113] | *2# R+R RMS* | 0 | 0 | | | 0%* | NR | NR | RMS could have been SD, PD or non-evaluable |
| Lexatumumab (MoA: TRAIL-R2 mab) | Merchant, 2012[22] | *3# relapsed RMS* | 0 | 0 | | | 0%* | NR | NR | Unclear if RMS patients were evaluable, had PD or SD |
| Lorvotuzumab Mertansine (IMGN901) (MoA: antibody-drug conjugate (CD56 and mertansine)) | Geller, 2020[78] | *16# 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[67] | 11 R+R RMS | 0 | 0 | 3 | 6 | 0%* | NR | NR | 2 additional patients evaluable but response not clearly reported |
| Ontuxizumab (MORAb-004) (MoA: anti-endosialin mab) | Norris, 2018[117] | 4 R+R RMS | 0 | 0 | 0 | 4 | 0%* | NR | NR | 1 additional RMS patient had PD so didn't complete cycle 1 (thus non-evaluable) |
| Rebeccamycin Analogue (NSC #655649) (MoA: topoisomerase inhibitor) | Langevin, 2008[99] | 20 R+R RMS | 1 | 2 | | | 15% (4.3-37.6%) | NR | NR | 1 not assessable, 16 evaluable patients NR - assumed to have PD.<br>Response duration: 19 months for pt with CR, 5 & 6 months for patients with PR. |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| Rebeccamycin Analog (NSC#655649) (MoA: topoisomerase inhibitor) | Langevin, 2003[34] | 1 Refractory RMS | 0 | 0 | 1 | 0 | 0%* | NR | NR | |
| Seprehvir (MoA: protease inhibitor) | Streby, 2019[128] | 1 R+R RMS | 0 | 0 | 0 | 1 | 0%* | 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 |
| **Novel agents - multiple agents** | | | | | | | | | | |
| Vinblastine + Sirolimus | Morgenstern, 2014[65] | *2# R+R RMS* | | 1 | | | NR | NR | NR | 1 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[131] | 3 R+R RMS | 0 | 0 | 0 | 3 | 0%* | NR | NR | |
| Celecoxib + vinblastine | Stempak, 2006[40] | 3 R+R RMS | 0 | 0 | 1 | | 0%* | NR | NR | 2 other RMS patients evaluable with either SD or PD.<br>1 RMS patient had SD and was taken off study at 30 weeks. |
| Erlotinib ± Temozolomide | Jakacki, 2008[90] | *8# R+R RMS* | 0 | 0 | | | 0%* | NR | NR | Between 5-8 RMS patients had either SD or PD. Up to 3 patients non-evaluable. |
| Regorafenib, vincristine, irinotecan **(This conference abstract represents a subset of patients. As trial is still active, not recruiting, the trial registry record has also been extracted - NCT02085148)** | Casanova, 2020[143] | 12 R+R RMS | 1 | 5 | | | 50%* | NR | NR | 6 other RMS didn't have a response but exact outcome NR (one did have PR after data cut-off) |
| Sorafenib + topotecan | Reed, 2016[47] | 1 R+R RMS | 0 | 0 | 0 | 1 | 0%* | 44 days | NR | |
| Talazoparib + Irinotecan | Federico, 2020b[72] | 3 R+R RMS | 0 | 0 | 0 | 3 | 0%* | NR | NR | PD after 1 course in 2 patients, and 2 courses in 1 patient. |
| Talazoparib + temozolomide | Schafer, 2020[26] | 1 R+R RMS | 0 | 0 | 0 | 1 | 0%* | NR | NR | RMS patient progressed after 1 cycle |
| Bevacizumab, Sorafenib, Low-Dose cyclophosphamide | Federico, 2020a[71] | 1 R+R RMS | 0 | 0 | 1 | 0 | 0%* | NR | NR | |
| Bevacizumab, Sorafenib, Low-Dose cyclophosphamide | Navid, 2013[116] | *2# R+R RMS* | 0 | 1 | 0 | | NR | NR | NR | 1 patient with RMS who had either PD or was not evaluable for response |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| Vincristine, oral Irinotecan + temozolomide (VOIT) + bevacizumab | Wagner, 2013[132] | 1 R+R RMS | 0 | 0 | 0 | 1 | 0%* | NR | NR | PD after 3 cycles |
| Cixutumumab + Temsirolimus | Fouladi, 2015[74] | *9# 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[133] | 11 R+R RMS | 0 | 0 | 2 | | 0%* | 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[54] | 1 R+R RMS | 0 | 0 | 0 | 1 | 0%* | NR | NR | |
| Reovirus (Reolysin) ± cyclophosphamide | Kolb, 2015[95] | *6# R+R RMS* | 0 | 0 | | | 0%* | 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. |
| Tariquidar + doxorubicin | Fox, 2015[75] | 1 R+R RMS | 0 | 1 | 0 | 0 | 100%* | 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[50] | *3# 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. |
| **Biomarker driven studies** | | | | | | | | | | |
| Atezolizumab (Known or expected PDL1 involvement) | Geoerger, 2020b[19] | 9 R+R RMS | 0 | 0 | 0 | 9 | 0%* | NR | NR | |
| Pembrolizumab (PDL1 positive only) | Geoerger, 2020a[18] | 5 R+R RMS | 0 | 0 | 3 | 2 | 0%* | NR | NR | |
| Ceritinib (ALK positive tumours) | Fischer, 2021[16] | *12# R+R RMS* | | | 2 | | NR | NR | NR | 1 patient with 'no-complete response or no-progressive disease'. Other 9 unreported. |
| Personalised medicine (RMS patients both received crizotinib) | Worst, 2016[28] | 2 relapsed RMS | 0 | 0 | 0 | 2 | 0%* | (6 weeks- 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). |
| **Metronomic chemotherapy** | | | | | | | | | | |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| Metronomic - thalidomide, celecoxib, alternating etoposide/cyclophosphamide | Kieran, 2005[33] | 2 R+R RMS | 0 | 0 | 0 | 2 | 0%* | 10.5 weeks* (9-12 weeks) | NR | |
| Metronomic - celecoxib, vinblastine, cyclophosphamide, methotrexate; plus radiotherapy | Ali, 2016[29] | 14 R+R RMS | | | | | NR | NR | 70.7% at 1 year | Response rate NR. |
| Metronomic - Cyclophosphamide, Etoposide, Valproic acid | El Kababri, 2020[70] | 14 RMS (most R+R; possibly not all) | 1 | 2 | 4 | 7 | 21.4%* | NR | NR | |
| **HSCT** | | | | | | | | | | |
| High dose chemotherapy with autologous HSCT | Shiriaev, 2013[144] | 3 R+R RMS (of total 8 RMS patients) | 0 | 3 | 0 | 0 | 100%* | 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.<br>Whole RMS population (n=8) had median PFS 142 days. |
| Allogeneic HSCT | Prete, 2010[148] | *8# relapsed,*<br>*3# refractory RMS* | | | | | NR | NR | See comment | At time of transplant, 10 had PR and 1 had PD.<br>5 RMS patients relapsed, other 6 RMS patients not clearly reported.<br>1 year EFS 0.14 (standard error 0.12)<br>1 year OS 0.37 (standard error 0.16)<br>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[118] | 1 R+R RMS | 1 | 0 | 0 | 0 | 100%* | NR | >56 (N/A) | RMS patient had PR prior to receiving SCT. |
| Haplo SCT with reduced intensity conditioning **(This full-text represents a subset of patients. The trial is still recruiting so the trial registry has also been extracted - NCT01804634)** | Llosa, 2017[101] | 2 R+R RMS | | | | | NR | 102.5 (61-144) days | 7.9 (6-9.8) months | 1 RMS patient in CR4 prior to treatment.<br>Responses NR. |
| Reduced intensity Allogeneic HSCT | Baird, 2012[14] | 2 R+R RMS | | | | | NR | 85 days* (70-100) | 45 months* (13-77+) | |
| **Cellular therapies** | | | | | | | | | | |
| Autologous MSCs with oncolytic virus Icovir-5 (Celyvir) | Ruano, 2020[122] | 1 R+R RMS | 0 | 0 | 0 | 1 | 0%* | NR | NR | |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| Autologous lymphocyte infusion (D2) and dendritic cell vaccines, plus CYT107 (recombinant human IL7) | Merchant, 2016a[112] | 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). |
| Consecutive donor-derived adoptive cellular immunotherapy after allogeneic HSCT | Merker, 2019[23] | 1 relapsed RMS | 1 | 0 | 0 | 0 | 100%* | 11 | NR | Patient died of relapsed disease |
| HER2 CAR-T cells **(This trial is still recruiting so total population number is up to date of current publication)** | Hegde, 2020[85] | 1 Refractory RMS | 1 | 0 | 0 | 0 | 100%* | 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[88] | *4# 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[87] | 1 1st relapse, 2 2nd relapse RMS | 0 | 0 | 3 | 0 | | NR | NR | Note: Patients had to express 1+ of the target tumour antigens: WT1, PRAME and/or survivin DOR: 12.5+, 10.9+ and 4.1+ months |
| **Other approaches** | | | | | | | | | | |
| AMORE | Blank, 2009[57, 61] | 9 relapsed RMS (1st or 2nd relapse only) | | | | | | 82% at 5 years (whole group B popn, includes 2 residual disease patient) | See comment | 3 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 tumour: fibrosarcoma, respectively. 4 patients had NED at the end of follow-up (14.1 years, 13.1 years, 6.0 years, 9.2 years). 2 patients were alive (at 0.8 years and 1.6 years, neither had recent follow-up data). |
| Intratumoral injection of HSV1716 (oncolytic herpes virus) | Streby, 2017[129] | 1 relapsed RMS | 0 | 0 | 1 | 0 | 0%* | NR | 8 | Patient had SD at 14 and 28 days. |
| Radiofrequency Ablation + chemotherapy | Hoffer, 2009[86] | 2 R+R RMS | | | | | NR | NR | 5 (5-5) | 1 RMS patient died from pneumonia, 1 RMS patient DOD. |
| Transarterial chemoembolization (TACE) | Jiang, 2016[91] | *6# R+R RMS* | | | | | NR | NR | 16.7 (95% CI 9.679 - 26.654) | Responses NR. Differences in cancer pain VAS scores reported in manuscript. |
| **Non-comparative multi-arm cohorts** | | | | | | | | | | |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| Dalotuzumab **(monotherapy arm of study)** | Frappaz, 2016[76] | *3rd R+R RMS* | 0 | 0 | | | 0%* | NR | NR | None of the RMS patients experienced a response or prolonged SD |
| Dalotuzumab + Ridaforolimus **(combination arm of study)** | Frappaz, 2016[76] | *1st R+R RMS* | 0 | 0 | | | 0%* | NR | NR | The RMS patient did not experience a response or prolonged SD |
| Doxorubicin, Cyclophosphamide, Etoposide, Ifosfamide, Tirapazamine **(Regimen 2 of study)** | Mascarenhas, 2019b[105] | 24 1st relapse RMS (ineligible for phase 2 window) | 6 | 7 | | | 54% | NR | See comments | 11 evaluable but response NR (either SD or PD)<br>3yr OS 39% (95% CI 20-57%)<br>FFS: 21% (95% CI 8-37%) |
| | | 49 1st relapse RMS (failed phase 2 window) | 0 | | | | 22% | NR | See comments | 3yr OS 24% (95% CI 13-37%)<br>FFS: 17% (95% CI 8-29%) |
| Doxorubicin, Cyclophosphamide, Etoposide, Ifosfamide **(Regimen 3 of study)** | Mascarenhas, 2019b [105] | 14 1st relapse RMS | | | | | NR | NR | See comments | 3yr OS 84% (95% CI 50-96%).<br>FFS: 79% (95% CI 47-93%) |
| Olaratumab + doxorubicin **(Specific arm of study)** | Mascarenhas, 2021[107] | 5 R+R RMS | 0 | 2 | 2 | 1 | 40%* | NR | NR | Response rate relates to patients with measurable disease |
| Olaratumab, Irinotecan, Vincristine **(Specific arm of study)** | Mascarenhas, 2021[107] | 5 R+R RMS | 1 | 0 | 2 | 2 | 20%* | NR | NR | Response rate relates to patients with measurable disease |
| Olaratumab + Ifosfamide **(Specific arm of study)** | Mascarenhas, 2021[107] | 1 R+R RMS | 0 | 0 | | | 0%* | NR | NR | RMS patient had either SD or PD |
| **Comparative studies** | | | | | | | | | | |
| Carboplatin + irinotecan | Petrilli, 2004[41] | *NR# (all RMS patients refractory)* | | | | | NR | NR | NR | |
| Irinotecan | | *At least 2nd refractory RMS* | | 2 | | | NR | NR | NR | |
| Allogeneic HSCT with Minimal conditioning regimen - sibling donor | Shook, 2013[125] | 1 second relapse, 1 refractory RMS | 0 | 0 | 1 | 1 | 0%* | 49.5 days* (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%* | 195 days | NR | |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | 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[103] | 40 primary refractory or 1st relapse RMS | 4 | 7 | | 11 | 28% (13.7-41.3%) | See comment | See comment | 18 responses NR<br>EFS:<br>● 6 months 54.6% (95% CI 39.8-69.3%)<br>● 12 months 18.2% (95% CI 6.8-29.6%)<br>● 24 months 6.8% (95% CI 0-14.3%)<br>OS:<br>● 6 months 84.1% (95% CI 73.3-94.9%)<br>● 12 months 59.1% (95% CI 44.6-73.6%)<br>● 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<br>EFS:<br>● 6 months 69.1% (95% CI 55.1-83%)<br>● 12 months 40.5% (95% CI 25.6-55.3%)<br>● 24 months 19.1% (95% CI 7.2-30.9%)<br>OS:<br>● 6 months 90.5% (95% CI 81.6-99.4%)<br>● 12 months 78.4% (95% CI 65.8-91.1%)<br>● 24 months 39.2% (95% CI 24.2-54.2%)<br>ORR were not significantly different between the two groups. EFS was significantly better for the TEM arm compared to the BEV arm (p=0.018), but no significant difference in OS (p=0.23). |
| Irinotecan - prolonged schedule (with other multimodal chemotherapy) | Mascarenhas, 2010[104] | 42 first relapse or refractory RMS | 5 | 6 | 12 | 19 | 26% (16-42%) | 0.5 years | 1.4 years | 1yr FFS: 37% (95% CIs 23-51%)<br>3yr FFS: 14% (95% CIs 5-27%)<br>1yr OS: 55% (95% CI 39-68%)<br>3yr OS: 34% (95% CI 20-49%) |
| 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 | 1yr FFS: 38% (95% CIs 25-52%)<br>3yr FFS: 15% (95 CIs 7-26%)<br>1yr OS: 60% (95% CI 44-72%)<br>3yr OS: 22% (95% CI 11-35%) |
| Vincristine + Irinotecan | Defachelles, 2021[15] | 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<br>PFS:<br>● 6 months 42% (95% CI 29-54%) |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| | | | 4 | 18 | 17 | 19 | Best ORR: 38% (26-52%) | | | • 1 year 28% (95% CI 17-40%)<br>• 2 years 15% (95% CI 8-26%)<br>OS:<br>• 6 months 70% (95% CI 57-80%)<br>• 1 year 43% (95% CI 30-55%)<br>• 2 years 22% (95% CI 12-34%) |
| 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<br>PFS:<br>• 6 months 45% (95% CI 32-57%)<br>• 1 year 33% (95% CI 21-45%)<br>• 2 years 18% (95% CI 9-29%)<br>• Unadjusted HR 0.74 (0.49-1.11)<br>OS:<br>• 6 months 80% (95% CI 67-88%)<br>• 1 year 56% (95% CI 42-67%)<br>• 2 years 33% (95% CI 21-45%)<br>• Unadjusted HR 0.73 (0.47-1.13)<br>(Additional outcome data available in manuscript) |
| | | | 9 | 24 | 16 | 9 | Best ORR: 57% (43-70%) | | | |
| Metronomic - thalidomide, celecoxib, alternating etoposide/cyclophosphamide | Pramanik, 2017[119, 120] | 3 R+R RMS | 0 | 0 | 2 | 1 | 0%* | 130 days* (69- 178 days) | 218 days* (87- 282 days) | |
| Best supportive care | **Some outcome data provided via email communication with authors** | 5 R+R RMS | 0 | 0 | 0 | 4 | 0%* | 41 days* (9-67 days) | 46 days* (9-141 days) | 1 RMS patient outcome unclear but OS 9 days. |
| **Vaccines** | | | | | | | | | | |
| Dendritic Cell Vaccine + Decitabine | Krishnadas, 2015[96] | 1 relapsed RMS | 0 | 0 | 0 | 1 | 0%* | NR | NR | Patient had 3 relapses. |
| Glypican-3-derived peptide vaccine therapy | Tsuchiya, 2018[27] | 1 R+R RMS | 0 | 1 | 0 | 0 | 100%* | 4 | 9 | Note: patients with histological confirmation of GPC3 expression in tumour cells, HLA-A24- or HLA-A2-positive status |

| Regimen | Author, date (Reference) | Total number of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median Survival (months), range | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| NCCV Cocktail-1 vaccine | Akazawa, 2019[48] | 3 Refractory RMS | | | 1 | 1 | 0%* | 2.33 (0.43->12.91) | >15.93 (>13.83->17.15) | 2 patients had SD status prior to vaccination and one was in remission. 1 patient maintained remission on treatment. |
| Personalised Peptide Vaccine | Oda, 2020[25] | 1 1st Relapse RMS | 0 | 0 | | 0 | 0%* | 37+ | 37+ | Patient disease free prior to administration of PPV. |
| Seneca Valley Virus (NTX-010) ± cyclophosphamide | Burke, 2015[60] | *3ᵃ R+R RMS* | 0 | 0 | 1 | | NR | NR | NR | 2 patients NR - either PD or not evaluable |
| WT1 peptide vaccination | Sawada, 2016[38] | 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<br>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. |

ˣmean, (SE); $ = evaluable, RMS patients; *calculated from provided information

ᵃ plus italicised indicates studies where exact number of evaluable RMS patients is unknown but is definitively >1

AMORE = Ablative surgery, Moulage technique brachytherapy & 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 = haematopoietic 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 = objective 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 & dose-escalated cyclophosphamide; VOIT = vincristine, oral irinotecan & temozolomide; VAS = visual analogue scale

## **Table 4.** Adverse Event data

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| **Standard systemic therapies - single agent** | | | | | | |
| Pegylated Liposomal Doxorubicin (Doxil) | Marina, 2002[72] | Haematological: 17 (number of RMS unclear) Nonhaematological: 21 (number of RMS unclear) | NR | 12 | 4 | 1 G3/4 **neutropenia**, specific G not reported.<br>Hypersensitivity infusion-related reactions complicated Doxil infusions & required premedication with diphenhydramine, hydrocortisone, & ranitidine. Once changes to duration of infusion & pre-medication scheme was changed, no further instances of infusion reactions.<br>G3-4 Toxicities in C1:<br>**Neutropenia**: 1 @ 40mg/m2, 5 @ 60mg/m2 [4 G3, 1 G4], 3 @ 70mg/m2 [1 G3, 2 G4], 2 @ 50mg/m2 (P who received anticonvulsant therapy) [1 G3, 1 G4]. **Mucositis**: 1 @ 60mg/m2 [G3], 2 @ 70mg [G3], 1 @ 50mg/m2 (P who received anticonvulsant therapy) [G3]. Infusion Reactions: 1 @ 40mg/m2 [G3], 1 @ 50mg/m2 [G3].<br>**AE Data is not clearly reported & is inconsistent** |
| Etoposide | Kebudi, 2004[61] | No toxicities reported | | | | No toxicities reported. |
| Gemcitabine | Wagner-Bohn, 2006[101] | 20 (8) | | | | G3/4: 35P. 39E of G3/4 toxicities across all C added up: 25E in C1, 8 in C2, 5 in C3, 1 in C4<br>34/94 evaluable infusions had to be reduced, dosages had to be reduced for G3 toxicity (30/34), or omitted for G4 toxicity (4/34).<br>Common G3/4 toxicities: haemoglobin (5 at C1, 1 at C3, 1 at C4), leukocytes (5 at C1, 3 at C2, 2 at C3), **platelets** (13 at C1, 3 at C2, 2 at C3), fever in the absence of neutropenia (1 at C1, 1 at C2), **nausea/vomiting** (1 at C1), constitutional symptoms (1 at C2). |
| High-dose Ifosfamide | Meazza, 2010[78] | NR | | 5 | 0 | Emergency hospitalisation for sepsis due to Staphylococcus epidermidis (N=1). RBC transfusions (n=2). 6C - **FN**.<br>20C delayed due to prolonged **neutropenia** - 2P had a 25% dose reduction & 2P had a 50% dose reduction. No G3/4 non-hematological toxicities were reported. |
| High dose Ifosfamide | Yalcin, 2004[107] | 39 (1) | | | | 36P - G3-4 **neutropenia**, 19P - G3-4 anaemia, 17 - G3-4 **thrombocytopenia**, 12P - G3-4 **FN**, 4P - G3-4 emesis (**nausea/vomiting**), G3 central neurotoxicity 2P, G3 hemorrhagic cystitis 1P.<br>**2 treatment related deaths: 1 - neutropenic sepsis, 1 - G-CSF induced vasculitic nephritis** |
| Temozolomide | De Sio, 2006[38] | 52 (2) | | | | G3/4 **thrombocytopenia** occurred in 21.4% of C, median of two transfusions per P (range 1-14)<br>3P required 25% dose reduction after the 2nd C because of prolonged **thrombocytopenia**. Emesis occurred in 3.1% during 1st C of temozolomide but was controlled with standard antiemetic treatment. Pulmonary distress reported in two cases: interstitial pneumonia (1), & asthma-like syndrome (1). No other toxicity or organ failure reported |
| Irinotecan | Vassal, 2007[17] | 35 (35) | | 21 haem | 14 haem | Dose reduced in 14% Ps & 5% C, mainly due to hematologic toxicity. Treatment delayed in 14% Ps & 14% C, mainly due to reasons other than toxicity.<br>G3 haematological toxicities: 8P leukopenia, 6P **neutropenia**, 3P **thrombocytopenia**, 4P anaemia.<br>G4 haematological toxicities: 4P leukopenia, 10P **neutropenia**.<br>G3/4 nonhaematological toxicities: 6P abdominal pain or cramping, 5P cholinergic syndrome, 4P **nausea**, 4P **vomiting**, 2P **diarrhoea**, 1P anorexia, 1P **constipation**, 1P dehydration, 1P gastroenteritis, 1P confusion, 1P shock, 1P pneumonitis/pulmonary infiltrates, 1P renal failure. |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Irinotecan | Makimoto, 2019[114] | 17 (4) | 4P | 24E (40mg/m2); 12E (45mg/m2) | 8E (40mg/m2); 6E (45mg/m2) | DLTs: 1 G3 **diarrhoea** @ 40mg/m2 (probably due to study drug) & 1 G3 **diarrhoea** @ 45mg/m2 (definitely due to study drug). 1 G3 infection with G4 **neutropenia** @ 45mg/m2 (definitely due to study drug) 1 G3 elevation of serum amylase @ 45mg/m2 (unlikely to be due to study drug).<br>Recommended Dose: 40mg/m2/day.<br>G3 AEs: **FN** (3 @ 40mg/m2, 3 @ 45mg/m2), **diarrhoea** (1 @ 40mg/m2, 1 @ 45mg/m2), anaemia (5 @ 40mg/m2), Leukopenia (3 @ 40mg/m2, 3 @ 45mg/m2), **Neutropenia** (2 @ 40mg/m2, 2 @ 45mg/m2), Lymphopenia (5 @ 40mg/m2), **Thrombocytopenia** (2 @ 40mg/m2, 2 @ 45mg/m2), AST increase (2 @ 40mg/m2), ALT increase (1 @ 40mgm/2), amylase increase (1 @ 45mg/m2). 1 G3 Fever mentioned in the 'all' column, not mentioned in the other columns.<br>G4 AEs: anaemia (1 @ 40mg/m2, 1 @ 45mg/m2), leukopenia (1 @ 40mg/m2, 1 @ 45mg/m2), **neutropenia** (4 @ 40mg/m2, 1 @ 45mg/m2), lymphopenia (2 @ 40mg/m2, 3 @ 45mg/m2). |
| Irinotecan | Shitara, 2006[91] | 32C in 16P (3) | | 58 | 24 | G3: WBC count 22C; granulocyte count 13C; **platelet count** 11C; **diarrhoea** 4C; **vomiting** 8C.<br>G4: WBC count 1C; granulocyte count 13C; **platelet count** 2C; **diarrhoea** 7C; **vomiting** 1C. |
| Irinotecan | Bomgaars, 2007[29] | 151 for haematological tox & 168 for non-haematological tox (number of RMS unclear) in both groups | | | | 35C G4 **neutropenia**. G3/4 **thrombocytopenia** in 7C. G3/4 **diarrhoea** in 46C. 29P were hospitalised with **diarrhoea**<br>Of 135P receiving at least 2C, 7 required a dose reduction for: **diarrhoea** (3), **thrombocytopenia** (3), **diarrhoea** & **thrombocytopenia** (1)<br>29P hospitalised for **diarrhoea**. Median duration of hospitalisation for **diarrhoea** = 4 days (range 1-14 days). 27P received atropine for the treatment of acute **diarrhoea** or cramping after at least 1 dose of IRN. Atropine was not required for the 5 day C in most cases. 4/21P who received 2+ C of irinotecan, required atropine in more than 1C (range 2-4C). |
| Irinotecan | Bisogno, 2005[26] | 32 (13) | | | | G3 anaemia & G4 **thrombocytopenia**: occurring after 5C in 3P.<br>G3-4 **neutropenia**: evident after 8C. 1 gastrointestinal candidiasis. 5E **FN**. **Diarrhoea**: 9E G3/4 (typically beginning in 2nd-3rd week & required hospitalisation).<br>Dose of irinotecan reduced in 3P (by 25%) in 2nd C due to gastrointestinal toxicity. 1 had 2nd C delayed because of infection. 1P refused further treatment because of severe **diarrhoea** despite evidence of tumour reduction after 1st 2C. **diarrhoea** was reported very frequently - 58%C with 9E G3/4, typically beginning in the 2nd-3rd week & requiring hospitalisation. No other major toxicities were reported |
| Irinotecan | Furman, 2006[46] | Without cefixime: 19 (number of RMS unclear) With cefixime: 15 (number of RMS unclear) | 3P (without cefixime), 2P with cefixime | 3 (without cefixime), 3 (with cefixime) | 2 (With cefixime) | 3 DLTs (without cefixime): G3 **diarrhoea** (2 at 45mg/m2/day, 1 at 40mg/m2/day). 2 DLTs (with cefixime): G3 **vomiting** (1), G3 **vomiting/diarrhoea** (1) - both at 75mg/m2 irinotecan<br>Non DLTs without cefixime: G3 abdominal pain (15mg/m2/day), G3 **thrombocytopenia** (25mg/m2/day)[no assessable], G3 **neutropenia** (45mg/m2/day).<br>Non DLTs with cefixime: 1P G3 **diarrhoea**/abdominal pain (60mg/m2) [non assessable because of noncompliance with imodium use at 1st change in bowel habits], 1P G3 **vomiting** & headache (75mg/m2), with G4 **diarrhoea** [not assessable] (75mg/m2), 1P G4 **neutropenia** & G3 **thrombocytopenia** & **diarrhoea** [not assessable] (75mg/m2) |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Irinotecan | Blaney, 2001[124] | 27 for non-haem toxicity & 24 for haem toxicity (number of RMS unclear) | 5 DLTs (in 4P) | | | DLTs: 1P - G4 **neutropenia** at 50mg/m2, 1P - G3-4 prolonged **neutropenia** & G2 **thrombocytopenia** at 50mg/m2.<br>In less heavily pre-treated group, 2P - dose-limiting **diarrhoea** treated at 65mg/m2.<br>Non-haematological:1 G3 **nausea/vomiting**, 4 G3 **diarrhoea**, 1 G3 elevated AST/ALT, 1 G3 electrolyte abnormalities, 1 G3 headache, 2 G3 bacterial infection<br>Haematological: 20% G4 **neutropenia**, <15% G4 **thrombocytopenia**, <15% G3 **neutropenia**, <10% G3 **thrombocytopenia** or anaemia |
| Irinotecan | Bomgaars, 2006[28] | 18 (2) | | 8E | 6E | STRATUM 1: 2Ps at 160mg/m2 DL had dose limiting **neutropenia**. Potentially 2Ps at 160mg/m2 had dose limiting **diarrhoea**, unclear reporting - & were responsive to atropine. Potential DLT of **diarrhoea**, hematochezia & severe abdominal pain for 1P at 125mg/m2 (unclear reporting).<br>STRATUM 2: DL **neutropenia** occurred in 2/3Ps at 200mg/m2 & 1/6Ps at 160mg/m2. At 160mg/m2, 1P G2 **neutropenia**, so the dose was reduced to 125mg/m2 for C3.<br>G3 toxicities in all 18Ps: 4E **ANC**, 1E **thrombocytopenia**, 2E **diarrhoea**, 1E infection.<br>G4 toxicities in all 18Ps; 4E **ANC**, 1E Anaemia, 1E **diarrhoea**. |
| Topotecan | Hawkins, 2006[53] | 53 (9) | | 30E during C1 | 9E during C1 | G3 toxicities: 6E **neutropenia**, 10E **thrombocytopenia**, 3E anaemia, 3E fatigue, 4E **nausea**, 4E dehydration<br>G4 toxicities: 2E **neutropenia**, 2E **thrombocytopenia**, 1E anaemia, 4E fatigue<br>P who received prior radiation therapy were more likely to experience **neutropenia** during the 1st C of treatment (p=0.036). Prior transplant was not related to **neutropenia** after accounting for radiation therapy. Prior therapy was not related to occurrence of **thrombocytopenia**. |
| Topotecan | Santana, 2003[131] | 11(1)P in 18C | | | | In cohort 1 (11C): 10C G4 **neutropenia,** 2C G3 & 9C G4 **thrombocytopenia**, 8C G3 anaemia, 1 G3/4 **diarrhoea**, 1 sepsis with E. coli, **1 sepsis/death**, 1 facial cellulitis<br>Cohort 2 (18C): 17C G4 **neutropenia,** 17C G4 **thrombocytopenia**, 15C G3 anaemia, 5 G3/4 **diarrhoea**, 1 C. Difficile enteritis |
| Docetaxel | Zwerdling, 2006[108] | 160 (number of RMS unclear) | NR | | | 34%C associated with severe **neutropenia**. Median duration of severe **neutropenia** was 3 days.<br>G3+G4 AE across all C: WBCs (1C=25, 2C=19, 3C=5, 4C=6, ≥5C =21). **ANC**: (1C=34, 2C=31, 3C=10, 4C=8, ≥5C =24). **Platelets**: (1C=4, 2C=7, 3C=2, 4C=3, ≥5C =6). Lymph (1C=11, 2C=13, 3C=3, 4C=3, ≥5C =17). LIVER: AST (1C=2). ALT (2C=1). Alkaline phosphatase: (1C=1). Clinical (2C=1). PANCREAS: Amylase (2C=1), Glucose (1C=1). Systolic blood pressure (2C=1), Diastolic blood pressure (2C=1). Stomatitis (1C=2, 2C=1), **diarrhoea** (1C=1, 2C=2, 5+C =1). **Nausea** (2C=1, 4C=1). Pulmonary Function (1C=1, 2C=1). Cardiac function (≥5C=1). Hypertension (1C=1). Hypotension (2C=1). Peripheral sensory (1C=2, 2C=2, 3C=1, 4C=2, ≥5C=2). Motor AEs (2C=1, 4C=1). Skin (1C=8, 2C=8, 4C=5, ≥5C =12). Allergy (1C=3, 2C=2). Blood Coagulation (2C=1). Sodium (1C=1), Potassium elevation (5+C =1), calcium elevation (5+C =1). Infection (1C=3, 2C=3, 3C=1, 4C=1). Fever (1C=1). Local = (1C=1). Mood (2C=1, ≥5C =1). **Weight** (≥5C =1). Performance (3C=1, 4C=1). Haemoglobin toxicities (C1=10, C2=7, C3=1).<br>1 of 8E of infection was fatal. 33P had G3/4 skin AE, & 4 of those P developed G4 toxicity, mostly erythematous rashes, but some had blistering & bulbous formations.<br>21P required dose reduction |
| Ixabepilone | Widemann, 2009[105] | 18 (3) | 3P | 27E | 4E | Myelosuppression increased in incidence & severity with increasing dose.<br>At 10 mg/m2 dose: 1P - DLT - G4 **neutropenia**, 1P - DLT - G3 fatigue<br>At 8 mg/m2 dose: 1P - DLT - G3 neuropathic pain/anorexia/stomatitis, G4 **neutropenia**<br>Toxicities at 3 mg dose: 1P - G3 haemoglobin toxicity, No G4 toxicities at this dose<br>Toxicities at 4.5 mg dose: 2P - G3 **neutrophils toxicity**, 1P - G3 **nausea**, No G4 toxicities at this dose |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | Toxicities at 6 mg dose: 1P - G3 **neutrophils toxicity**, 1P - G3 **platelet toxicity**, 1P - G3 **nausea**, 1P - G3 **vomiting**, No G4 toxicities<br>Toxicities at 8 mg dose: 2P - G3 haemoglobin, 4P - G3 **neutrophils toxicity**, 1P - **platelets toxicity** - this P also had G3 anorexia, dehydration, **nausea**, stomatitis, **FN**, dizziness, sensory neuropathy & myalgia, as well as G4 **neutrophils toxicity**, 1P - G3 **vomiting**<br>Toxicities at 10 mg dose: 2P - haemoglobin toxicity, 1P - G3 fatigue, 3P - G4 **neutrophils toxicity** |
| Ixabepilone | Jacobs, 2010[58] | 59 (47 age 3-18 yo; number of RMS unclear) | 11 (C 1) | 7 (3 - 18 yo), 2 (19 - 36 yo) | 4 (3-18 yo), 5 (19 -36 yo) | DLTs: Ages 3-18: **Neutropenia** (2 G4), Myalgia (1 G3, 1 G4), Other Pain (1 G3), Sensory Neuropathy (1 G3), Aphasia (1 G3), Fever (1), Anorexia (1), Hyponatremia (1 G3), CNS Haemorrhage (1 G4). Ages 19-36: **Neutropenia** (3 G4), **Thrombocytopenia** (2 G4), Fatigue (1 G3), Dehydration (1 G3).<br>6P experienced DLTs in subsequent C (3 of whom had >1 DLT). 4/6 had a DLT in C1. **13P died within 1 month of terminating protocol therapy.**<br>Treatment related DLTs judged to be related to Ixabepilone are **neutropenia**, anorexia, **thrombocytopenia**, anorexia, pain, sensory neuropathy, **FN**, elevated lipase, hyperglycemia & hypertension.<br>Non-DLTs in >5%C include fatigue, **nausea**, **vomiting**, hyperglycemia, hypomagnesemia, hyponatremia, anaemia, **thrombocytopenia**, Myelosurpression most common non-DLT. Most non-DLTs were G1. |
| Nab-paclitaxel | Amoroso, 2020[20] | 42 (14 RMS) | | | | >=1 G3/4 TEAEs toxicities: 88% P<br>G3/4 TEAEs: **neutropenia** (21), anaemia (20), leukopenia (16), **thrombocytopenia** (7), **FN** (4), Lymphopenia (2) general physical health deterioration (3), headache (3), hypokalemia (2), peripheral neuropathy (2) |
| Nab-paclitaxel | Moreno, 2018[82] | 64 (14) | 2 P | | | 88%P experienced >/= to 1 G3/4 AE.<br>DLTs: G3 dizziness (1P at 120mg/m2), G4 **neutropenia** (1P at 270mg/m2).<br>All 64P discontinued treatment; of these, 35(55%) discontinued due to PD, 11(17%) due to AEs, 11(17%) due to clinical symptomatic deterioration, 5(8%) due to withdrawal by P or parent/guardian & 1(2%) due to physician decision.<br>240 mg/m2 was identified as the recommended phase II dose. 270mg/m2 considered non-tolerable dose based on toxicity & safety information including G3/4 toxicity during 1st 2C (**neutropenia** in 5/7 P; skin toxicity in 2 of 7P & peripheral neuropathy in 1 of 7P).<br>G3/4 toxicities: 23P **neutropenia**, 23P leukopenia, 16P lymphopenia, 2P skin pain, 2P HFS, 4P hyponatremia, 3P hypotension, 2P peripheral neuropathy, 3P arthralgia, 2P **nausea**<br>17%P had 1 or more dose reductions. 36%P had 1 or more dose interruptions |
| Oxaliplatin | Beaty, 2010[23] | 113 (10) | | 111E | 29E | Hematologic: **Platelets** (23 G3, 15 G4), **Neutrophils/Granulocytes** (10 G3, 3 G4), Hemoglobin (7 G3, 4 G4), Lymphopenia (7 G3, 1 G4), Leukocytes (6 G3). Non-Hematologic: Larynegopharyngeal dysesthesia (6 G3), Paresthesias/Dysesthesia (6 G3), Cold related dysesthesia (4 G3), Muscle camping/spasm jaw pain (1 G3), Decreased motor function (1 G3), Decreased Sensory Function (3 G3), thoracic pain (1 G3), extremity pain (1 G3), decreased upper extremity pain (1 G3), Allergic reaction/hypersensitivity (3 G3), Seizure (1 G3), Anorexia (2 G3), Dehydration (1 G3), **Nausea** (3 G3, 1G4), Ileus (1 G4), Obstruction (1 G3), **Vomiting** (3 G3), Upper GI hemorrhage (1 G3), Elevated ALT (5 G3, 1 G4), Elevated AST (3 G3), Hypercalcemia (1 G4), Hypokalemia (3 G3, 1 G4), Hyponatremia (1 G3, 1 G4), Dyspnea (2 G3), Hypoxia (1 G3), Fatigue (1 G3), Bladder infection (normal ANC) 1 G3, Lung infection (1 G3), Catheter-related infection (1 G3)<br>10 required dose reduction at a median of the 3rd C (range 2-17), primarily secondary to myelosuppression. |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Oxaliplatin | Geoerger, 2008[125] | 28 in dose escalation stage (number of RMS unclear) | 4 during C 1 | | | DLTs during C1: 1 G3 sepsis at 50mg/m2, 1 G3 dysesthesia at 110mg/m2, 1 G3 paresthesis at 110mg/m2, 1 G3 dysesthesia at 90mg/m2<br>6P in dose escalation had delays for > 5 days due to AEs. 3P discontinued treatment due to AEs.<br>23P had at least 1 G3-4 AE in the dose escalation stage.<br>G3-4 AEs for P in the dose escalation phase: 82.1% P had any G3-4 AE, 3.6% paresthesia, 10.7% abdominal pain, 3.6% pyrexia, 28.6% **thrombocytopenia**, 7.1% headache, 3.6% **vomiting**, 7.1% dysesthesia, 14.3% bone pain, 7.1% anaemia, 3.6% pain not specified |
| Oxaliplatin | Spunt, 2007[133] | 11(1) from regimen A | 7 DLTs in 3P | | | DLTs: 1P - dose limiting myositis at 130mg/m2, 2P - G3 pharyngolaryngeal dysesthesias, sensory neuropathy & ataxia at 160mg/m2<br>G3/4 AEs reported in regimen A: 2 ataxia (DLTs), 3 low haemoglobin, 1 myalgia, 1 myositis (DLT), 1 **nausea**, 2 pharyngolaryngeal dysesthesia (DLTs), 2 sensory neuropathy (DLTs), 2 **neutropenia**, 1 **thrombocytopenia**. |
| Pemetrexed | Warwick, 2013[102] | 70 (number of RMS unclear) | | 71C | 28C | 70P received 112C.<br>Toxicities possibly, probably or definitely related to pemetrexed that occurred in 10%+C:<br>anaemia (G3 in 10C, G4 in 1C), leukocytes (G3 in 6, G4 in 7), lymphopenia (G3 in 7) **neutrophils** (G3 in 13C, G4 in 14C), **platelets** (G3 in 5C, G4 in 5C), fatigue (G3 in 2C) pruritus (G3 in 1), rash (G3 in 2C), **nausea** (G3 in 3C), **vomiting** (G3 in 3C), elevated ALT (G3 in 14C), elevated AST (G3 in 4C), hypophosphatemia (G3 in1 C, G4 in 1C). 3P discontinued study participation in C1: 2 with allergic reaction, & 1P with prolonged elevation of ALT. 1P with prolonged elevation of ALT received reduced-dose of pemetrexed. |
| Trabectedin | Baruchel, 2012[13] | Phase 1: 11 (number of RMS unclear) Phase 2: 41 (number of RMS unclear) | 1P - Phase 1 (1.3mg/m2). 9P - Phase 2) | 8 Phase 1 (7 reversible) | | Phase 1 DLT (1.3mg/m2) = GGT & fatigue (1 G3). Phase 2 DLTs in 9P: Fatigue (1 G3), GGT (7 G3), AST (2 G3), ALT (2 G3), **ANC** (1 G4), deep venous thrombosis(1 G3). 8/9 DLTs in phase 2 were during the 1st C of treatment.<br>Other AEs reported for phase 2 (N=41) but unsure whether they are G3/4: haemoglobin (3), leucocytes (11), lymphopenia (7), **ANC** (14), **Platelets** (5), Fatigue (2), ALT SGPT (13), AST SGOT (10), GGT (6), Hypokalemia (2), Thrombosis (2). |
| Vinorelbine | Kuttesch, 2009[66] | 50 (11) | | 4P | | 25 of the 1st 35Ps on the higher dose experienced G3 or 4 **neutropenia** during the initial 2Cs of therapy, 26% of which required delay &/or dose modification. 10 of the 15Ps on the lower dose experienced G3 or 4 **neutropenia** but none required a delay or modification. So, altogether 35Ps developed G3/4 **neutropenia**. 20%Ps developed anaemia.<br>9Ps required delay dose modification, 5 with initial bone marrow involvement.<br>G3 sensory neuropathy in 4Ps |
| Vinorelbine | Casanova, 2002[32] | 33 (13) | | 13 | 12 | No life-threatening AEs observed.<br>G3 **Neutropenia**: 9P, G4 **Neutropenia**: 12P. G4 **neutropenia** was short lived (median 3 days), 8P received G-CSF for **FN**. None required hospitalisation. G3/4 **neutropenia** in 7 of 14P (50%) of those who had previously received high-dose chemotherapy with stem cell rescue, & in 74% of those who had not.<br>G3 anaemia in 3P (2 requiring RBC transfusion), **Thrombocytopenia** was rare, G3 toxicity on **platelets** was observed in 1P with bone marrow involvement. |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Vinorelbine | Johansen, 2006[126] | 29 (at least 1) | DLTs not clearly reported | 25 | 35 | **1P (non-RMS) died on treatment at DL1 (24mg/m2) but this was due to PD, not AEs.**<br>Haematological toxicities: 6 G3 leukopenia (1 at 24mg/m2, 2 at 37.5mg/m2 & 3 at 33.75mg/m2), 10 G4 leukopenia (3 at 30mg/m2, 4 at 37.5mg/m2, & 3 at 33.75mg/m2), 3 G3 **neutropenia** (1 at 24mg/m2, 1 at 37.5mg/m2, & 1 at 33.75mg/m2), 15 G4 **neutropenia** (1 at 24mg/m2, 3 at 30mg/m2, 5 at 37.5mg/m2, & 6 at 33.75mg/m2), 3 G3 **thrombocytopenia** (1 at 24mg/m2, 1 at 30mg/m2, & 1 at 37.5mg/m2), 3 G4 **thrombocytopenia** (1 at 30mg/m2, 1 at 37.5mg/m2 & 1 at 33.75mg/m2), 7 G3 anaemia (1 at 30mg/m2, 4 at 37.5mg/m2, 2 at 33.75mg/m2), 2 G4 anaemia (1 at 24mg/m2, & 1 at 30mg/m2)<br>Non-haematological toxicities: 3 G3 increased transaminase (1 at 24mg/m2, 1 at 33.75mg/m2 & 1 at 37.5mg/m2), 1 G4 increased transaminase (at 30mg/m2), 1 G4 fever (at 30mg/m2), 1 G3 **diarrhoea** (at 30mg/m2), 1 G3 increased bilirubin (at 33.75mg/m2), 1 G4 increased bilirubin (at 30mg/m2) - leukaemiaP with concurrently documented sepsis & active lung abscess, 1 G3 cough (at 30mg/m2), 2 G4 **mucositis** (1 at 30mg/m2 & 1 at 33.75mg/m2) |
| **Standard systemic therapies – multiple agents** | | | | | | |
| Cisplatin, Irinotecan, Amifostine | Souid, 2003[93] | 24 (3) | 7 | | | DLTs: 2/3P heavily pre-treated without amifostine (irinotecan 40mg/m2) experienced DLT (**thrombocytopenia** & **neutropenia**). 1/6P less heavily pretreated without amifostine (irinotecan 40mg/m2) experienced DLT (**thrombocytopenia**). 2/6P less heavily pretreated without amifostine (irinotecan 65mg/m2) experienced DLT (**thrombocytopenia** & **neutropenia**). 2/5P less heavily pretreated with amifostine experienced DLT (hypocalcemia).<br>Cisplatin, Irinotecan & Amifostine: **Nausea** & **vomiting** (G>= 2) occurred in 6/7C. Hospitalisation for rehydration in 1P (cisplatin, irinotecan & amifostine). Asymptomatic hypokalemia (G3) in 1P, associated with G1 **diarrhoea** & line infection. 1P - G4 hypocalcemia 2 h after 1st amifostine dose & responded to calcium supplements.<br>**Diarrhoea** (G<= 3) occurred in 50%P. 5P received treatment with loperamide (1-4 days) alone, 3 with loperamide (2-12 days) & atropine (2-4 days). 2P hospitalised for **diarrhoea** (1 received Sandostatin). |
| Cisplatin + topotecan | Wells, 2002[104] | NR | | | | **Thrombocytopenia** requiring platelet transfusions for most Ps; **neutropenia** <7 days for almost all Ps.<br>14E Non-DLTs G3/4: 4P **nausea and vomiting**, 2 low diastolic blood pressure; 1 each: transient decreased vision, decreased vital capacity, skin lesions, proteinuria, increased bilirubin, amylase or alkaline phosphatase, decreased fibrinogen level. |
| Escalation of cyclophosphamide in VETOPEC regimen | McCowage, 2011[76] | NR | 1 | | | 1 protocol-defined DLT (episode of life threatening hemorrhagic cystitis). 13P withdrew because of toxicities that did not meet DLT (hemorrhagic cystitis [n = 7], VOD [1], VOD with ARDS [1], ARDS & sepsis [1], restrictive lung disease [1], deteriorating lung function [1], white matter changes [1].<br>Other AEs (no G mentioned): pain, **diarrhoea**, **nausea**, **vomiting**; GI, lung & neurologic disturbances. Evidence of more AEs at higher cyclophosphamide doses (about twice as high in 85 & 90mg cohorts compared to 70 & 75mg cohorts).<br>**FN** occurred following 67% mobilisation C & 59% of intensive cycles. Mobilisation was followed by median 2 (Range 0-7) blood transfusions & median 1 (0-8) **platelet transfusions**. Intensive cycles was followed by median 2 (Range 0-27) blood transfusions & median 2 (0-26) **platelet transfusion** |
| Cyclophosphamide + topotecan | Saylors, 2001[90] | 83 (15) (307C) | | | | 53%C G3/4 **neutropenia**, 44%C G3/4 **thrombocytopenia**, 27%C G3/4 anaemia. G3 or greater **nausea and vomiting** (2C), **mucositis** (1C), transaminase elevation (1C) & hematuria (2C). 34E G3/4 infection |
| Decitabine, Doxorubicin, Cyclophosphamide | George, 2010[51] | Stratum A: 9 (1 RMS < 18 years) | 3 (at 10mg/m2) | 29E (C1), 15 (C2-9) | 49 (C1), 23 (C2-9) | DLTs: **neutropenia** & **thrombocytopenia**. At 10 mg/m2, 3/3 had **neutropenia** & 1 also had **thrombocytopenia**. No non-haematological DLTs were observed.<br>G3 Toxicities across all C: haemoglobin (6 @ 5mg/m2 & 2 @ 10mg/m2), Leukocytes (3 @5mg/m2), Lymphopenia (8 @ 5mg/m2), **Platelets** (5 @ 5mg/m2), Fever (9 @ 5mg/m2, 1 @ 10mg/m2), Infection (3 @ 5mg/m2, 1 @ 10mg/m2), Infection with normal |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | ANC or G1/2 neutrophils (2 @ 5mg/m2), **Mucositis**/Stomatitis (1 @ 5mg/m2), Elevated transaminase (1 @ 5mg/m2) Hypophosphatemia (1 @ 5mg/m2), Hypokalemia (1 @ 5mg/m2)<br>G4 Toxicities across all C: Haemoglobin (2 @ 5mg/m2), Leukocytes (19 @ 5mg/m2 & 4 @ 10mg/m2), Lymphopenia (3 @ 5mg/m2, 1 @ 10mg/m2), **Neutrophils/Granulocytes** (23 @ 5mg/m2, 4 @ 10mg/m2), **Platelets** (13 @ 5mg/m2, 2 @ 10mg/m2), Elevated transaminase (2 at 5mg/m2), Fever without neutropenia (1 @ 5mg/m2) |
| Etoposide, Vincristine, Epirubicin, High dose cyclosporin (EVE/cyclosporin) | Davidson, 2002[35] | 15 (4 RMS < 18 years) | | | | GRADE NOT REPORTED. Transient hypertension - 4P (3P required antihypertensives). 1P - severe acute reactions on commencement of cyclosporin (treated with lorazepam, ondansetron & paracetamol). 1P - reaction to cyclo but severity varied in C (chest pain on 1, dizziness & tremulousness on another). 1 Self-limiting generalised seizure four days after commencing EVE-cyclosporin. Myelosuppression with **neutropenia** was predominant feature. Moderate-severe infection developed after 13C leading to resultant hospitalisation.<br>2P had cardiac toxicity (reduction in fractional shortening on ECG), with no clinical evidence of cardiac impairment. Renal toxicity observed after 2C. 1P - creatinine rise, 1P severe rise in creatinine & urea. Did not cause delay in subsequent therapy.<br>3P - hypomagnesaemia. 5P (after 7C) - Hyperbilirubinaemia, GI disturbances common (most G1 & G2), severe **vomiting** in 1P after 2C, accompanied by **diarrhoea** & abdominal pain. |
| Gemcitabine + oxaliplatin | Geoerger, 2011[48] | 93 (12) | | | | **3 early deaths due to PD.**<br>10P discontinued treatment due to AE: Discontinued treatment due to haematological toxicity (6), hepatic toxicity (1), peripheral neuropathy following accidental overdose of 500mg/m2 in 60 min at C3 (1), allergy & dyskinesia (1), increasing tumour pain (1)<br>82P some form of G3/4 haematological toxicity: 21P anaemia, 50P leukopenia, 68P **neutropenia**, 49P **thrombocytopenia**<br>58P some form of G3/4 extra-haematological toxicity: 2P allergic reaction, 7P **vomiting**, 2P **diarrhoea**, 5P **FN**, 13P infection with normal ANC, 7P peripheral sensory neuropathy, 19P pain, 6P pulmonary toxicity, 16P hepatic toxicity, 7P fatigue |
| Ifosfamide, Carboplatin, Etoposide | Loss, 2004[129] | 21 (2) | | | | A total of 93C delivered in 21P.<br>**1P died due to severe thrombocytopenia (RMS P)**<br>G3-4 AEs (C): G3-4 leucopenia in 82C, G3-4 **neutropenia** in 82C, G3-4 anaemia in 62C, G3-4 **thrombocytopenia** in 73C, G3-4 **nausea** & **vomiting** in 5C, G3-4 **diarrhoea** in 4C, G3-4 nephrotoxicity in 2C, G3-4 stomatitis in 1C, G3-4 fever in 26C, G3-4 hepatotoxicity in 3C, G3-4 infection in 14C<br>Median time to full haematological recovery was 28 days (range 25-46 days) |
| Ifosfamide, Oxaliplatin, Etoposide (IOE) | Lam, 2015[67] | 17 (3) | 3 | 86 (C1: 24. C2-7: 62) | 76. (C1: 19. C2-7: 57) | **DLTs:** two developed G4 **neutropenia** >7 days at DL1, & 1P developed G4 **neutropenia** >7 days at DL0. 3P discontinued due to toxicity (G3/4 myelosuppression in all; G3/4 hypokalemia in two). Other toxicities: G4 **neutropenia** & G4 **thrombocytopenia** in around half of all C. **FN** was the only non-haematologic G4 toxicity.<br>G3 toxicities in C1: 4 **thrombocytopenia**, 2 **neutropenia**, 5 leukopenia, 1 anaemia, 1 hypokalemia, 2 **FN**, 2 hypophosphatemia, 1 **vomiting**, 3 infection, 2 **diarrhoea**, 1 hyponatremia. G4 toxicities in C1: 3 **thrombocytopenia**, 9 **neutropenia**, 5 leukopenia, 2 anaemia. G3 toxicities in C2-7: 8 **thrombocytopenia**, 6 **neutropenia**, 7 leukopenia, 20 anaemia, 6 hypokalemia, 3 **FN**, 2 hypophosphatemia, 3 **vomiting**, 1 **diarrhoea**, 2 haemorrhage, 1 allergic reaction/hypersensitivity, 1 anorexia, 1 AST elevation, 1 PTT elevation. G4 toxicities C2-7: 25 **thrombocytopenia**, 18 **neutropenia**, 11 leukopenia, 2 anaemia, 1 **FN** |
| Irinotecan + VAC | Bisogno, 2021[25] | NR (68 IrVAC C evaluable for toxicity) | | 32 C (haem toxicity) | 54 C (haem toxicity) | 14P required blood transfusions (across both groups).<br>G4 **neutropenia** occurred in 72%C in P receiving IrVAC.<br>Haematological toxicity for P treated with IrVAC (total C = 68): anaemia (G3 in 10C), **Thrombocytopenia** (G3 in 8C, G4 in 5C), **Neutropenia** (G3 in 14C, G4 in 49C). |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | Non-haematological toxicities **(for all P as these were not separated by group):** 6P experienced 19E of G3 non-haematological toxicity. Other G3 Non-Haem Toxicities: 3 G3 C of hepatic/pancreatic toxicity; 3 G3 C of **mucositis**; 6 G3 C of peripheral neurotoxicity, 3 G3 C of **constipation**, 1 G3 C with central neurotoxicity; 3 G3 C with **diarrhoea** (in twoP of which 1P experienced 2E during **FN**). Irinotecan C delayed by 1+ week in 7C, & not administered in 2C (due to **FN**)- dose never reduced. Actinomycin withdrawn during radiotherapy in 7C.<br>Median interval between 1st & 9th C was 195 days (range 170 to 231 days). Median interval between C was 23 days (range 19-51 days) with 151/181C administered on time or without significant delays. |
| Oxaliplatin + Doxorubicin | Mascarenhas, 2013[74] | 17 (2) | 5P across the three different DLs | 22E in C1. 44E in C2-8 (total 42C) | 35E in C1. 56E in C2-8 (total 42C) | At DL1, 1P cardiac DLT. At DL2, 2P **thrombocytopenia** DLTs. At DL3, 1P cardiac DLT & 1P **thrombocytopenia** DLT.<br>G3 toxicities in C1: 5E anaemia, 3E leukopenia, 1E **neutropenia**, 1E **thrombocytopenia**, 1E ALT toxicity, 1E cardiac toxicity, 4E **FN**, 3E infection, 1E **nausea**, 2E **vomiting**<br>G4 toxicities in C1: 3E anaemia, 9E leukopenia, 12E **neutropenia**, 11E **thrombocytopenia**<br>G3 in C2-8: 9E anaemia, 4E leukopenia, 5E **neutropenia**, 10E **thrombocytopenia**, 2E ALT toxicity, 1E colitis, 8E **FN**, 1E haemorrhage, 1E hypoalbuminemia, 1E hypokalemia, 1E hyponatremia, 1E infection<br>G4 in C2-8: 8E anaemia, 11E leukopenia, 14E **neutropenia**, 17E **thrombocytopenia**, 4E **FN**, 1E infection |
| Oxaliplatin + Irinotecan | McGregor, 2009[115] | 13 (2) | 6 | C1: 21; C2-6: 15 | C1: 2; C2-6: 6 | DLTs: oxaliplatin @ 60mg/m2, irinotecan @ 20mg/m2: **diarrhoea** (3P), lipase (3P), amylase (2P), colitis (1P), abdominal pain (1P), headache (1P). Oxaliplatin @ 40mg/m2, irinotecan @ 15mg/m2: **diarrhoea** 1P. Oxaliplatin @ 60mg/m2, irinotecan @ 15mg/m2: 1P **diarrhoea**, 1P hypokalemia.<br>G3 toxicities: haemoglobin (1 in C1), leukocytes (2 in C1, 1 in C2-6), lymphopenia (3 in C1, 1 in C2-6), **neutrophils** (1 in C1), **platelets** (2 in C2-6), **weight loss** (1 in C1), anorexia (3 in C1, 3 in C2-6), dehydration (5 in C1, 1 in C2-6), **diarrhoea** (1 in C1, 2 in C2-6), **nausea** (1 in C1, 1 in C2-6), emesis (1 in C1, 1 in C2-6), ALT (1 in C1), AST (1 in C1), hypomagnesemia (1 in C2-6), abdominal pain, NOS (2 in C2-6).<br>G4 toxicities: leukocytes (1 in C2-6), lymphopenia (1 in C1), **neutrophils** (1 in C1, 4 in C2-6), **platelets** (1 in C2-6). |
| Topotecan + Temozolomide | Le Teuff, 2020[69] | 91 (9) | | 119P; 325C | 58P; 91C | Dose reduction: For 18C in 7P both agents were reduced; for 15C (9P) tem alone; & 4C in 3P in TOP alone were reduced. For 26C in 8P, dose reduction was due to hematologic toxicity. Excluding 1st C, 49 of 215C delayed for more than 5 days in 23P<br>AEs (reported for the whole study population): **thrombocytopenia** (G3 68C, 16P; G4 38C, 23P), leukopenia (G3 80C, 30P; G4 8C, 7C), **neutropenia** (G3 122C, 43P; G4 40C, 22P), anaemia (G3 31C, 20P; G4 5C, 5P), **FN** (G3 5C, 5P, G4 1C, 1P), anorexia (G3 11C, 2P), AST elevation (G3 1C, 1P), ALT elevation (G3 7C, 2P) |
| Topotecan + temozolomide | Rubie, 2010[130] | 16 (1) | 5 DLTs in 4P | | | DL2 - 150 temo & 0.75 topo: 1P with G3 **thrombocytopenia** > 7 days, 1P with G3/4 **thrombocytopenia** > 7 days requiring transfusions (inconsistent between text & table)<br>DL3 - 150 temo & 1.0 topo: 1P G3-4 **thrombocytopenia** > 7 days (inconsistent between text & table), 1P G4 **neutropenia** & G3 **thrombocytopenia** > 7 days<br>46 clinical non-DLTs in 14P but only 2 were G3: 1 G3 **vomiting** & 1 G3 **FN** without infection.<br>Haematological toxicities: 12P G3/4 **neutropenia** & 11P G3/4 **thrombocytopenia** (not clear if these were dose limiting or not) |
| Temsirolimus, Irinotecan, Temozolomide | Bagatell, 2014[22] | 62 (3) | 8 | 63 (C1), 66 (C2-17) | 9 (C1), 10 (C2-17) | DLTs: 2/4 experienced DLT at 100mg/m2 Temozolomide, 50mg/m2 Irinotecan, Temsirolimus at 25mg/m2 (Elevated Cholesterol). 1/5P at 100mg/m2 Temozolomide, 65mg/m2 Irinotecan, Temsirolimus at 35mg/m2 (**diarrhoea** & GGT increase). 1/6P at 125mg/m2 Temozolomide, 90mg/m2 Irinotecan, Temsirolimus at 35mg/m2 (Headache, hydrocephalus, intracranial haemorrhage, **nausea**. 4/11P at 150mg/m2 Temozolomide, 90mg/m2 Irinotecan, Temsirolimus at 35mg/m2 (ALT increase (1), Anorexia (1), Hypertriglyceridemia (1), **Platelet Count Decrease** (2). |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | Other AE: C1: anaemia (2 G3), WBC decreased (11 G3, 1 G4), Lymphocyte count decreased (14 G3, 1 G4), **Neutrophil count decreased** (11 G3, 4 G4), **Platelet Count Decreased** (5 G3, 2 G4). Anorexia (1 G3), **diarrhoea** (2 G3), **Mucositis** (1 G3), **Nausea** (3 G3), **Vomiting** (5 G3). Elevated cholesterol (1 G3, 1 G4), Hypokalemia (3 G3), Hypophosphatemia (2 G3), Increased ALT (1 G3), Headache (1 G3).<br>C2-17 anaemia (3 G3), WBC count decreased (12 G3, 1 G4), Lymphocyte Count Decreased (13 G3, 1 G4), **Neutrophil count decreased** (13 G3, 5 G4), **Platelet count decreased** (3 G3, 2 G4). Abdominal Pain (1 G3), Anorexia (1 G3), **diarrhoea** (2 G3), **Nausea** (2 G3), **Vomiting** (1 G3), **Weight loss** (1 G3), Elevated triglycerides (3 G3), Hypokalemia (5 G3), Hypophosphatemia (2 G3), Increased ALT (3 G3), Increased AST (1 G3, 1 G4). |
| Topotecan, carboplatin, Cyclophosphamide, Etoposide | Compostella, 2019[33] | 38 (38) | 0 | 2P | 24P (69 E) | 24P - G4 hematologic toxicity (**neutropenia** & **thrombocytopenia** in 24 cases, anaemia in 16) & 5 of them had G4 **FN**. G3 **mucositis** during reirradiation & transient nephrotoxicity in 1P each. |
| Topotecan + ifosfamide | Kawamoto, 2010[139] | 11 (4) | 6 DLTs in 4P | | | 6 DLTs in 4P occurred at level 1 (0.75mg/m2/day of topotecan): **Platelet transfusions** twice/C (3/4), Red blood cell transfusion (2/4), Prolonged **FN** (1/4)<br>Recommended dose was determined as 1.2g/m2/day ifosfamide & 0.6mg/m2/day topotecan<br>No severe non-hematological toxicity was reported except for temporary **nausea** & anorexia. |
| Topotecan, Ifosfamide, Carboplatin | Radhakrishnan, 2015[87] | 14 (1) | 1P | | | 1P had DLT due to **thrombocytopenia** lasting greater than 7 days **(NOTE that this is a slight discrepancy to the conference abstract which says two DLTs)**.<br>Of the 1st 6P who were given 3000 mg/m2 ifosfamide over 3 days, 2 developed ifosfamide-related neurotoxicity, specially seizures & encephalopathy - both fully recovered with supportive treatment. 9 further P enrolled on a lower dose (1800mg/m2/day for 5 days) with no neurotoxicity reported. No P required dose modifications for renal or hepatic toxicity. |
| Topotecan, Vincristine, Doxorubicin | Meazza, 2009[79] | 9 (all RMS including 1 25 year old) | | | | Pneumonia was major infection. Hospitalisations were required in 3P. All P received G-CSF.<br>8P G3-4 **neutropenia**, 5P G3-4 **thrombocytopenia**, 4P G3-4 anaemia, 1P pneumonia, 3P red blood cell transfusions, 3P **platelet transfusions**<br>G3/4 **neutropenia** occurred after 11/12C, **thrombocytopenia** after 2C & anaemia after 1C<br>No non-hematological toxicities reported |
| Vincristine, Irinotecan, Temozolomide | McNall-Knapp, 2010[77] | 25 (1) | 0 at DL1. 2P at DL2 | | | 49E with any G3/4 haematologic toxicities. 26E with any G3/4 non-haematologic toxicities.<br>49E any G3/4 hematologic toxicity: 14E G3 **neutropenia**, 37E G4 **neutropenia**, 8E G3 **thrombocytopenia**, 3E G4 **thrombocytopenia**.<br>26E any G3/4 non-haematologic toxicities: 5E G3/4 **diarrhoea**, 4E G3/4 **vomiting**, 3E G3/4 dehydration, 1E G3/4 amylase/lipase, 1E G3/4 ALT/AST toxicity, 5E G3/4 fever without source, 5E G3/4 fever with source, 6E G3/4 **FN**, 1E G3/4 hypokalemia, 1E G3/4 deep vein thrombus |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Vincristine, Oral Irinotecan, Temozolomide (VOIT) | Wagner, 2010[100] | 36 (number of RMS unclear) | Schedule A: 1 (35mg/m2 irinotecan), 4 (50mg/m2 irinotecan). Schedule B: 1 at 90 mg/m2 irinotecan | 17E (Schedule A, C1), 19E (Schedule A, C2-8), 8E (Schedule B, C1), 6E (Schedule B, C2-8) | 6E (Schedule A, C1), 8E (Schedule A C2-8) | Schedule A DLTs. 35mg/m2: 1P hypoalbuminemia. 50mg/m2: 1E **platelets**; 1E anorexia, 1E ALT, SGPT; 1E hypokalemia; 1E abdominal pain; 1E hepatic failure. **1P (metastatic sarcoma) in Schedule A experienced fatal liver failure (associated with irinotecan)**. Schedule B: 1P DLT **nausea** & **vomiting** (90mg/m2/day).<br>Three toxicity inevaluable P had disease progression during the 1st C, 1 withdrew consent prior to treatment, 1 unable to take temozolomide, & 1 removed for non-compliance.<br>Non DLT AEs. SCHEDULE A: haemoglobin (1 G3 in C2-8), Leukocytes (2 G3 in C1, 3 G3 & 1 G4 in C2-8), lymphopenia (3 G3 & 2 G4 in C1, 3 G3 & 2 G4 in C2-8) **neutrophils/ granulocytes** (4 G3 in C1, 2 G3 & 5 G4 in C2-8), **platelets** (1 G4 in C1, 1 G3 in C2-8), fatigue 1 G3 in C2-8), **weight loss** (2 G3 in C2-8), anorexia (1 G3 in C1, 1 G3 in C2-8), **diarrhoea** (2 G3 in C1, 1 G3 in C2-8), **nausea** (1 G3 in C2-8), hypoalbuminemia (1 G3 in C1), alkaline phosphatase (1 G3 in C1), ALT SGPT (1 G3 & 1 G4 in C1, 1 G3 in C2-8), AST SGOT (1 G4 in C1), hypocalcemia (1 G3 in C1), hypophosphatemia (1 G3 in C2-8), hypokalemia (1 G4 in C1), abdominal pain (1 G3 in C1, 1 G3 in C2-8).<br>Non DLT AEs. SCHEDULE B: lymphopenia (2 G3 in C2-8), **neutrophil/granulocytes** (3 G3 in C1, 2 G3 in C2-8), **diarrhoea** (1 G3 in C1), **vomiting** (2 G3 in C1, 2 G3 in C2-8), ALT SGPT (1 G3 in C1), hyponatremia (1 G3 in C1).<br>Use of cefixime prophylaxis reduced number of **diarrhoea** AEs (only in 11% of all evaluable P). |
| Vinorelbine + Low-Dose cyclophosphamide | Casanova, 2004[31] | 18 (9) | 2 | | | DLTS were 2 cases of G4 **neutropenia** & 1 of these P also had pulmonary infection (who required hospitalisation). No P discontinued treatment from toxicity. 4P received GCS-F, & median treatment for this was 4 days. **Neutropenia**: G3/4 in 13P in 43C (G3 in 5/11C at 15mg/m2, in 6/17C at 20mg/m2, G3/4 in 15/41C at 25mg/m2 & 17/21 at 30mg/m2). 2P received GCS-F for a period of 3-6 days. 5P had the start of 2nd C delayed by <= 3 days due to **neutropenia**.<br>Only 1 P (who entered at Step1 & developed a prolonged G2 **mucositis**) experienced a major delay in the start of 2nd C. |
| Vinorelbine + low-dose cyclophosphamide | Minard-Colin, 2012[16] | 117 (50) | | 69 (no. P) | 43 (no. P) | G3/4 AES: Leukopenia (G3=11C, 8P, G4=4C, 4P), **Neutropenia** (G3=27C, 19P, G4=39C, 26P), Febrile Neutropenia (G3=12C, 11P, G4=9C, 7P), **Thrombocytopenia** (G3=5C, 5P), Anaemia (G3=22C, 15P, G4=3C, 2P). Anorexia (G3=1C, 1P), Asthenia (G3=2C, 2P), Peripheral Neuropathy (G3=2C, 2P, G4=1C, 1P), **Vomiting** (G3=1C, 1P, G4=1C, 1P), Epistaxis with **Thrombocytopenia** (G3=1C, 1P), Hyponatremia (G3=1C, 1P), **Mucositis** (G4=1C, 1P), Intraperitoneal bleeding without **thrombocytopenia** (G3=1C, 1P), Infection with Neutropenia (G4=1C, 1P), Infection without Neutropenia (G3=2C, 2P).<br>Median 2C per P. Vinorelbine dose reduced in 50P (reducing number of injections or reducing dose), CPM dose reduced in 15P. Treatment delayed for 7 days or more in 9% of P, mainly due to reasons other than toxicity. In total, 72P (62%) had at least 1 G3/4 AE in 123C<br>Treatment discontinuation due to PD (n=85), no further benefit (n=4), surgical excision of measurable disease (n=3),P decision (n=2), haematological toxicity (n=1) & radiotherapy (n=2) |
| **Novel agents - single agent** | | | | | | |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Everolimus **(This conference abstract represents data from a study with an unknown trial status, and so the trial registry record has also been extracted - NCT01216839)** | Epelman, 2015[136] | NR | | 1P | | 5P experienced AE due to everolimus but only 1P experienced G3 toxicity. Only AEs related to treatment reported |
| Temsirolimus | Geoerger, 2012[49] | 52 (16) | | | | 23 had any G3+ AE. 31E of G3+ AEs altogether.<br>**G3+ AE for >10% of P: Thrombocytopenia** (9), Hyperlipidaemia (2), Aesthenia (1), Anaemia (4), Leucopenia (1), SGPT increased (4), Fever (1), SGOT increased (4), **Neutropenia** (3), Anorexia (1), **Mucositis** (1).<br>A greater percentage of P with neuroblastoma (58%) required a delay in temsirolimus administration versus those with high-grade glioma (41%) & RMS (31%). Also, ≥1 dose reduction was required for 58% of P with neuroblastoma, 12% with high-grade glioma & 25% with RMS. Overall, **thrombocytopenia** was predominant AE requiring dose delay (18P; 35%) or dose reduction (13P; 25%). 1P with neuroblastoma discontinued treatment because of G4 pneumonitis (listed above as dyspnoea) considered possibly related to temsirolimus. **All 6 deaths that occurred within 30 days of last dose were due to disease progression.** |
| Alisertib | Mossé, 2019[118] | 137 (10) | 18P (C1) | 525 | 258 | DLTs: myelosuppression, **mucositis**, **FN**, enterocolitis, **diarrhoea**, depression, hypersomnia, photophobia, tumour lysis syndrome, hyperbilirubinemia, electrolyte abnormalities.<br>ALISERTIB-RELATED G3/4 TOXICITIES:<br>G3 AEs: anaemia (63), **FN** (18), lymphopenia (47), **Neutropenia** (124), **Thrombocytopenia** (54), Serum amylase increase (1), leukopenia (117), photophobia (1), **diarrhoea** (2), enterocolitis (1), oral **mucositis** (19), oral pain (5), **nausea** (2), **vomiting** (2), ALT increased (17), AST increase (10), hyperbilirubinemia (3), GGT increased (1), INR increased (1), infection (1), pneumonia (1), UTI (1), anorexia (1), dehydration (1), hypoalbuminemia (1), hypocalcemia (1), hypokalemia (4), hyponatremia (3), hypophosphatemia (1), dizziness (14), hypersomnia (1), palmar-plantar erythrodysesthesia (2).<br>G4 Toxicities: anaemia (5), lymphopenia (14), **neutropenia** (137), **thrombocytopenia** (50), leukopenia (48), hyperuricemia (1), hypokalemia (1), tumour lysis syndrome (1), depression (1).<br>**G5 Toxicities: hepatic haemorrhage (1P with hepatoblastoma), resp failure (1P with pelvic soft tissue sarcoma)** |
| Apatinib | Liu, 2020[70] | 42 (6) | | 11P | 0 | G3 Hypertension (5), G3 HFS (3), G3 Proteinuria (1), G3 Fatigue (1), G3 Pain (1) |
| Lenvatinib | Gaspar, 2021[111] | 23 (5) | 3P (14mg/m2) | | | DLTs at 14mg/m2: 2P G3/4 hypertension (resolved after dose reduction or discontinuation); 1P increased serum ALT levels.<br>TEAEs: led to dose modifications in 18P, dose interruptions in 10/23P, & dose reductions in 10/23P. All P experienced at least 1 TEAE. 1 TEAE led to drug discontinuation (G4 hypertension)<br>Most Common Treatment Emergent G3+ AEs in 10%+P (PHASE 1 ONLY):<br>Decreased appetite (1 @ 14mg/m2), Hypertension (2 @ 14mg/m2, 3@ 17mg/m2), fatigue (1 @ 17mg/m2), proteinuria (1 @ 14mg/m2, 1 @ 17mg/m2), **weight decrease** (1 @ 11mg/m2, 1 @ 14mg/m2), ALT increase (1 @ 14mg/m2), arthralgia (1 @ 17mg/m2), myalgia (1 @ 11mg/m2). |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Regorafenib **(This full-text represents data from the dose escalation stage of a trial. As trial is still active, not recruiting, the trial registry record has also been extracted)** | Geoerger, 2021[50] | 41 (3) | 5 | | | Table 1: DLTs: 1 G4 **thrombocytopenia** (60mg/m2), 1 G3 rash (72mg/m2), 1 G3 pyrexia (82mg/m2), 1 G3 hypertension (93mg/m2), 1 G3 exfoliative dermatitis (93mg/m2).<br>Table 2: All 41P experienced at least 1 TEAE (treatment-emergent AE). 15 G3+ TEAEs: rash (3 @ 72mg/m2), hyperbilirubinemia (2 @ 82mg/m2), hand foot skin reaction (1 @ 82mg/m2), **Thrombocytopenia** (1 @ 60mg/m2, 1 @ 72mg/m2, 1 @ 82mg/m2, 1 @ 93 mg/m2), pyrexia (1 @ 82mg/m2), **neutropenia** (1 @ 72mg/m2, 1 @ 93mg/m2), lymphopenia (1 @ 82mg/m2, 1 @93 mg/m2). 63%P with G3/4 haematologic toxicities had previously received myeloablative treatment such as high-dose chemo with SC rescue or craniospinal irradiation.<br>**Unable to determine if P included in Table 1 are also reported in Table 2**<br>27P had dose modifications, 90% due to TEAEs. Most common TEAEs that led to dose reduction were pyrexia, **thrombocytopenia** & maculopapular rash. Drug-related TEAEs led to dose reduction in 14P across cohorts. |
| Pazopanib | Lee 2015/ clinical trial 2020[137] | 57 (12) | | | | 9/57P had all-cause mortality (including 3 RMS P).<br>SAEs (exact G not reported): 1 **thrombocytopenia**, 1 cardiopulmonary failure, 1 left ventricular dysfunction, 1 **diarrhoea**, 1 rectal haemorrhage, 1 pain (RMS P), 1 cellulitis, 1 sepsis, 1 skin infection, 1 upper respiratory tract infection, 1 wound infection, 1 wound dehiscence, 1 blood creatinine increase (RMS P), 1 gamma-glutamyltransferase increase, 1 hepatic enzyme increase, 2 dehydration, 1 muscular weakness, 1 myalgia, 2 pain in extremity, 1 intracranial pressure increase, 2 pleural effusion (1 RMS P), 1 pneumothorax. |
| Pazopanib | Glade Bender, 2013[52] | 48 (number of RMS unclear) | Unable to determine - inconsistently reported in tables | Pazopanib-related AEs (across all C): tablet: 20 G3 of which 12 were DLT; suspension: 5 G3 of which 2 were DLT | Pazopnib-related AEs (across all C): tablet: 2 G4 - both DLT. 0 G4 for suspension | **DLTs & AEs inconsistently reported in tables**<br>8P reported to have a DLT as per Table A1, but **uncertainty** with this as it is unclear whether the DLTs are associated to C 1 or all C owing to inconsistent reporting.<br>*Table A2 - C1 toxicity*<br>Tablet:<br>At 275mg/m2 – 1 G4 lipase increase (DLT & RPT)<br>At 450mg/m2 – 1 G3 back/tumour pain (DLT)*, 1 G3 ALC, 1 G3 **ANC**, 1 G3 proteinuria (DLT & RPT) & 1 G3 hypertension (DLT & RPT) [the latter two occurred in the same P]<br>At 600mg/m2 – 1 G3 amylase increase (DLT), 1 G3 hypophosphatemia, 1 G3 hypertension (DLT)<br>Suspension:<br>At 160mg/m2 – 2 G3 ALC, 1 G4 CNS haemorrhage (DLT & RPT) – **not deemed to be related to pazopanib.**<br>At 225mg/m2 – 2 G3 ALT increase (DLT & RPT), 1 G3 **ANC**<br>*Table A3 - C2 onwards toxicity*<br>Tablet:<br>At 275mg/m2 – 1 G4 **ANC** (DLT & RPT)<br>At 350mg/m2 – 1 G3 rash/HFS (DLT & RPT), 1 G3 **ANC**<br>At 450mg/m2 – 1 G3 anorexia (DLT), 1 G3 ALT increase (DLT & RPT), 1 G3 lipase increase (DLT), 1 G3 back/tumour pain (DLT), 3 G3 **ANC**, 1 G3 anaemia, 1 G3 growth plate (DLT & RPT) - **inconsistently reported***<br>At 600mg/m2 – 1 G3 anaemia (DLT & RPT)<br>Suspension:<br>At 160mg/m2 – 1 G4 amylase increase (DLT) – **not deemed to be related to pazopanib**<br>At 225mg/m2 – 1 G3 tissue necrosis (DLT & RPT) - **not deemed to be related to pazopanib**<br>1 G3 sensory neuropathy DLT (inconsistent reporting of this AE, so unable to determine whether the DLT occurred in the 1st or |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | 2nd C)<br>*AEs occurred in the same P. |
| Sorafenib | Kim, 2015[63] | 20 (10) | 7P | 20E | | G3: 1P lymphocyte count decrease, 2P **neutrophil count decrease**, 1P **platelet count decrease**, 1P fatigue, 1P palmar-plantar erythrodysesthesia, 2P rash maculo-papular, 1P anorexia, 2P with alkaline phosphatase increase, 1P blood bilirubin increase, 1P hypoalbuminemia, 1P hypocalcemia, 1P Hypokalemia, 1P hypophosphatemia, 1P abdominal pain, 1P back pain, 1P pain in the extremity, 1P dyspnea |
| Sorafenib | Widemann, 2012[106] | 50 (both Solid Tumour & Leukaemia Cohorts). 30 from solid tumour cohorts. (number of RMS unclear) | 13P; 8 from Solid tumour cohort | 11 (C1), 10 (C2+) | 0 | DLTs at 150mg/m2: 1P G3 **platelets**, 1P G2 hypertension & G3 back pain, 1P G3 rash/desquamation & G3 urticaria, 1P G3 ALT & AST, 1P G3 lipase. DLTs at 200mg/m2: 1P G3 ALT, 2P G3 rash/desquamation, 1P G3 hypertension & G3 back & chest pain. DLTs at 250mg/m2: 1P G3 hand/foot skin reaction, 1P G3 hyponatremia.<br>Leukaemia group at 200: 1P G3 anorexia, 1P G4 GI haemorrhage in their abdomen.<br>AE: Haemoglobin (2 G3 in C1, 1 in C2+), Leukopenia (2 G3 in C1, 2 G3 in C2+), Lymphopenia (3 G3 in C1, 1 G3 in C2+), **Neutropenia** (2 G3 in C1, 2 G3 in C2+), Hypertension (1 G3 in C2+), **Nausea** (1 G3 in C2+), **Vomiting** (1 G3 in C2+).<br>Hyperphosphatemia (1 G3 in C1), Hypomagnesemia (1 G3 in C1), Hypokalemia (1 G3 in C2+) |
| Ispinesib | Souid, 2010[94] | 19 (number of RMS unclear) | 5P | 12 in C1; 3 in C2-7 | 4 in C1; 1 in C2-7 | DLTs: elevated ALT/AST (1) at 7mg/m2; **neutropenia** (1) at 9mg/m2; **neutropenia** (2) & hyperbilirubinemia (1) at 12mg/m2<br>Haematological toxicities during C1: 1P - G3 anaemia, 2P - G3 lymphopenia, 1P - G4 lymphopenia, 5P - G3 **neutropenia** & 3P - G4 **neutropenia**, 1P - **thrombocytopenia**<br>Haematological toxicities during C2-7: 2P - G3 lymphopenia, 1P - G3 **neutropenia**, 1P - G4 **neutropenia**<br>Non-hematological toxicities during C1: 1P - G3 ALT, 1P - G3 AST, 1P - G3 Hyperbilirubinemia |
| Sonidegib (LDE225) | Kieran, 2017[62] | 60 (4) | 1 | | | Drug-related G3/4 AEs: 5<br>All G3/4 AEs: 38<br>Drug-related G3/4 AEs: Blood creatine phosphokinase increased (n = 2), **Vomiting** (n = 1)<br>2 NR in the table even though 5 specified in total<br>Any 3/4 AE: **vomiting** (7), headache (8), fatigue (2), **nausea** (1), pain in extremity (1), myalgia (1), abdominal pain (1), decreased appetite (4), ataxia (4), blood creatine phosphokinase increased (2), WBC decrease (1), arthralgia (1), lymphocyte count decrease (5), asthenia (2), convulsion (5), hyponatremia (3), pruritus (1), confusional state (4), somnolence (5)<br>DLT: reversible G4 CPK elevation in 1 RMSP treated at 372mg/m2 at the end of the 1st C of therapy |
| Bevacizumab | De Pasquale, 2011[37] | 17 (2 eligible RMS) | | 10 | 3 | G3 lymphopenia in 7P, G3 wound dehiscence in 1 RMS P so stopped therapy. 1P - G3 hypertension during acute renal failure, 1P - G3 proteinuria. 3 SAEs (G4 AEs): reversible posterior leukoencephalopathy syndrome, G4 entero-cutaneous fistula & G4 hypertension. Bevacizumab was discontinued in all cases. |
| Cixutumumab | Weigel, 2014[103] | 100 (number of RMS unclear) | 5P removed due to DLTs | 56E | 6E | G3: anaemia - 9E, WBC decrease - 2E, lymphocyte cell decrease - 5E, **neutrophil count decrease** - 3E, **platelet count decrease** - 3E, fatigue - 3E, anaphylaxis - 2E, pruritus - 1E, bilirubin increase - 1E, cough - 1E, anorexia - 2E, dehydration - 4E, **diarrhoea** - 1E, **vomiting** - 4E, infections/infestations - 4E, hypoalbuminemia - 2E, ALT, SGPT - 4E, AST, SGOT - 2E, hypophosphatemia - 1E, headache - 1E, **nausea** - 2E.<br>G4: anaemia - 1E, lymphocyte cell decrease - 1E, **neutrophil count decrease** - 2E, **platelet count decrease** - 2E. |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Depsipeptide | Fouladi, 2006[42] | 18 (number of RMS unclear) | 4 | 20 (C1) 4 (C2-7) | 3 (C1), 1 (C2-7) | DLTs: asymptomatic, reversible T-wave inversion at 22mg/m2 (2), & in the lateral leads (1 at 13m/gm2). No change in troponin levels or ejection/shortening fraction. Changes resolved within 24 hours in 2P. 1P developed reversible, asymptomatic sick sinus syndrome & G3 hypocalcemia (17mg/m2)<br>Haemoglobin: 1 G3 @ 17mg/m2, 1 G4 at 22mg/m2 in C1; 1 G3 at 17mg/m2 in C2-7. Leukocytes: 1 G3 at 13mg/m2 in C1, 1 G3 at 17mg/m2 in C1. Lymphopenia: 1 G3 at 17mg/m2, 1 G3 at 22mg/m2. in C1 ,; 1 G3 at 17mg/m2 in C2-7. **Neutrophils/Granulocytes**: 2 G3 at 13mg/m2, 3 G3 at 17mg/m2, 1 G3 at 22mg/m2 in C1 . **Platelets**: 1 G3 at 13mg/m2, 1 G3 at 17mg/m2, 1 G3 at 22mg/m2 in C1. T-wave inversion: 2G3 at 13mg/m2, 1 G3 at 22mg/m2. in C1. Coagulopathy: 1 G4 at 22mg/m2 in C1. 1 G3 **Vomiting** at 13mg/m2 in C1. AST 1 G3 at 17mg/m2 in C1. 1 G3 in 17mg/m2 in C2-7. Infection without neutropenia: 1 G3 at 17mg/m2 in C2-7. Hypocalcemia: 1 G4 at 17mg/m2 in C1, 1 G4 at 17mg/m2 in C2-7. Hyponatremia: 1 G3 at 22mg/m2 in C1. |
| Ipilimumab | Merchant, 2016b[81] | 31 (number of RMS unclear) | 4 | | | G3-4 toxicities: 9P<br>1P had DLT at 5mg/kg (pancreatitis requiring hospitalisation [week 2]), 3P had DLT at 10mg/kg (G3 colitis [week 1]. G3 transaminitis [week 4], G3 pleural effusions + pneumonitis [week 2]).<br>Immune related toxicities: At 5mg/kg: G4 pancreatitis. At 10mg/kg: G3 colitis, G3 pleural effusions + pneumonitis & G3 transaminitis.<br>G3/4 toxicities: colitis/**diarrhoea** (3), transaminitis (2), endocrinopathies (1), other irAE (3), more than 1 irAE (2).<br>**(inconsistent reporting between table & text)** |
| Lexatumumab | Merchant, 2012[116] | 24 (3) | 1P (2 DLTs) | | | 1P in 8mg/kg group had DLT due to hypoxia & pleural effusion associated with a change in pleural-based tumour, probably related to treatment<br>No mention of G3/4 toxicities for P in DLs 3/5/8 mg/kg. But does state that there were no G3/4 toxicities in the 10mg/kg group<br>2P had propagation of venous thrombi, judged possibly related to drug administration (BUT NO GRADE REPORTED). |
| Lorvotuzumab Mertansine (IMGN901) | Geller, 2020[47] | 52 (number of RMS unclear) | 1 | 18 | 1 | No dose reduction for any P; At the discretion of the treating physician, 1P received approximate 50% dosing during C5 & 6 of treatment; this coincided with concurrent radiotherapy<br>1P DLT (G3 hyperglycemia possibly related to lorvotuzumab mertansine).<br>G3 toxicities: 2P anaemia, 1P dental caries, 1P **nausea**, 1P **vomiting**, 1P tooth infection, 3P ALT increase, 1P AST increase, 2P lymphocyte count decrease, 1P hyperglycemia (unclear whether this is the DLT), 1P hyperuricemia, 1P hypokalemia, 1P hypophosphatemia, 1P peripheral motor neuropathy, 1P peripheral sensory neuropathy<br>G4 toxicities: 1P colonic fistula<br>**G5 toxicities: 1P colonic perforation** |
| Nivolumab | Davis, 2020[36] | Part A: 12 (number of RMS unclear) Part B: 63 (number of RMS unclear) | 0 (Part A) 5 (Part B) | 33 (Haem & Non-Haem AEs) & 8 (Immune AEs) | 12 (Haem & Non-Haem AEs) & 1 (Immune AE) | DLTs in part B: G3 elevated lipase for more than 7 days (1), G4 **neutropenia** (1), G3 pain at tumour site (1), G3 upper gastrointestinal haemorrhage (1), G2 enterocolitis infection (1). 2P required dose modifications in Part B (both G2).<br>Drug related G3/4 occurred in 27 of 75P. Common toxicities attributable to therapy include anaemia (G3+ in 5/75P), decreased WBCs (G3+ in 3P), decreased lymphocytes (G3+ in 10P), **decreased platelets** (G3+ in 2P). AST (G3 in 1P), ALT (G3 in 1P), Lipase increased (G3 in 2P, G4 in 1P), Pleural effusion (G3 in 2P), Autoimmune disorder (G3 in 1P), Gastritis (G3 in 1P).<br>7/72P in part B discontinued therapy due to AEs (2 prolonged liver enzymes, 1 prolonged elevated lipase, 1 prolonged fever, 1 GI bleeding, 1 infection, 1 autoimmune disorder (including thyroiditis, elevated creatine kinase, elevated creatinine). |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Ontuxizumab (MORAb-004) | Norris, 2018[84] | 22 (4) | 2 P | 3 in C1. 1 in C2-5 | 0 | DLTs: 1P Staph epidermidis bacteremia, 1P hyponatremia- both received 12mg/kg ontuxizumab<br>G3 toxicities after C1: 1E anaemia, 1E hyponatremia, 1E hypophosphatemia<br>G3 toxicities in C2-5: 1P anaemia |
| Rebeccamycin Analogue (NSC #655649) | Langevin, 2008[68] | 129 (unclear) | 0 | | | G3/4 haematological toxicities after C1:<br>30E haemoglobin toxicity, 40E leukocytes (total WBC) toxicity, 53E **neutrophil/granulocyte toxicity**, 20E **platelet toxicity**, 17E **transfusion platelet toxicity**, 19E transfusion pRBCs toxicity<br>G3/4 haematological toxicities after other Cs:<br>35E haemoglobin toxicity, 67E leukocyte (total WBC) toxicity, 116E **neutrophil/granulocyte toxicity,** 91E **platelet toxicity**, 37E **transfusion platelet toxicity**, 31E transfusion pRBCs toxicity<br>Pancreatitis & elevation of amylase & lipase in 6Ps. Reversible hepatotoxicity (all Gs) in 14%Cs (37/265) |
| Rebeccamycin Analog (NSC#655649) | Langevin, 2003[128] | 16 (1) | 9 haem DLTs | 20 | 7 | DLTs: 4P dose limiting **neutropenia** at 760mg/m2 (all of these P also had sepsis that necessitated hospitalisation), 5P dose limiting **thrombocytopenia** - 1 at 585mg/m2 & 4 at 760mg/m2<br>G3 AEs: 3P **neutropenia** (1 at 450mg/m2 & 2 at 585mg/m2), 3P **thrombocytopenia** (1 at 450mg/m2 & 2 at 760mg/m2), 10P anaemia (2 at 450mg/m2, 2 at 585mg/m2 & 6 at 760mg/m2 (3 in each stratum)), 3P transient G3 transaminase elevation without hyperbilirubinemia (1 at 585mg/m2 & 2 at 760mg/m2), 1P G3 **nausea** & **vomiting**<br>G4 AEs: 4P **neutropenia** (2 at 585mg/m2 & 2 at 760mg/m2), 2P **thrombocytopenia** (2 at 585mg/m2), 1P **mucositis** (dose NR) |
| Seprehvir | Streby, 2019[95] | 9 (1 RMS <18 years) | 0 | 5E | | Hypotension (1 G3), Anorexia (1 G3), **Nausea** (1 G3) & Flu-like symptoms (1 G3) possibly attributed to seprehvir.<br>1 Pneumothorax (1 G3 - definitely associated with trial procedure). **1P had a G5 (GI) haemorrhage (HSV01) related to disease progression.** |
| **Novel agents - multiple agents** | | | | | | |
| Vinblastine + Sirolimus | Morgenstern, 2014[34] | 12 (number of RMS unclear) | 1P | | | 31 G3/4 toxicities across 12P. 6 G3/4 at DL1. 5 G3/4 at DL2. 20 G3/4 at DL3.<br>G3 **mucositis** DLT in 1P: lasted for 4 weeks in total, associated with G3/4 **neutropenia** (not meeting criteria DLT)<br>G3/4 toxicities across all DLs (toxicities by DL also available): 10P **neutropenia**, 4 anaemia, 2 **thrombocytopenia**, 3 lymphopenia, 3 **FN**, 3 other infections, 2 **mucositis**, 1 abn triglycerides/cholesterol toxicity, 1 fever, 1 **diarrhoea**, 1 dehydration<br>2P required dose reductions (6mg/m2 to 5mg/m2 vinblastine). 1 for **FN**(G3) & **diarrhoea** (G3) |
| Sirolimus, Cyclophosphamide, Topotecan | Vo, 2017[97] | C 1: 21 (3)<br>C 2-12: 6 (number of RMS unclear) | 3 at DL2. 2 at DL3 | C1: 26E. C2-12: 4E | C1: 11E. C2-12: 2E | DLTs at DL2: 1P Prolonged **thrombocytopenia** (C1), 1P G4 hypertriglyceridemia (C12), 1P G3 stomatitis (C4). DLTs at DL3: 1P prolonged ALT elevation (C1), 1P prolonged **neutropenia** (C1).<br>8P not evaluable for C1 DLT.<br>AEs: anaemia (3 G3, C1), Leukopenia (4 G3, 3 G4 in C1; 1 G3 in C2-12), Lymphopenia (8 G3 & 1 G4 in C1), **Neutropenia** (3 G3, 4 G4 in C1, 1 G3 & 1 G4 in C2-12), **Thrombocytopenia** (6 G3, 3 G4 in C1). Hypertriglyceridemia (2 G3 in C1, 1 G3 & 1 G4 in C2-12), **Mucositis** (1 G3 in C2-12) |
| Celecoxib + vinblastine | Stempak, 2006[134] | 30 (3) | | | | Combination of celecoxib & low-dose chemotherapy was well tolerated.<br>Some SAE but none likely to be related to treatment: 1P focal seizures, 3P G3/4 **neutropenia** (2 treated with vinblastine), 1P 3 local septic event who was eventually removed, 1P skin rash which resolved spontaneously |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Erlotinib ± Temozolomide | Jakacki, 2008[59] | 36 (number of RMS unclear) | 7P | 1 | 0 | 1 G3 (AST increase).<br>Non-Haematologic DLTs in 1st C: 3 rash/desquamation (2 @ 85mg/m2, 1 @ 110mg/m2); hyperbilirubinemia (1 @ 110mgm/m2); **diarrhoea** (1 @ 85mg/m2). Non-Haematologic DLTs in 2nd C (erlotinib & temozolomide): **platelets** & **neutrophils** (1 @ 85mg/m2) & **mucositis**/stomatitis (1 @85mg/m2).<br>Hematologic toxicity, although commonly observed, was dose limiting in only 1 heavily pretreated P who developed prolonged G4 **neutropenia** & **thrombocytopenia**. Mild hematologic toxicity was observed, primarily in the heavily pretreated P. |
| Regorafenib, vincristine, irinotecan | Casanova, 2020[135] **(This conference abstract represents a subset of patients. As trial is still active, not recruiting, the trial registry record has also been extracted - NCT02085148)** | NR | 8 G3 DLTs in 4P | | | 62% of P required a dose reduction of irinotecan.<br>8 G3 DLTs in 4P: 1P - peripheral neuropathy & liver injury (received 72mg/m2 regorafenib in concomitant group), 1P - pain, **vomiting** & febrile aplasia (received 72mg/m2 regorafenib in concomitant group), 1P - rash & elevated AST (received 72mg/m2 regorafenib in sequential group), 1P - thrombocytopenia (received 82mg/m2 regorafenib in sequential group)<br>As both P in concomitant group had DLTs, the concomitant dosing schedule was discontinued.<br>G3+ TEAEs: 71% **neutropenia**, 33% **thrombocytopenia**, 29% leukopenia, 24% anaemia, 24% ALT increased. |
| Sorafenib + topotecan | Reed, 2016[88] | 12 (1) | 3 | 21E | 17E | ALT increased (2 G3 (1 at DL2, 1 at DL3)), anaemia (5 G3 (1 at DL1, 4 at DL2)), ejection fraction decrease (1 G3 (DL1)), **FN** (3 G3 (1 at DL2, 2 at DL3)), hypertension (1 G3 (DL3)), hypokalemia (1 G3 (DL2), **nausea** (1 G3 (DL2)), **neutrophil count decreased** (3 G3 (1 at DL1, 1 at DL2, 1 at DL3), 7 G4 (1 at DL1, 4 at DL2, 2 at DL3), **platelet count decreased** (1 G3 (DL2), 10 G4 (2 at DL1, 5 at DL2, 3 at DL3)), radiation recall reaction [dermatologic] (1 G3 (DL3), **vomiting** (1 G3 (DL2)), **weight loss** (1 G3 (DL1)).<br>Severe treatment-related AE: 3 **FN** admissions, 2 admissions for blood product transfusion (outpatient facilities not available).<br>DLTs were: 1P **platelet count decrease** on DL2. 2P **neutrophil count decrease** on DL3. |
| Talazoparib + Irinotecan | Federico, 2020b[41] | Stratum A: 29 (3) | 7P with 15 DLTs (STRATUM A) | 60P across all C in stratum A | 48P across all C in stratum A | DLTs in stratum A: **neutropenia** (1 at 400mcg/m2 of TAL 20mg/m2 of IRN, 1 at 600mcg/m2 of TAL 30mg/m2 of IRN, 1 at 600mcg/m2 of TAL 40mg/m2 of IRN, 2 at 600mcg/m2 of TAL 50mg/m2 of IRN); elevated GGT levels (1 at 400mcg/m2 of TAL 20mg/m2 of IRN, 1 at 600mcg/m2 of TAL 50mg/m2 of IRN); **thrombocytopenia** (2 at 600mcg/m2 of TAL 50mg/m2 of IRN, 1 at 400mcg/m2 of TAL 50mg/m2 of IRN & PEG); colitis (1 at 600mcg/m2 of TAL 50mg/m2 of IRN, 1 at 400mcg/m2 of TAL 50mg/m2 of IRN & PEG); **diarrhoea** (2 at 400mcg/m2 of TAL 50mg/m2 of IRN & PEG), sepsis (1 at 400mcg/m2 of TAL 50mg/m2 of IRN & PEG). Myeloid growth factor support was added in to the DL5 dose strategy (1 at 400mcg/m2 of TAL 50mg/m2 of IRN & PEG) due to neutropenic DLTs.<br>AEs stratum A only (number of P): increase in ALT levels (3 G3), anorexia (2 G3), colitis (4 G3), **diarrhoea** (6 G3), enterocolitis (1 G3), **FN** (6 G3, 1 G4), increase in GGT levels (2 G4), sepsis (1 G4), **vomiting** (1 G3), anaemia (9 G3, 3 G4), lymphocyte count |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | decreased (13 G3, 5 G4), **neutrophil count** (5 G3, 17 G4), **platelet count decrease** (2 G3, 10 G4), WBC count decrease (8 G3, 9 G4). |
| Talazoparib + temozolomide | Schafer, 2020[120] | 37 (1) | 13 DLTs in 7P | | | G3+ Toxicities across all DLs: 76.<br>DLTs:<br>600ug/m2 Tal, 30mg/m2 Tem: 1P **neutropenia**.<br>600ug/m2 Tal, 40mg/m2 Tem: 1P intra-abdominal haemorrhage & **thrombocytopenia**; 1P **thrombocytopenia**, ALT increase (1) & **neutropenia** (1)<br>600ug/m2 Tal, 55mg/m2 Tem: 1P - **neutropenia**, sepsis & **thrombocytopenia**. 1P - **neutropenia** & **thrombocytopenia**.<br>PHASE 2 (this phase did not include RMS patients): 600ug/m2 Tal & 30mg/m2 Tem: 2P **thrombocytopenia**.<br>G3+ TOXICITIES POSSIBLY, PROBABLY OR DEFINITELY RELATED TO PROTOCOL THERAPY AT ALL DLs (number ofP C): **neutropenia**(20), lymphopenia(11), leukopenia (11), **thrombocytopenia** (10), anaemia (9), **FN** (3), abdominal pain (1), ALT increased (1), AST increased (1), catheter-related infection (1), hydrocephalus (1), hypophosphatemia (1), intra-abdominal haemorrhage (1), lymphocytosis (1), **nausea** (1), sepsis (1), typhlitis (1), **vomiting** (1) |
| Bevacizumab, Sorafenib, Low-Dose cyclophosphamide | Federico, 2020a[40] | 24 (number of RMS unclear) | 2 | | | 58E of G>= 3<br>DLTs = 2 (G3 prolonged QTc interval, G3 HFS during C 1). 6P were taken off study for treatment toxicity - 3 haemorrhagic cystitis, 1 **weight loss**, 1 elevated lipase & 1 pneumothorax.<br>Most common G3/4 toxicities: hypertension (4), HFS (3), elevated lipase (3), **neutropenia** (7) & lymphopenia (17), **thrombocytopenia** (3), leukopenia (11), elevated amylase (2) & lipase (3), hyponatremia (2), pneumothorax (1), proteinuria (2), **vomiting** (1), **weight loss** (2) |
| Bevacizumab, Sorafenib, Low-Dose cyclophosphamide | Navid, 2013[83] | 19 (2) | 2 (sorafenib at 110mg/m2). 1 (bevacizumab at 10mg/kg. 1 (bevacizumab at 15mg/kg) | 20 (all doses during C1); 27 (all doses, after C1) | 4 (all doses, during C1); 9 (all doses, after C1) | DLTs: G3 HFS, G3 elevated lipase (sorafenib 110mg/m2), G3 thrombus (bevacizumab at 10mg/kg), G3 HFS & anorexia (bevacizumab at 15mg/m2). 5P discontinued for unacceptable toxicities, 1 pneumo-thorax (C3), 1 hemorrhagic cystitis (C7), 1 thrombosis (C1), 1 HFS (C5), & 1 with HFS & anorexia (C1).<br>Dose modification in 5P, which has an improvement of HFS symptoms in 3P. (1P had exacerbation after 2C). 4P had cyclophosphamide dose reduction(from 50 to 25 mg/m2), 3 for **neutropenia**, & 1 for **thrombocytopenia**. 3/12 P with lung nodules developed pneumothorax, **1 of which died from complications.** Pneumothorax was associated with tumour response. 1P discontinued therapy due to cystitis. Sorafenib was reduced from twice daily to once daily for 3P, all for HFS.<br>G3 during C1: DL1: 1 hypokalemia, 1 **neutropenia**. DL2: 1 elevated lipase, 1 HFS, 1 lymphopenia, 1 anaemia. DL5: 2 hypophosphatemia, 1 lymphopenia, 1 **neutropenia**, 1 thrombosis. DL6: 1 anorexia, 1 HFS, 2 leucopenia, 2 lymphopenia, 1 **neutropenia**, 2 anaemia.<br>G4 during C1: DL2:1 **neutropenia**, DL5: 1 leucopenia, 1 **neutropenia**. DL6: 1 lymphopenia.<br>G3 after C1: DL1: 1 **weight loss**, 1 **vomiting**, 1 HFS, 2 leucopenia, 2 lymphopenia, 2 **neutropenia**, 1 anaemia, 1 **FN**.<br>G4 after C1: DL2: 1 HFS, 1 leucopenia, 2 lymphopenia, 2 **neutropenia**. DL5: 1 hypophosphatemia, 1 hyponatremia, 2 HFS, 1 lymphopenia,1 bladder. DL6:1 lymphopenia, 1 **neutropenia**, 1 **FN**, 1 infection with **neutropenia**<br>G4 after C1: DL1: 1 leucopenia, 1 lymphopenia, 1 **neutropenia**, 1 **thrombocytopenia**. DL2: 1 lymphopenia, 2 **neutropenia**. DL5: 1 lymphopenia. DL6: 1 **neutropenia**<br>**1P with G5 pneumothorax toxicity** |
| Vincristine, oral Irinotecan, | Wagner, 2013[98] | 13 (1) | 8 | 7E in 5P | 1E in 1P | DMTs in C1: G3 **nausea**, G3 anorexia & G3 dehydration (all same P); G3 neuropathy; G3 **nausea**.<br>DMTs in later C: G4 **neutropenia**; G3 **diarrhoea**; G3 abdominal pain |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| temozolomide (VOIT) + bevacizumab | | | | | | Other AEs:<br>G3 **nausea** - 2P, G3 anorexia - 1P, G3 dehydration - 1P, G3 neuropathy in 1P, G3 **diarrhoea** in 1P, G3 abdominal pain in 1P, G4 **neutropenia** in 1P. |
| Cixutumumab + Temsirolimus | Fouladi, 2015[43] | 33 (number of RMS unclear) | 8 | 29 non-DLTs(Across all C) | 2 non-DLTs (Across all C) | DLTs reported: 5/12P at DL1 (6 mg/kg of cixu & 15 mg/m2 tems): 1P with G3 hypercholesterolemia, 1 with G3 **mucositis**, 1 with G3 ALT, 1 with G3 fatigue & 1 with G3 prolonged **thrombocytopenia** > 14 days. - these DLTs results in a dose de-escalation. DL0 (cix @ 6mg/kg & tem @ 10mg/m2): 2/6 experienced DLT (2 G3 x **mucositis**). At intermediate DL (cix @6mg/kg & tem@8mg/m2) 1/6 experienced G3 **mucositis**. DL-1 (cix @4mg/kg & tem@8mg/m2) no DLTs.<br>G3 Toxicities: anaemia (3, C1); Lymphocyte (1 in C1 & 2 in C2-20), **Neutrophil count decrease** (3 in C1, & 1 in C2-20), **Platelet count decrease** (4 in C1 & 2 in C2-20) & WBC decrease (2 in C1, & 2 in C2-20); ALT increased (1 G3 in C2-20), hypophosphatemia (3 in C1 & 2 in C2-20), **mucositis** oral (2 G3 in C2-20) & **nausea** (1 in C2-20).<br>G4 Toxicities: lymphocyte count decreased (1 in C1), **neutrophil count decreased** (1 in C1). |
| Cixutumumab + temsirolimus | Wagner, 2015[99] Toxicities only reported if at least possibly related to protocol | 44 (11) | 19 | 46 | 3 | G3: 6E **neutropenia**, 3 leukopenia, 3 anaemia, 3 **thrombocytopenia**, 5 hypokalemia, 4 oral **mucositis**, 4 hypophosphatemia, 3 AST, 2 ALT, 2 hypertriglyceridemia, 2 pain, 1 alkaline phosphatase, 1 anaphylaxis, 1 ascites, 1 hyperbilirubinemia, 1 elevated creatinine, 1 epistaxis, 1 intestinal obstruction, 1 hyperglycemia, 1 hypermagnesemia.<br>G4: 2 **thrombocytopenia**, 1 hyperuricemia<br>DLTs: ALT elevation (1), anaphylaxis (1), hyperglycemia (1), hypertriglyceridemia (1), hypoalbuinaemia (1), hypokalemia (1), hyponatremia (1), hypophosphatemia (1). AST-elevation (2), creatinine increase (2), **platelet count decrease** (3), oral **mucositis** (4)<br><br>Toxicities only reported if at least possibly related to protocol |
| Perifosine + Temsirolimus | Becher, 2017[24] | NR | 0 | | | 39E of G3/4 toxicities<br>G3/4 AEs: decreased haemoglobin (1), **Decreased platelets** (8), decreased leukocytes (2), increased PTT (1), **decreased neutrophils** (5), lymphopenia (5). Hyperglycemia (2), Increased AST (2), Increased ALT (3), Hypercholesterolemia (4), Hypertriglyceridemia (1), Hypokalemia (2), Hypernatremia (1), Hypophosphatemia (1), Hyponatremia (3), **Infection with G3 neutropenia**, urinary tract not otherwise specified (1). |
| Reovirus (Reolysin) ± cyclophosphamide | Kolb, 2015[64] | 24 (number of RMS unclear) | 2P | 38E (C1), 2E (C2-3) | 4E (C1), 2E (C2-3) | **DLTs: 1 G5 respiratory failure (death attributed to PD). 1 G5 thromboembolism (Possible related to Reolysin, probably related to synovial sarcoma & probably related to progressive metastatic disease).**<br>Non-DLTs: anaemia (3 G3 in C1, 1 G3 & 1 G4 in C2-3), Leukopenia (8 G3 in C1), Lymphopenia (8 G3 & 3 G4 in C1, 1 G3 in C2-3), **Neutropenia** (10 G3 & 1 G4 in C1), **Thrombocytopenia** (1 G3 in C1, 1 G4 in C2-3). ALT increase (3 G3 in C1), AST increase (2 G3 in C1), Fever (3 G3 in C1). |
| Tariquidar + doxorubicin | Fox, 2015[44] | 26 (number of RMS unclear) | 2 | 22E | 9E | Doxorubicin Toxicities. 1mg/kg: G3 **Neutropenia** (1), G4 **neutropenia** (2), anaemia (1G3 & 1G4), G3 **thrombocytopenia** (1), G3 **FN** (1), G3 alopecia (1). 1.5mg/kg: **neutropenia** (1 G3, 1 G4 which was a DLT), G4 **Thrombocytopenia** (1), G3 **FN** (1), G3 **mucositis** (1). 2mg/kg: G3 **Neutropenia** (2), G4 **Neutropenia** (2, 1 of which is a DLT), G3 **Thrombocytopenia** (4), G3 anaemia (2), G3 **FN** (2), G3 Infection without Neutropenia (1), G3 **Vomiting** (1), G3 Esophagitis (1), G3 **Diarrhoea** (1), G4 Hypocalcemia (1), G4 Hypomagnesemia (1).<br>No DLT related to tariquidar. No G3+4 AEs to tariquidar |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Tirapazamine + Cyclophosphamide | Aquino, 2004[21] | 21 (number of RMS unclear) | 250mg /m2 (1), 325mg /m2 (1), 420mg /m2 (5) | | | DLTs: G4 **neutropenia** for longer than 7 days (n = 1 in 250mg/m2, n = 2 in 420mg/m2); G4 **thrombocytopenia** for longer than 7 days (n = 1 in 325mg/mg2, n = 1 in 420mg/m2). G3 ototoxicity (n = 2 in 420mg/m2 - these P (ES & wilm's tumour) went on to report complete hearing loss within 24 hours (both resolved within 1 week)). G4 anaemia in 1P (unsure at what dose). Other toxicities include hypoalbuminemia (n = 1 at 325mg/m2). G2/3 **nausea** seen at all DLs.<br>NUMBER OF G3/4 TOXICITIES (**lack of clarity about whether this relates to C or P)**: G3/4 toxicities at 250 mg/m2 dose: 17 WBC, 18 **ANC**, 2 APC, 2 lymphocytes, 5 **platelets**, 3 haemoglobin, 1 prothrombin time, 1 bacterial sepsis, 1 **nausea**, 1 **vomiting**, 1 creatinine, 1 headache, 1 hearing loss. **325mg/m2 dose:** 11 WBC, 21 **ANC**, 10 lymphocytes, 7 **platelets**, 7 haemoglobin, 1 other bacterial, 2 **vomiting**, 1 **diarrhoea**, 1 albumin. **420 mg/m2 dose:** 4 WBC, 4 **ANC**, 1 **platelets**, 1 **nausea**, 2 **vomiting**, 1 **diarrhoea**, 1 pulmonary function, 1 headache, 2 hearing loss. |
| **Biomarker driven studies** | | | | | | |
| Atezolizumab (Known or expected PDL1 involvement) | Geoerger, 2020b[113] | 87 (number of RMS unclear) | | 142 (32 treatment-related) | 25 (5 treatment-related) | ALL G3 AES: Abdominal abscess (1), abdominal distension (1), abdominal pain (1), agitation (1). ALT increase (4), anaemia (18), ascites (1), baceraemia (1), bone pain (1), catheter site erythema (1), chest pain (1), **constipation** (2), cough (1), decreased appetite (3), decreased lymphocyte count (6), decreased O2 saturation (1), **decreased platelet count** (2), decreased WBC count (4), dehyradtion (2), device related infection (5), dyspnoea (2), fanconi syndrome (1), fatigue (1), **FN** (3), flank pain (1), generalised oedema (1), headache (1), hydrocephalus (1), hydronephrosis (1), hyperbilirubinaemia (1), hyperglycaemia (1), hypertension (1), hypoaesthesia (1), hypokalaemia (2), hypomagnesaemia (1), hyponatraemia t5(3), hypophosphataemia (1), hypovalaemic shock (1), incision site abscess (1), increased amylase (2), increased AST (2), increased blood alkaline phosphatase (1), increased blood creatine (1), increased gamma glutamyltransferase (1), increased lipase (2), influenza-like illness (1), leukopenia (1), lung infection (1), maculo-papular rash (1), migrane (1), **nausea** (1), neck pain (1), neuralgia (1), **neutropenia** (1), oliguria (1), pain (4), pain in extremity 2), parasthesia (1), pelvic pain (1), pleural effusion (2), pneumothorax (1), post-operative abscess (1), procedural hypotension (1), procedural pain (1), pyelonephritis (1), pyrexia (2), rash (1), respiratory tract infection (1), staphylococcal infection (1), staphylococcal sepsis (1), stomatitis (1), tachypnoea (1), **thrombocytopenia** (5), toxicity to various agents (1), transaminases increased (1), tumour pain (2), upper GI haemorrhage (2), urethritis (1), UTI (1) urinary tract obstruction (1), VIth nerve disorder (1), **vomiting** (3).<br>ALL G4 AES: anaemia (1), cholestasis (1), decreased lymphocyte count (1), **decreased neutrophil count** (5), **decreased platelet count** (2), decreased WBC count (1), diabetic ketoacidosis (1), haemorrhagic shock (1), hyperkalaemia (1), hypokalaemia (2), hypophosphataemia (1), increased amylase (1), large intestinal obstruction (1), neuralgia (1), **neutropenia** (1), pancreatitis (1), papilloedema (1), septic shock (1), superior vena cava syndrome (1).<br>TREATMENT RELATED AES: abdominal pain (1 G3), anaemia (4 G3, 1 G4), cough (1 G3), decreased appetite (1 G3), decreased lymphocyte count (3 G3), diabetic ketoacidosis (1 G4), dyspnoea (1 G3), fanconi syndrome (1 G3), **FN** (1 G3), hypertension (1 G3), hypophosphataemia (1 G3), increased ALT (2 G3), increased amylase (2 G3, 1G4), increased AST (1 G3), increased lipase (1 G3), increased transaminases (1 G3), influenza-like illness (1 G3), leukopenia (1 G3), maculo-papular rash (1), **neutropenia** (1 G3, 1G4), papilloedema (1 G4), pleural effusion (1 G3), **thrombocytopenia** (3 G3), sixth nerve disorder (1 G3), **vomiting** (1 G3).<br>3P withdrew from study treatment due to AEs: 1P with diabetic ketoacidosis (G4) & renal Fanconi syndrome (G3), 1 with increased transaminases (G3), & 1P with lung infection (G3).<br>57 (66%)P had at least 1 AE considered to be related to the study drug.<br>AESI: rash (2 G3+ AEs), hepatitis & AST/ALT elevation (10 G3+ AEs), pancreatitis (6 G3+ AEs), & diabetes (1 G3+ AEs) |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Pembrolizumab (PDL1 positive only) | Geoerger, 2020a[112] | 154 (7) | 0 in phase 1 | 11P with treatment-related G3 | | TREATMENT-RELATED AE:<br>G3 toxicities: anaemia (2), decreased lymphocyte count (3), increased AST (1), pruritus (1), colitis (1), gastric ulcer (1), **decreased neutrophil count** (1), hypertension (1), photosensitivity reaction (1), dyspnoea (1)<br>No G4 toxicities<br>**G5 toxicities: 2 P, 3 AEs. pleural effusion (1), pneumonitis (1), pulmonary oedema (1)**<br>Immune-mediated AEs:<br>G3 toxicities: severe skin reaction (1), colitis (1).<br>No G4 toxicities<br>**G5 toxicities: Pneumonitis (1)**<br>Treatment interrupted in 18P because of AEs: increased ALT (3), abdominal pain (2), device related infection (2), **decreased neutrophil count** (2), anaemia (1), arthritis (1), blindness (1), colitis (1), gastric ulcer (1), hyperthyroidism (1), influenza (1), laryngitis (1), lichenification (1), nasopharyngitis (1), pyrexia (1), sinusitis (1), thyroiditis (1), tonsilitis (1), viral infection (1).<br>7P discontinued treatment due to AEs, 4 considered treatment related: (G3 AST increase, G3 hypertension, **G5 pleural effusion & G5 pneumonitis [in the same P; pneumonitis being the reason for discontinuation], & G5 pulmonary oedema).**<br>**6P had 1 or more AEs that resulted in deaths: gastric adenocarcinoma (1), increased blood creatinine (1), malignant ependymoma (1), pulmonary oedema (1), sepsis (1) & 1 with pleural effusion & pneumonitis. Two of these deaths were considered potentially treatment related; a 15-year-old boy with chest sarcoma had pneumonitis at day 13 & pleural effusion at day 14 of treatment, & a 14-year-old girl with renal medullary carcinoma had pulmonary oedema at day 21 in the setting of sepsis following the 1st pembrolizumab administration.**<br>2P had multiple drug-related serious E: 1 had peripheral oedema, pyrexia, & enterocolitis infectious; & 1 had dyspnoea, pneumonitis, adrenal insufficiency, & pleural effusion.<br>Treatment was modified (ie, interrupted or withdrawn) in 4P(3%) because of an immune-mediated AE (thyroiditis, pneumonitis, hyperthyroidism, or colitis).<br>Median time to onset of immune-mediated AE & infusion-related reactions: 13-164 days after initiation of treatment. |
| Ceritinib (ALK positive tumours) | Fischer, 2021[110] | 83 (12) | 4 DLTs (2 fasted, 2 fed group): 3 being treatment-related DLTs in escalation phase (2 fasted & 1 fed | 70 treatment-related E in 32P (across all doses & groups) | 22 treatment-related E in 20P (across all doses & groups) | 52P with G3/4 treatment-related AE<br>DLTs: 24/25 evaluable for DLT in fasted group during dose-escalation phase: 1 G2 abdominal pain (related to ceritinib at 560mg/m2), 1 G3 alamine aminotransferase increase (related to ceritinib at 560mg/m2). This led to drop to 450mg/m2 but no DLTs so went back up to 510mg/m2 with no DLTs reported.<br>13/15 evaluable for DLT for fed group during dose-escalation phase: 1 G3 ALT increase (related to ceritinib at 400mg/m2), 1 G3 influenza (at 500mg/m2)<br>In the expansion cohort, 3/10P in the fed group did develop DLTs: 1P - G3 ALT increase & G3 upper abdominal pain, 1P - G3 lipase increase, 1P - G4 AST increase & G4 ALT increase<br>AEs: All 83P had at least 1 AE of any G (81P had at least 1 AE due to ceritinib).<br>46P required dose reduction or interruption due to AE (37 due to G3/4).<br>40P reported at least 1 SAE (SAE; 15P related to ceritinib) & 31 had at least 1 G3/4 SAE.<br>9/83P discontinued treatment due to AE (6 were G3/4).<br>**14 deaths during study treatment or within 30 days after last dose but 0 due to study treatment.**<br>Treatment-related AEs (across all doses & groups): **vomiting** (8 G3 - **inconsistent with supplementary data which says 0**), **diarrhoea** (2 G3), ALT increase (20 G3 & 12 G4), AST increase (16 G3 & 5 G4), abdominal pain (4 G3), y-glutamyl transferase increase (9 G3 & 2 G4), decreased appetite (1 G3), fatigue (1 G3), blood creatinine increase (1 G4), anaemia (5 G3) & **neutropenia** |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | groups) | | | (4 G3 & 2 G4) |
| Personalised medicine (crizotinib for RMS patients) | Worst, 2016[122] | N/A - not measured in this study | | | | N/A - not measured in this study |
| **Metronomic chemotherapy** | | | | | | |
| Metronomic - thalidomide, celecoxib, alternating etoposide/cyclophosphamide | Kieran, 2005[127] | NR | | 70E in 1st 6 months | 0 in 1st 6 months | Table 2 reports 20P completing 321 weeks of therapy.<br>1P discontinued therapy due to G3 deep venous thrombosis.<br>G3 AEs during 1st 6 months of treatment across all P: 1 Amenorrhea (1P), 21 **ANC** (10P), 2 **diarrhoea** (1P), 4 haemoglobin (3P), 1 infection with **neutropenia** (1P), 36 leukocytes (17P), 1 level of consciousness (1P), 1 lymphopenia (1P), 1 cranial neuropathy (1P), 1 syncope (1P),<br>1 deep venous thrombosis (1P) |
| Metronomic - celecoxib, vinblastine, cyclophosphamide, methotrexate; plus radiotherapy | Ali, 2016[123] | 64 (14) | | 0 | 0 | 23P reported no toxicities. 26 reported G1 haematological toxicities, 10P reported G1 non-haematological toxicities & 5 reported a combination of both. |
| Metronomic - Cyclophosphamide, Etoposide, Valproic acid | El Kababri, 2020[39] | NR | | | | G3/4 anaemia: 28C (5%), G4 **thrombocytopenia**: 11C (2%). In 28C, transfusion was needed (5%).<br>Analgesic treatment was used in 107C of metronomic treatment (19%). |
| **HSCT** | | | | | | |
| High dose chemotherapy with autologous HSCT | Shiriaev, 2013[138] | NR | | | | Moderate toxicity observed (WHO G1-2) - but specific toxicities not specified |
| Allogeneic HSCT | Prete, 2010[140] | NR | | | | Acute GVHD of G2-4 occurred in 6P |
| Haplo-SCT with non-myeloablative conditioning | Perez-Martinez, 2012[85] | NR | | | | NR |
| Haplo SCT with reduced intensity | Llosa, 2017[71] | NR | NA | NR | NR | Median number of rehospitalisations following BMT until 100 days: 1 (range 0-5), median inpatient days (7.5 [range 0-63]).<br>Infectious complications: candida krusei (1 definite), b-D-glucan+ pneumonia (2 probable), esophageal candidiasis (1 possible). |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| conditioning **(This full-text represents a subset of patients. The trial is still recruiting so the trial registry has also been extracted)** | | | | | | Viral (1st 180 days): EBV reactivation (3), BK virus HC (3), BK viremia (3), adenovirus viremia (2), adenovirus enteritis (1), rhinovirus URI (4), influenza URI (I), parainfluenza URI (1), HHV6 encephalitis (1).<br>GVHD: 3P acute GVHD: 1 G4 GVHD (stage 4 skin & stage 1 gut). 1 G3 gastrointestinal acute GVHD, 1 acute GVHD with G3 **diarrhoea**, overlapping with chronic GVHD features (anorexia & **weight loss**). |
| Reduced intensity Allogeneic HSCT | Baird, 2012[109] | 23 (2 RMS <18 years) | | 6 (post-HSCT EOCH), 4 (Post HSCT-RT) | 6 (Post HSCT-RT) | G3 Toxicities- Post-HSCT EOCH: 4P **mucositis**, 1P esophagitis, 1P liver toxicity. POST-HSCT-RT: 3P **mucositis**, 1P skin toxicity.<br>G4 Toxicities (only in Post HSCT-RT): 1P GI, 1P pancreatitis, 2P LFTs, 1P skin, 1P enteritis.<br>**1P G5 lung AE in post-HSCT RT (radiation-induced bronchiolitis obliterans).** No deaths attributed to GVHD<br>There were 20 documented infectious events in 6P, including 7 pneumonias (4 viral, 2 fungal, & 1 bacterial), 3 bacteremias, & 2E of cholecystitis, 1 of which was associated with septic shock |
| **Cellular therapies** | | | | | | |
| Autologous MSCs with oncolytic virus Icovir-5 (Celyvir) | Ruano, 2020[89] | 9 (1) | | 0 | 0 | No G2-5 treatment-related toxicities related to children. AE for adults or a mixed population also reported in the article & supplementary material. |
| Autologous lymphocyte infusion (D2) and dendritic cell vaccines, plus CYT107 (recombinant human IL7) | Merchant, 2016a[80] | NR | | 8 possibly related to regimen | 2E attributed to CYT107 | **INCONSISTENCY BETWEEN TEXT AND TABLE**<br>No G3/4 AEs were attributed to the autologous lymphocyte infusion or dendritic cell vaccines.<br>G2 injection site reactions attributable to the dendritic cell vaccines occurred in 17% of P. Transaminitis in 31% P (G2: 24%; G3: 7%), G4 fever (n=1), & G4 anaphylaxis (n=1) were attributed to CYT107. All toxicities were fully reversible. Transient lymphopenia was commonly observed during the 1st 48 hours following CYT107 as previously described due to alterations in lymphocyte trafficking & was not graded as toxicity (37, 43).<br>From supplementary table - toxicities possibly related to regime:<br>G3 toxicities: 2P ALT increase, 1P AST increase, 1P WBC decrease, 4P anaphylaxis<br>G4 toxicities: 0 reported |
| Consecutive donor-derived adoptive cellular immunotherapy after allogeneic HSCT | Merker, 2019[117] | 18 (including 1 RMS P with relapse) | N/A | 3 (2 related to CIK) | 0 | G3 acute GVHD seen in 3P. GVHD was manageable in all P. Treatment of aGVHD including mycophenolate mofetil (MMF) or cyclosporine A (CsA). P with aGVHD G3 also received steroids & in 2P multiple administrations of MSC, while 1 of these 2P received extracorporeal photopheresis (ECP) as GVHD-therapy.<br>Relapsed RMS P didn't develop GVHD<br>**1P died due to respiratory failure in the context of pneumonia, & 1 due to multiple organ failure in the context of cumulative toxicity, & viral infection after successful immunosuppressive treatment of aGVHD. Hence, non-relapse mortality in both cases was not clearly due to ACIs** |
| HER2 CAR-T cells **(This trial is still recruiting so total** | Hegde, 2020[54 270] | 6 (1) | | | | Toxicity as reported for the 1 RMS P:<br>Developed G3 **neutropenia**, G4 lymphopenia & G4 leukopenia after 1st flu/cy conditioning.<br>Developed G4 **neutropenia**, G4 lymphopenia & G4 leukopenia after 2nd flu/cy conditioning |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| **population number is up to date of current publication)** | | | | | | Developed G4 **neutropenia**, G4 lymphopenia & G4 leukopenia after third flu/cy conditioning<br>No cardiac or pulmonary toxicities observed |
| LAK-cell therapy + whole-body hyperthermia | Ismail-zade, 2010[57] | Not extractable (foreign language) | | | | "all children tolerated the procedure well. The day after the session they did not in practice need to stay in bed." |
| TAA cytotoxic T cells (TAA-Ts) | Hont, 2019[56] | 14 (3) | 0 | 0 | 0 | No infusion-related AE<br>No G3/4 E recorded (possibly/probably related to protocol therapy). |
| **Other approaches** | | | | | | |
| AMORE | Blank, 2009[27] | 11 (11) | | | | Parameningeal P: Short-term toxicity consisted of nerve damage: temporary N.VII palsy & deafness after labyrinthectomy (1P) & permanent infraorbital palsy (1P). 1P experienced wound infection leading to partial removal of the muscle transplant. Late side effects were growth retardation (2P), severe caries (1P), impatency of the lacrimal system (1P), & trismus caused by fibrosis (1P). 1 2nd primary (medulloblastoma) within field of prior EBRT.<br>Non-parameningeal P: No acute toxicities were observed. Dental problems were assessed in all four quadrants of 2P, 1 of whom also had mild swallowing problems. 1 2nd primary (fibrosarcoma) within the radiation fields. |
| Intratumoral injection of HSV1716 (oncolytic herpes virus) | Streby, 2017[96] | 9 (2) | 0 | 2 | | 2P experienced G3 back pain related to the study injection. Only AEs related to study intervention reported |
| Radiofrequency Ablation + chemotherapy | Hoffer, 2009[55] | NR | | 23E | 5E | G3 AEs: diaphragmatic hernia (1), hypoxia (8), dyspnea (1), forced expiratory volume in 1 second (1), pleural effusion (1), bronchopleural fistula (1), pulmonary edema (1), skin burn (1), bradycardia (1), hyperthermia (1), pain (2), fatigue (2), leukocytosis (1), ALT (1).<br>G4 AEs: Diaphragmatic hernia (1), dyspnea (2), forced expiratory volume in 1 second (1), AST (1).<br>Pain reported in 36/37 sessions. Pain lasted 1 to 23 days (median 9 days). Only 2P had G3 toxicity of postprocedural pain. Hospitalisation occurred 17 times (median 3 days, 2-25 days). RMSP had max G1 & G2 AEs. |
| Transarterial chemoembolization (TACE) | Jiang, 2016[60] | NR | | NR | NR | The TACE procedures failed in 9P (23.1 %) owing to catheter not placing into feeding artery. None of the 39P had AVF, & no major TACE-related complications were observed during the follow-up period. However, all P suffered minor complications, which required no therapy or only symptomatic attention & which spontaneously resolved within several days after treatment; they included transient fevers observed in all P & emesis in 23P. |
| **Non-comparative multi-arm cohorts** | | | | | | |
| Dalotuzumab **(monotherapy arm of study)** | Frappaz, 2016.[45] | 20 (3) | 0 | | | Drug Related G3/4 AEs: 2P experienced 7AEs.<br>Drug Related G3/4 AEs for all Dalotuzumab Monotherapy: fatigue (1), ALT increase (2), AST increase (2), lymphocytopenia (1), abdominal pain (1). 2P had 1 or more G3/4 AE.<br>ALL CAUSE AEs **(no Grade specified)**: 20P experienced 1 or more AE. **Constipation** (8), **vomiting** (8), fatigue (8), pyrexia (7), |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | headache (7), abdominal pain (6, includes upper abdominal pain), hyponatremia (6), decreased appetite (6), ALT increase (5), **nausea** (5), leukopenia (5), γ-glutamyltransferase increased (4), rash (4 includes macular, papular, & pruritic rashes), **neutropenia** (4), back pain (3), AST increased (3), lymphopenia (3), pain in extremity (3), **thrombocytopenia** (3), somatitis (1). |
| Dalotuzumab + Ridaforolimus **(combination arm of study)** | Frappaz, 2016.[45] | 4 (1) | 1P (2 DLTs) | | | Drug Related G3/4 AEs: 3P experienced 6 AEs.<br>1P with 2 DLTS during 1st C (G3 anal fissure & stomatitis). All P experienced at least 1 AE of any G.<br>Drug Related G3/4 AEs: **thrombocytopenia** (2), anaemia (1), decreased appetite (1), hypophosphatemia (1), lymphocytopenia (1).<br>3P experienced 1 or more G3/4 AE.<br>ALL CAUSE AEs **(no Grade specified)**: 4P experienced 1 or more AE. **Constipation** (4), **vomiting** (2), fatigue (2), pyrexia (3), headache (1), abdominal pain (3, includes upper abdominal pain), decreased appetite (2), ALT increase (3), **nausea** (3), leukopenia (2), γ-glutamyltransferase increased (1), rash (1, includes macular, papular, & pruritic rashes., **neutropenia** (1), back pain (3), AST increase (2), lymphopenia (2), pain in extremity (2), **thrombocytopenia** (4), stomatitis (4) |
| Doxorubicin, Cyclophosphamide, Etoposide, Ifosfamide, Tirapazamine **(Regimen 2 of study)** | Mascarenhas, 2019b.[15] | 91 (including 61P who did not respond to VI phase 2 window) | | | | Regimen 2: G3+ toxicities after 6 weeks (2C): **vomiting** (26.8%), stomatitis (12%), myalgia (8.5%), infection (5%), heart failure (6%) & ototoxicity (2.4%).<br>**1 death due to congestive heart failure occurred immediately after 1st dose of tirapazamine administered to a P who was refractory to regimen 1A.** |
| Doxorubicin, Cyclophosphamide, Etoposide, Ifosfamide **(Regimen 3 of study)** | Mascarenhas, 2019b.[15] | NR | | | | NR |
| Olaratumab + doxorubicin **(Specific arm of study)** | Mascarenhas, 2021.[75] | 10 (number of RMS unclear) | | | | 13P had 1 or more G3/4 TEAE, 10 of which were deemed to be related to study treatment.<br>6P with 1 or more SAE, 3 of which were deemed to be related to the study treatment. 1P discontinued treatment due to AE, but it was not deemed to be related to the study treatment.<br>G3+ TREATMENT RELATED TEAEs FOR ALL P: PART A: anaemia (2), **nausea** (1), **neutrophil count decrease** (5), WBC decrease (3), **platelet count decrease** (2), lymphocyte count decrease (1). PART B: AST increase (1), GGT increase (1), ALT increase (1). PART C: anaemia (2), leukopenia (3), lymphopenia (2), **neutropenia** (3), **thrombocytopenia** (1), **FN** (2), **neutrophil count decrease** (1), WBC count decrease (1).<br>**MONOTHERAPY (C 1):** In Part A (olaratumab [15 mg/kg] monotherapy, N = 30), 1P (3%) had G4 elevated ALT (confounded by concurrent antibiotic therapy). In Part B (olaratumab [20 mg/kg] monotherapy, N = 24), 1P (4%) had a DLT of G3 elevated gamma-glutamyl transferase, & 1P (4%) had a DLT of G3 lung infection. |
| Olaratumab, Irinotecan, Vincristine **(Specific arm of study)** | Mascarenhas, 2021.[75] | 22 (number of RMS unclear) | | | | 21P had 1 or more G3/4 TEAE, 16 of which were deemed to be related to study treatment<br>10P with 1 or more SAE, 5 of which were deemed to be related to the study treatment. 1P discontinued treatment due to AE, that was deemed to be related to the study treatment.<br>G3+ TREATMENT RELATED TEAEs FOR ALL P: PART A: anaemia (2), leukopenia (1), lymphopenia (1), **neutropenia** (1), **thrombocytopenia** (1), **vomiting** (1), **diarrhoea** (1), lung infection (1), **neutrophil count decrease** (2), ALT increase (1), peripheral motor neuropathy (1). PART B: anaemia (2), lymphopenia (1), **neutropenia** (2), **FN** (1), **vomiting** (1), **diarrhoea** (2), **nausea** (1), |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | **neutrophil count decrease** (1), WBC count decrease (1), lymphocyte count decrease (1), dehydration (1), acute kidney injury (1) .<br>PART C: anaemia (2), leukopenia (2), **neutropenia** (4), **FN** (1), **diarrhoea** (1), WBC count decrease (1), lymphocyte count decrease (1), ALT increase (1).<br>**MONOTHERAPY (C1):** In Part A (olaratumab [15 mg/kg] monotherapy, N = 30), 1P (3%) had G4 elevated ALT (confounded by concurrent antibiotic therapy). In Part B (olaratumab [20 mg/kg] monotherapy, N = 24), 1P (4%) had a DLT of G3 elevated gamma-glutamyl transferase, & 1P (4%) had a DLT of G3 lung infection. |
| Olaratumab + Ifosfamide **(Specific arm of study)** | Mascarenhas, 2021.[75] | 24 (number of RMS unclear) | | | | 23P had 1 or more G3/4 TEAE, 22 of which were related to study treatment<br>12P with 1 or more SAE, 11 of which were deemed to be related to the study treatment. 1P discontinued treatment due to AE, but it was not deemed to be related to the study treatment.<br>G3+ TREATMENT RELATED TEAEs FOR ALL P: PART A: anaemia (5), **vomiting** (1), penile infection (1), **neutrophil count decrease** (4), WBC count decrease (5), **platelet count decrease** (6), lymphocyte count decrease (5), AST increase (1), GGT increase (1), ALT increase (1), hypokalemia (1), seizure (1). PART B: anaemia (7), lymphopenia (2), leukopenia (2), **neutropenia** (2), **thrombocytopenia** (3), **FN** (7), **nausea** (2), stomatitis (1), **neutrophil count decrease** (2), WBC count decrease (3), **platelet count decrease** (4), hypokalemia (3), hypohosphatemia (1), hyponatremia (1), hypocalcemia (1), headache (1), fanconi syndrome acquired (1). PART C: anaemia (3), leukopenia (2), lymphopenia (2), **neutropenia** (2), **FN** (3), **neutrophil count decrease** (1), WBC count decrease (1), **platelet count decrease** (1), lymphocyte count decrease (1).<br>**MONOTHERAPY (C1):** In Part A (olaratumab [15 mg/kg] monotherapy, N = 30), 1P (3%) had G4 elevated ALT (confounded by concurrent antibiotic therapy). In Part B (olaratumab [20 mg/kg] monotherapy, N = 24), 1P (4%) had a DLT of G3 elevated gamma-glutamyl transferase, & 1P (4%) had a DLT of G3 lung infection. |
| **Comparative Studies** | | | | | | |
| Carboplatin+ irinotecan | Petrilli, 2004[141] | NR | | | | G3-4 infection/**FN** 45%P, G3-4 **diarrhoea** 41%P, G3-4 **vomiting** 35%P, G3-4 abdominal pain/cramping 23%P, G3-4 **nausea** 14%P, G3-4 **thrombocytopenia** 20%P, G3-4 **neutropenia** 19%P, G3-4 anaemia 24%P Additional AEs for CNS tumours available |
| Irinotecan | | NR | | | | G3-4 infection/**FN** 35%P, G3-4 **diarrhoea** 42%P, G3-4 **vomiting** 35%P, G3-4 abdominal pain/cramping 18%P, G3-4 **nausea** 23%P, G3-4 **thrombocytopenia** 3%P, G3-4 **neutropenia** 9%P, G3-4 anaemia 14%P |
| Allogeneic HSCT with Minimal conditioning regimen - sibling donor | Shook, 2013[92] | NR | | | | 2 G4 acute GvHD, 1 limited, chronic GvHD & 3 extensive, chronic GvHD in matched sibling donor. 4 G3 &2 G4 acute GvHD, 3 limited, chronic GvHD & 3 extensive, chronic GvHD in matched unrelated donors.<br>G4 toxicities: blood counts, electrolytes; infectious complications (catheter related infection in 6P).<br>**2P died from infectious complications. 1P had multiple-relapsed HL that had sclerodermatous chronic GVHD approximately 18mo after transplantation requiring corticosteroids & cyclosporine A. Died of pulmonary aspergillosis (day +887) 1P with RMS (over 18) who had significant acute skin, liver & gut GVHD & pulmonary aspergillus infection. Died with complications of disseminated aspergillosis (day +250). Both had no evidence of disease.** |
| Allogeneic HSCT with Minimal conditioning regimen - MUD | | NR | | | | DLT: Pain initially reported as G2, then as G3 pain requiring analgesics (in part A). Non-dose limiting non-hematologic toxicities occurred in at least 10% of the evaluableP & at least possibly attributable to NTX-010<br>PART A<br>- NTX-010 DL1 (n=6) - C1: Lymphocyte count decreased (2 G3), **neutrophil** (1 G3, 1 G4), white blood cell decrease (1 G3).<br>-NTX-010 DL2 (n=3)- C1: Lymphocyte count decreased (1 G3). Post documented clearance C: lymphocyte count decreased (2 G3), **Platelet count decreased** (1 G4). |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | -NTX-010 DL3 (n=3)- C1: **Neutrophil count decreased** (1 G3), Post documented clearance C: 1 G3 lymphocyte count decreased, 1 G3 white blood cell count decreased.<br>PART B<br>NTX-010 DL3 (10e11) & cyclophosphamide (n=6). C1: anaemia (2 G3), Lymphocyte count decreased (2 G3, 2 G4), **Neutrophil count decreased** (4 G3), **Platelet count decreased** (1 G3), White blood cell decreased (3 G3), Alanine aminotransferase increased (1 G3), **nausea** (1 G3), **vomiting** (1 G3). |
| Bevacizumab, vinorelbine, cyclophosphamide | Mascarenhas, 2019a[14] | 42(42) | 3 | | | DLTs in BEV (intervention arm): G3 hypertension (1), G3 bleeding (1), G3 oral **mucositis** (1)<br>DLTs in TEM (comparator arm): G3 oral **mucositis** (4), G3 hypertriglyceridemia (2), G3 pneumonitis (1), G3 elevation of ALT that did not resolve to less that G1 in 14 days (1)<br>G3+ Toxicities (BEV): **FN** (Reporting Period (RP1)- 11.9%, RP2-18.5%, RP3- 13.6%, RP4-14.3%), Oral **Mucositis** (RP1-2.4%, RP2= 0%, RP3= 4.5%, RP4= 0%), Hypokalemia (RP1-2.4%, RP2-3.7%, RP3-4.5%, RP4-0%).<br>G3+ Toxicities (TEM): **FN** (Reporting Period (RP1)- 26.2%, RP2-17.6%, RP3- 18.2%, RP4-23.1%), Oral **Mucositis** (RP1-11.9%, RP2= 0%, RP3= 0%, RP4= 7.7%), Hypokalemia (RP1-11.9%, RP2-5.9%, RP3-0%, RP4-0%).<br>Non-Haem G3+ Toxicities for BEV: hypertension (2.4%), bleeding (4.5%), wound infection (4.5%). Non-Haem G3+ Toxicities for TEM: hypertriglyceridemia (9.5%), **mucositis** (11.9%), pneumonitis (2.4%) & liver enzyme elevation (4.8%).<br>1P in the temsirolimus arm suffered acute kidney injury that was attributed to temsirolimus |
| Temsirolimus, vinorelbine, cyclophosphamide | | 42(42) | 8 | | | No severe PPV-related AEs. |
| Irinotecan - prolonged schedule (with other multimodal chemotherapy) | Mascarenhas, 2010[73] | NR | | | | G3+ toxicity: Regimen 1A: 50%P; Regimen 1B: 66%P<br>**Diarrhoea**: 1A 22%; 1B 13%; anaemia: 1A 39%, 1B 28%; Packed Red Cell Transfusion: 1A 31%, 1B 21%; **FN** 1A 4%; 1B 13%.<br>**Neutropenia**: 1A: 16%, 1B: 34%. 2%P had G3+ **thrombocytopenia** on both regimens. |
| Irinotecan - short schedule (with other multimodal chemotherapy) | | NR | | | | 1 G3 toxicity (alanine aminotransferase) judged to be associated with vaccine. P had comorbidity (fatty liver disease). Other 3AEs were back pain, **thrombocytopenia** or anaemia. |
| Vincristine + Irinotecan | Defachelles, 2021[8] | 54(54) | | 103 | 24 | P in the VIT arm experienced significantly more treatment-related AEs G>=3 compared to VI arm (93% vs 69%, p=0.002).<br>VI ARM<br>G3 AES: 1 hyperkalaemia, 1 hypoalbuminemia, 1 hypokalaemia, 1 hyponatremia, 2 hypophosphataemia, 1 abdominal pain, 1 ascites, 1 colitis, 1 **constipation**, 9 **diarrhoea**, 2 **nausea**, 2 pancreatitis, 9 **vomiting**, 1 anorexia, 2 general physical health deterioration, 1 hyperthermia, 3 pain, 1 **weight decreased**, 11 anaemia, 4 leukopenia, 5 lymphopenia, 14 **neutropenia**, 2 **thrombocytopenia**, 1 liver disorder, 1 transaminases increased, 1 cholecystitis infective, 9 **FN**, 1 lower respiratory tract infection, 2 viral infection, 2 dehydration, 2 musculoskeletal pain, 2 tumour pain, 1 headache, 1 seizure, 1 agitation, 1 anxiety, 1 depression, 1 alopecia<br>G4 AEs: 1 large intestine perforation, 14 **neutropenia**, 2 **thrombocytopenia**, 1 device related infection, 4 leukopenia, 2 lymphopenia. |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | VIT Arm:<br>G3 AEs: 1 hypoalbuminemia, 4 hypokalaemia, 1 hyponatraemia, 3 abdominal pain, 2 **constipation**, 13 **diarrhoea**, 1 intussusception, 4 **nausea**, 1 small intestinal obstruction, 2 stomatitis, 14 **vomiting**, 5 anorexia, 4 asthenia, 1 pain, 1 **weight decreased**, 15 anaemia, 9 leukopenia, 6 lymphopenia, 25 **neutropenia**, 1 cholestasis, 1 gamma-glutamyltransferase increased, 7 transaminases increased, 1 device related infection, 1 bacterial infection, 2 clostridium difficile colitis, 12 **FN**, 1 infection nos, 1 UTI, 1 wound infection, 3 dehydration, 1 musculoskeletal pain, 2 headache, 4 peripheral neuropathy, 2 syncope, 1 anxiety, 1 dyspnoea, 1 alopecia, 1 radiodermatitis, 1 rash.<br>G4 AEs: 1 **diarrhoea**, 1 anorexia, 1 anaemia, 2 leukopenia, 4 lymphopenia, 21 **neutropenia**, 1 **thrombocytopenia**, 1 fungal infection, 1 sepsis, 1 hemiplegia, 1 seizure. |
| Vincristine, Irinotecan, Temozolomide | | 58(58) | | 157 | 35 | 1P had G3 drug fever; 1P had G3 epilepsy & G3 depressed level of consciousness; 1P had G3 fever, G3 spasticity & G3 increase aspartate aminotransferase level. 0 G4 reported. None deemed to be related to peptide vaccine. No G2/3/4 toxicities reported in the RMS progressed P |
| Metronomic - thalidomide, celecoxib, alternating etoposide/cyclophosphamide | Pramanik, 2017[86,251] | 56 (3 RMS under 18 years) | | | | 31E G3-4 toxicities<br>In the metronomic group: 11E G3-4 anaemia, 6E G3-4 **neutropenia**, 6E G3-4 **thrombocytopenia**, 5E G3-4 febrile neutropenia, 3E G3-4 oral **mucositis**<br>8P required dose reductions & 9P had dose delays<br>6P received GCSF & 11 received antibiotics |
| Best supportive care | | 52 (5 RMS under 18 years) | | | | 4E G3-4 toxicities<br>In the placebo group: 4E G3-4 anaemia<br>0P required dose reductions but 2P had dose delays.<br>0P received GCSF or antibiotics |
| **Vaccines** | | | | | | |
| Dendritic Cell Vaccine + Decitabine | Krishnadas, 2015[65] | 10 (1) | | 2 | 4 | Based on table: G4 **Neutropenia** (n = 3), G3 **neutropenia** (1), G3 increase ALT (1), G4 Myelotoxicity (1). Based on text: Major DLT included reversible myelosuppression (**ANC<500/µl**), managed with dose reductions in DAC & the use of GCSF. 5P - transient myelosuppression (4P - G4 myelosuppression (**ANC<500**), & 1P G3 myelosuppression) 3 received growth factor support & 2 experienced treatment delays. |
| Glypican-3-derived peptide vaccine therapy | Tsuchiya, 2018[121] | 18 (1 progressive RMS) | 0 | 6E in 3P | 0 | 1P had G3 drug fever; 1P had G3 epilepsy & G3 depressed level of consciousness; 1P had G3 fever, G3 spasticity & G3 increase AST level. 0 G4 reported. None deemed to be related to peptide vaccine. No G2/3/4 toxicities reported in the RMS progressed P |
| NCCV Cocktail-1 vaccine | Akazawa, 2019[19] | 12 (3) | | 4 | 0 | 1 G3 toxicity (ALT) judged to be associated with vaccine. P had comorbidity (fatty liver disease). Other 3AEs were back pain, **thrombocytopenia** or anaemia. |
| Personalised Peptide Vaccine | Oda, 2020[119] | 4 (1) | | | | No severe personalised peptide vaccine-related AEs. |
| Seneca Valley Virus (NTX-010) ± | Burke, 2015[30] | 18 (number of RMS | 1 | All doses: | All doses: | DLT: Pain initially reported as G2, then as G3 pain requiring analgesics (in part A). Non-DLT, non-hematologic toxicities occurred in at least 10% of the evaluableP & at least possibly attributable to NTX-010 |

| Intervention (refs) | Comments | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| cyclophosphamide | | unclear) | | 21 (C1), 4 (post documented viral clearance C) | 3 (C1), 1 (post documented viral clearance C) | PART A<br>- NTX-010 DL1 (n=6) - C1: Lymphocyte count decreased (2 G3), neutrophil (1 G3, 1 G4), WBC decrease (1 G3).<br>-NTX-010 DL2 (n=3)- C1: Lymphocyte count decreased (1 G3). Post documented clearance C: lymphocyte count decreased (2 G3), Platelet count decreased (1 G4).<br>-NTX-010 DL3 (n=3)- C1: Neutrophil count decreased (1 G3), Post documented clearance C: 1 G3 lymphocyte count decreased, 1 G3 WBC count decreased.<br>PART B<br>NTX-010 DL3 (10e11) & cyclophosphamide (n=6). C1: anaemia (2 G3), Lymphocyte count decreased (2 G3, 2 G4), Neutrophil count decreased (4 G3), Platelet count decreased (1 G3), WBC decreased (3 G3), ALT increased (1 G3), nausea (1 G3), vomiting (1 G3). |
| WT1 peptide vaccination | Sawada, 2016[132] | NR | | 4 | 0 | 13/26P did not complete the 12 vaccinations mainly due to PD/relapse or GvHD in 1 case.<br>All P showed local reactions to injection sites such as pain, redness, swelling & itching, but these were all tolerable.<br>1P (non-RMS) developed skin acute GvHD which was successfully treated, but they later developed gut GvHD followed by lethal thrombotic microangiopathy.<br>G3 AEs: 1 leukopenia, 1 neutropenia, 1 increases in ALT, 1 proteinuria |

AE = adverse event; ALT = alanine aminotransferase; AMORE = Ablative surgery, Moulage technique brachytherapy & surgical Reconstruction; ANC = absolute neutrophil count; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; C = cycle(s); DL = dose level; DLT = dose limiting toxicity; E = event(s)/episode(s); EVE = etoposide, vincristine, epirubicin; FN = febrile neutropenia; G = grade, G-CSF = granulocyte-colony stimulating factor; GGT = gamma-g transpeptidase; GI = gastrointestinal; GVHD = graft-versus-host disease; HFS = hand-foot syndrome; HSCT = haematopoietic stem cell transplantation; IRN = irinotecan; IrVAC = irinotecan-vincristine-actinomycin D-cyclophosphamide; MSC = mesenchymal stromal cells; Non-DLT = non-dose limiting toxicity; NR = not reported; P = patients(s); PD = progressive disease; RMS = rhabdomyosarcoma; RPT = removal from protocol therapy; SAE = serious adverse event; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TACE = transarterial chemoembolization; TEAE = treatment emergent adverse event; UTI = urinary tract infection; VAC = vincristine-actinomycin D-cyclophosphamide; VETOPEC = vincristine, etoposide & dose-escalated cyclophosphamide; VIT = vincristine, irinotecan & temozolomide; VOD = veno-occlusive disease; VOIT = vincristine, oral irinotecan, temozolomide; WBC = white blood cell(s)

## **Table 5.** Clinical trial registry records

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| **Recruitment status: Not yet recruiting** | | | | | | | | |
| NCT04890093[206] | Vincristine and Temozolomide in Combination With PEN-866 for Adolescents and Young Adults With Relapsed or Refractory Solid Tumors | USA; Academic | 64 (E) | 23/03/2022 to 31/12/2026 | Vincristine + Temozolomide in combination with PEN-866 | Response rates, Adverse events (toxicity), Progression Free Survival, Maximum Tolerated Dose, Duration of Response, PKs | Relapsed, Refractory, Children, Young adults, Solid tumours (excluding CNS tumours and lymphoma). Phase 2 includes EWS or alveolar/embryonal RMS | 12-39 years |
| NCT04715191[191] | Interleukin-15 and -21 Armored Glypican-3-specific Chimeric Antigen Receptor Expressed in T Cells for Pediatric Solid Tumors | USA; Academic | 24 (E) | 03/07/2023 to 09/07/2041 | CAR-T cells (GPC3-CAR and the IL15 plus IL21) + Fludarabine and Cytoxan | Response rates, Dose Limiting Toxicities, Median T-cell persistence | Relapsed, Refractory, Children, Young adults, GPC3-positive solid tumours | 1-21 years |
| NCT04791228[171] | A Pilot Study of Thermodox and MR-HIFU for Treatment of Relapsed Solid Tumors | NR but sponsor/ contact in USA; Academic | 14 (E) | 01/06/2022 to 01/06/2024 | LTLD, followed by MR-HIFU | Response rates, Adverse events, Patient reported impact of pain on daily activities, Patient reported target tumour pain intensity | Relapsed, Refractory, All solid tumours, Children, Young adults, Tumour located in areas accessible to HIFU | 12 years and older |
| NCT04897321[172] | B7-H3-Specific Chimeric Antigen Receptor Autologous T-Cell Therapy for Pediatric Patients With Solid Tumors (3CAR) | USA; Academic | 32 (E) | 01/04/2022 to 01/03/2027 | Autologous B7-H3-CAR-T cells after lymphodepleting chemotherapy (fludarabine, cyclophosphamide & MESNA) | Response rates, Maximum Tolerated Dose (safety) | Relapsed, Refractory, All solid tumours, Children, Young adults, B7-H3 positive solid tumour | Up to 21 years |
| **Recruitment status: Recruiting** | | | | | | | | |
| NCT04625907 (ISRCTN45535982; 2018-000515-24-IE)[231] | FaR-RMS: An Overarching Study for Children and Adults With Frontline and Relapsed RhabdoMyoSarcoma (FaR-RMS) | UK, Australia, New Zealand, Denmark, Greece, Israel, Netherlands, Norway, Slovenia, Spain, Switzerland, Austria, Belgium, Canada, Croatia, Czech Republic, Finland, France, Germany, Ireland, Italy, Portugal, Slovakia, Sweden; Academic | 1672 (E) | 17/09/2020 to 01/06/2030* | Vincristine, Irinotecan & Temozolomide (Comparator: Vincristine & Irinotecan) | Response rates, Adverse events, Overall Survival, Event free survival, Duration of response, Dose limiting toxicity, Maximum Tolerated Dose | RMS only. Newly diagnosed and relapsed. | Ages vary according to cohort. For relapsed cohort: 6 months and older |
| NCT04730349[182] (2020-000854-85) | A Study of Bempegaldesleukin (BEMPEG: NKTR-214) in Combination With Nivolumab in Children, Adolescents and Young Adults With Recurrent or Treatment-resistant Cancer (PIVOT IO 020) | USA, Australia, France, Germany, Italy, Netherlands, Spain, UK; Pharmaceutical company | 234 (E) | 03/06/2021 to 29/10/2024 | Bempegaldesleukin with Nivolumab | Response rates, Adverse events, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, PKs | Relapsed, Refractory, All solid tumours, Children, Young adults, Curative treatments lacking, Leukaemia and lymphoma included | Part A: < 18 years; Part B: < 30 years old (for RMS Cohort) |
| NCT04544995[244] (2020- | A Phase 1, Multicentre, Open-Label, | France, Spain, UK; | 116 (E) | 06/10/2020 to | Dostarlimab & Niraparib | Response rates, Progression | Relapsed, Refractory, All solid | 6 months to 17 |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
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| 002359-39) | Dose-Escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Paediatric Patients with Recurrent or Refractory Solid Tumours | Pharmaceutical company | | 05/09/2030 | | Free Survival, Adverse events, Dose Limiting Toxicities, RP2D, Duration of response, PKs, Acceptability and palatability | tumours, Children, Young adults | years (inclusive) |
| NCT03838042[240] (2018-000127-14) | INFORM2 Study Uses Nivolumab and Entinostat in Children and Adolescents With High-risk Refractory Malignancies (INFORM2 NivEnt) | Australia, Austria, France, Germany, Netherlands, Sweden, Switzerland; Academic | 128 (E) | 26/07/2019 to 01/03/2023* | Nivolumab & Entinostat | Response rates, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, PKs, Time to Response, Duration of Response, Disease Control Rate | Relapsed, Refractory, All solid tumours, Children, Young adults, Progressive high risk but excludes low grade glioma or tumours with unknown malignant potential/bulky CNS tumour | 6-21 years (inclusive) |
| NCT01505569[165] | Auto Transplant for High Risk or Relapsed Solid or CNS Tumors | USA; Academic | 20 (E) | 20/10/2011 to 01/03/2024* | Ifosfamide, Etoposide, Mesna, G-CSF, Busulfan, Melphalan, Thiotepa, Autologous Stem Cell Transplant and Radiation | Overall Survival, Progression Free Survival, Treatment Related Mortality, Number of patients achieving transplant engraftment | Relapsed, All solid tumours, All ages, Metastatic at time of diagnosis and/or relapsed after therapy. Stable or non-progressive disease at enrolment | Up to 70 years |
| NCT04483778[168] | B7H3 CAR T Cell Immunotherapy for Recurrent/Refractory Solid Tumors in Children and Young Adults | USA; Academic | 68 (E) | 13/07/2020 to 01/12/2040* | Autologous CD4+ and CD8+ T-cells genetically modified to express an B7H3-specific CAR (Comparator: Autologous CD4+ and CD8+ T-cells genetically modified to a specific B7H3xCD19 CAR) | Adverse events, Maximum Tolerated Dose, Dose Limiting Toxicities, Persistence of T-cells, Feasibility | Relapsed, Refractory, All solid tumours, Children, Young adults, Excluding primary CNS solid tumours | Up to 26 years |
| NCT04530487[188] | Donor Stem Cell Transplant After Chemotherapy for the Treatment of Recurrent or Refractory High-Risk Solid Tumors in Pediatric and Adolescent-Young Adults | USA; Academic | 40 (E) | 19/08/2020 to 09/05/2025 | Conditioning Regimen (Thiotepa, Etoposide, Melphalan and Fludarabine Phosphate) followed by allogeneic hematopoietic stem cell transplantation. Followed by GVHD prophylaxis (tacrolimus or cyclosporine) | Adverse events, Overall Survival, Progression Free Survival, Transplant-related mortality, Incidence of relapse | Relapsed, Refractory, All solid tumours, Children, Young adults, Suitable HSCT donor | Up to 25 years |
| NCT03618381[166] | EGFR806 CAR T Cell Immunotherapy for Recurrent/Refractory Solid Tumors in Children and Young Adults | USA; Academic | 36 (E) | 18/06/2019 to 01/06/2038* | Autologous CD4+ and CD8+ T cells that have been genetically modified to express the EGFR 806CAR(2G) -EGFRt (Comparator: Autologous CD4+ and CD8+ T cells that have been genetically | Response rates, Adverse events, Maximum Tolerated Dose, Number Successfully Manufactured CAR-T cell products, Persistence of CAR-T cells | Relapsed, Refractory, Children, Young adults | 1-30 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
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| | | | | | modified to express the EGFR806CAR(2G)-EGFRt and CD19CAR(2G)-T2A-HER2tG) | | | |
| NCT03478462[226] | Dose Escalation Study of CLR 131 in Children, Adolescents, and Young Adults With Relapsed or Refractory Malignant Tumors Including But Not Limited to Neuroblastoma, Rhabdomyosarcoma, Ewings Sarcoma, and Osteosarcoma (CLOVER-2) | USA, Australia, Canada; Pharmaceutical company | 30 (E) | 30/04/2019 to 01/12/2024* | CLR 131 | Overall Survival, Progression Free Survival, Dose Limiting Toxicities, RP2D, Therapeutic Activity | Relapsed, Refractory, All solid tumours, Children, Young adults, Includes lymphoma | 2-25 years |
| NCT04377932[190] | Interleukin-15 Armored Glypican 3-specific Chimeric Antigen Receptor Expressed in T Cells for Pediatric Solid Tumors | USA; Academic | 24 (E) | 08/12/2021 to 01/02/2040 | GPC3-CAR & IL15 (AGAR T cells) with lymphodepleting chemotherapy (cyclophosphamide and fludarabine) | Response rates, Dose Limiting Toxicities, Median T-cell persistence | Relapsed, Refractory, All solid tumours, Children, Young adults, GPC3-positive tumours | 1-21 years |
| NCT01858168[210] | Phase I Study of Olaparib and Temozolomide for Ewings Sarcoma or Rhabdoomyosarcoma | USA; Academic | 93 (E) | 01/07/2013* to 01/07/2024* | Olaparib & Temozolomide (Comparator: Olaparib & Temozolomide & Irinotecan - not clear if this will be included for RMS patients) | Response rates, Adverse events, Maximum Tolerated Dose, poly (ADP-ribose) polymerase activity and tumour characteristics | Relapsed, Refractory, Young adults, Presence of Measurable Disease | 16 years and older |
| NCT04308330[189] | Vorinostat in Combination With Chemotherapy in Relapsed/Refractory Solid Tumors and CNS Malignancies (NYMC195) | USA; Academic | 30 (E) | 17/03/2017 to 17/12/2022 | Cycle 1: Vincristine, Temozolomide, Irinotecan & Cefixime<br>Cycle 2-12: same chemotherapy regimen above + Vorinostat | Response rates, Maximum Tolerated Dose | Relapsed, Refractory, All solid tumours, Children, Young adults | 1-30 years |
| NCT04901702[242] | Study of Onivyde With Talazoparib or Temozolomide in Children With Recurrent Solid Tumors and Ewing Sarcoma | USA, Canada; Academic (St Judes) and Pharmaceutical company (Ipsen & Pfizer) | 160 (E) | 09/06/2021 to 31/12/2025 | Nanoliposomal Irinotecan (nal-IRN, onivyde) plus Talazoparib (Comparator: Nanoliposomal Irinotecan plus Temozolomide on a different schedule) | Response rates, Adverse events, Progression Free Survival, RP2D, Duration of Response, Disease Control Rate, PKs | Relapsed, Refractory, All solid tumours, Children, Young adults, Excludes CNS tumours. Phase II for patients with EWS only | 12 months to 30 years |
| NCT02574728[143] | Sirolimus in Combination With Metronomic Chemotherapy in Children With Recurrent and/or Refractory Solid and CNS Tumors (AflacST1502) | USA; Academic (Emory University) and Charity (Cannonball Kids' Cancer Foundation and Hyundai Hope on Wheels) | 60 (E) | 01/06/2015* to 01/01/2024* | Sirolimus, Celecoxib, Etoposide, and Cyclophosphamide | Response rates, Adverse events | Relapsed, Refractory, All solid tumours, Children, Young adults | 12 months to 30 years |
| NCT03709680[174] | Study Of Palbociclib Combined With Chemotherapy In Pediatric Patients With Recurrent/Refractory Solid Tumors | USA; Academic (COG) and Pharmaceutical company | 167 (E) | 24/05/2019 to 26/09/2024 | Phase 1: Palbociclib, Temozolomide, Irinotecan, Topotecan & Cyclophosphamide | Response rates, Adverse events, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, | Relapsed, Refractory, Children, Young adults, Solid tumour (including CNS tumours but not lymphomas) | 2-20 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
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| | | | | | | Duration of Response, PKs | | |
| NCT03458728[156] | Safety, Tolerability, Efficacy and Pharmacokinetics of Copanlisib in Pediatric Patients | USA; Pharmaceutical company | 142 (E) | 30/04/2018 to 21/04/2027 | Phase 1: BAY806946 (Copanlisib)<br>Phase 2: BAY806946 (Copanlisib) RP2D will be defined by phase 1 study | Response rates, Adverse events, Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Dose Limiting Toxicities, Disease Control Rate, PKs, Duration of Response | Relapsed, Refractory, All solid tumours, Children, Young adults, Phase 2: only for neuroblastoma, osteosarcoma, RMS or EWS | 6 months to 21 years |
| NCT02048371[196] | SARC024: A Blanket Protocol to Study Oral Regorafenib in Patients With Selected Sarcoma Subtypes | USA; Non-profit organisation (Sarcoma Alliance for Research through Collaboration) | 150 (E) | 01/07/2014* to 01/02/2022* | Regorafenib | Response rates, Adverse events, Progression Free Survival | Relapsed, Children, Young adults, Fusion-positive alveolar RMS, or Embryonal RMS/fusion-negative alveolar RMS | 5 years and older |
| NCT02945800[200] | Nab-Paclitaxel and Gemcitabine for Recurrent/Refractory Sarcoma | USA; Academic | 72 (E) | 25/10/2016 to 01/12/2023* | Nab-Paclitaxel & Gemcitabine | Response rates, Adverse events, Progression Free Survival | Relapsed, Refractory, Soft-tissue sarcomas only, Children, Young adults | 3-30 years |
| NCT03507491[145] | Nab-paclitaxel in Combination With Gemcitabine for Pediatric Relapsed and Refractory Solid Tumors | USA; Academic | 24 (E) | 27/08/2018 to 01/12/2013* | Nab-Paclitaxel & Gemcitabine | Adverse events, Maximum Tolerated Dose, Anti-tumour activity of nab-paclitaxel | Relapsed, Refractory, All solid tumours, Children, Young adults, Newly diagnosed patients with malignancy. No CNS tumours included | 6 months to 30 years |
| NCT04299113[230] | Mocetinostat With Vinorelbine in Children, Adolescents & Young Adults With Refractory and/or Recurrent Rhabdomyosarcoma | USA; Academic (Jonsson Comprehensive Cancer centre) and Pharmaceutical company (Mirati Therapeutic and Phase One Foundation) | 38 (E) | 14/05/2020 to 01/12/2023* | Vinorelbine & Mocetinostat | Response rates, Adverse events, Maximum Tolerated Dose, Dose Limiting Toxicities, PKs, Disease control, Duration of response, progression free survival | Relapsed, Refractory, RMS only, Young adults, Also includes locally advanced & unresectable or metastatic | 13 years and older |
| NCT04213794[209] | Heated Intra-peritoneal Chemotherapy With Doxorubicin and Cisplatin for the Treatment of Resectable, Refractory, or Recurrent Pelvic and Abdominal Malignancies in Pediatric Patients, T.O.A.S.T. I.T. Study | USA; Academic | 43 (E) | 01/12/2019 to 30/01/2025 | Cytoreduction and Heated Intra-peritoneal Chemotherapy with Doxorubicin and Cisplatin and sodium thiosulfate | Adverse events, Overall Survival, Progression Free Survival, Length of Hospital Stay, Incidence of Mortality, Morbidity, Disease Free Survival | Relapsed, Refractory, Children, Young adults. | 1-25 years |
| NCT04238819[146] (2019-002931-27) | A Study of Abemaciclib (LY2835219) in Combination With Temozolomide and Irinotecan and Abemaciclib in Combination With Temozolomide in Children and Young Adult Participants With Solid Tumors | USA, Belgium, France, Germany, Italy, Japan, Spain; Pharmaceutical company | 60 (E) | 09/11/2020 to 21/12/2023 | Phase A: Abemaciclib + Irinotecan + Temozolomide<br>Phase B: Abemaciclib + Temozolomide | Response rates, Dose Limiting Toxicities, PKs, Acceptability Questionnaire, Duration of Response, Disease Control Rate, Clinical Benefit Rate | Relapsed, Refractory, All solid tumours (except lymphoma), Children, Young adults | Up to 18 years |
| NCT01661400[167] | Anti-Angiogenic Therapy Post Transplant (ASCR) for Pediatric Solid Tumors (ASCR) | USA; Academic | 20 (E) | 26/10/2012 to 23/11/2022 | Cyclophosphamide post-transplant (Comparator: Thalidomide | Response rates, Adverse events | All solid tumours (excluding lymphoma), Children, Young adults, Prior therapy | 6 months to 21 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
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| | | | | | post-transplant) | | permitted | |
| NCT02644460[157] | Abemaciclib in Children With DIPG or Recurrent/Refractory Solid Tumors (AflacST1501) | USA; Academic | 60 (E) | 01/02/2016* to 01/12/2022* | Abemaciclib | Adverse events, Maximum Tolerated Dose, PKs | Relapsed, Refractory, All solid tumours, Children, Young adults | 2-25 years |
| NCT02508038[161] | Alpha/Beta CD19+ Depleted Haploidentical Transplantation + Zometa for Pediatric Hematologic Malignancies and Solid Tumors | USA; Academic | 22 (E) | 12/02/2016 to 01/11/2025* | ATG, fludarabine, thiotepa and melphalan prior to transplant with a KIR/KIR ligand mismatched haploidentical donor peripheral blood stem cell graft depleted of TCR-αβ+ and CD19+ cells. Zoledronate | Incidence of GVHD, Graft failure, Immune reconstitution and performance of CliniMACs reagent system | Relapsed, Refractory, All solid tumours, Children, Young adults, Hematologic malignancy also included, Availability of an eligible haploidentical donor, Can have 1st complete remission but be high risk | 7 months to 21 years |
| NCT04236414 (2018-003355-38[232]) | Investigating Safety, Tolerability, Efficacy and PK of Olaparib in Paediatric Patients With Solid Tumours | USA, Australia, Canada, Denmark, France, Germany, Hungary, Israel, Italy, Republic of Korea, Poland, Russian Federation, Spain, Ukraine, UK; Pharmaceutical company | 30 (E) | 14/01/2020 to 30/12/2025 | Olaparib | Response rates, Adverse events, Dose Limiting Toxicities, PKs, Disease control rate, Duration of response | Relapsed, Refractory, Children, Young adults | 6 months to 18 years |
| NCT03155620[177] | Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders (The Pediatric MATCH Screening Trial) | USA, Puerto Rico; Academic | 1500 (E) | 24/07/2017 to 30/09/2027 | Ensartinib, Erdafitinib, Larotrectinib, Olaparib, Palbociclib, Samotolisib, Selpercatinib, Selumetinib Sulfate, Tazemetostat, Tipifarinb, Ulixertinib, Vemurafenib | Response rates, Adverse events, Progression Free Survival, Proportion of patients with actionable targets, PKs, Genomic outcomes | Relapsed, Refractory, All solid tumours, Children, Young adults | 12 months to 21 years |
| NCT04284774[186] | Tipifarnib for the Treatment of Advanced Solid Tumors, Lymphoma, or Histiocytic Disorders With HRAS Gene Alterations, a Pediatric MATCH Treatment Trial | USA, Puerto Rico; Academic | 49 (E) | 13/07/2020 to 30/09/2027 | Tipifarnib | Response rates, Adverse events, Progression Free Survival, Biomarker analysis, Change in tumour genomics | Relapsed, Refractory, Children, Young adults, Advanced solid tumours with radiographically measurable disease. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621M based on the presence of an actionable mutation | 12 months to 21 years |
| NCT03526250[183] | Palbociclib in Treating Patients With Relapsed or Refractory Rb Positive Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders | USA, Puerto Rico; Academic | 49 (E) | 25/06/2018 to 30/06/2025 | Palbociclib | Response rates, Adverse events, Progression Free Survival, PKs, Tumour genomic changes | Relapsed, Refractory, Children, Young adults, Patient must have enrolled onto APEC1621SC and must | 12 months to 21 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
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| | With Activating Alterations in Cell Cycle Genes (A Pediatric MATCH Treatment Trial) | | | | | | have been given a treatment assignment to MATCH to APEC1621I based on the presence of an actionable mutation. Positive Rb expression by immunohistochemistry is required for study enrolment | |
| NCT04195555[185] | Ivosidenib in Treating Patients With Advanced Solid Tumors, Lymphoma, or Histiocytic Disorders With IDH1 Mutations (A Pediatric MATCH Treatment Trial) | USA, Puerto Rico; Academic | 49 (E) | 08/06/2020 to 31/12/2025 | Ivosidenib | Response rates, Adverse events, Progression Free Survival, Biomarker analysis, PKs, Change in tumour genomics | Relapsed, Refractory, All solid tumours, Children, Young adults, Presence of an actionable mutation as defined in APEC1621SC. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621K based on the presence of an actionable mutation | 12 months to 21 years |
| NCT03213704[180] | Larotrectinib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With NTRK Fusions (A Pediatric MATCH Treatment Trial) | USA, Puerto Rico; Academic | 49 (E) | 24/07/2017 to 30/09/2024 | Larotrectinib sulfate | Response rates, Adverse events, Progression Free Survival, PKs, Detect NTRK fusions in DNA in plasma | Relapsed, Refractory, All solid tumours, Children, Young adults. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to Molecular Analysis for Therapy Choice (MATCH) to APEC1621A based on the presence of an actionable mutation as defined in APEC1621SC | 12 months to 21 years |
| NCT02013336[199] | Phase 1 Dose-escalating Study of MM-398 (Irinotecan Sucrosofate Liposome Injection) Plus Intravenous Cyclophosphamide in Recurrent or Refractory Pediatric Solid Tumors | USA; Academic | 30 (E) | 01/12/2013* to 01/12/2023* | MM-398 (Irinotecan Sucrosofate) + cyclophosphamide | Maximum Tolerated Dose, Dose Limiting Toxicities, PKs | Relapsed, Refractory, Children, Young adults, EWS, RMS, neuroblastoma, or osteosarcoma | 12 months to 20 years |
| NCT04337177[195] | Flavored, Oral Irinotecan VAL-413 (Orotecan®) Given With Temozolomide for Treatment of Recurrent Pediatric Solid Tumors | USA; Pharmaceutical company | 20 (E) | 25/10/2021 to 01/11/2022* | Irinotecan & Temozolomide | Response rates, Adverse events, RP2D, PKs, Palatability | Relapsed, All solid tumours, Children, Young adults, No known curative therapy available. Patients who previously relapsed when on temozolomide or irinotecan | 1-30 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
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| | | | | | | | excluded | |
| NCT02520713[248] | The iCat2, GAIN (Genomic Assessment Informs Novel Therapy) Consortium Study | USA; Academic | 825 (E) | 01/10/2015* to 01/10/2025* | Targeted therapy matched to an individualised cancer therapy recommendation based on genetic testing and sequencing | Response rates, Overall Survival, Progression Free Survival, Psychological wellbeing, Molecular alterations | Relapsed, Refractory, Children, Young adults, Solid malignancy excluding brain tumours and lymphoma. Newly diagnosed high risk disease and rare tumours with unclear diagnosis | Up to 30 years |
| NCT01582191[245] | Vandetanib and Everolimus in Treating Patients With Advanced or Metastatic Cancer | USA; Academic | 174 (E) | 14/05/2012 to 31/05/2026 | Vandetanib & Everolimus | Response rates, Maximum Tolerated Dose, PKs | Relapsed, Refractory, All ages, Advanced or metastatic cancer | All ages |
| NCT01804634[142] | Reduced Intensity Haploidentical BMT for High Risk Solid Tumors **Full-text paper with a subset of patients from this trial has also been extracted (Llosa 2017)** | USA; Academic | 60 (E) | 27/03/2013 to 01/01/2025* | Reduced intensity chemotherapy (fludarabine and melphalan), haploidentical bone marrow, post-transplant cyclophosphamide and shortened duration tacrolimus | Adverse events, Overall Survival, Progression Free Survival, Relapse, Non-relapse mortality, GVHD | All solid tumours, Children, Young adults, High-risk tumours (inc. stage 4 RMS). Patients expected to have received upfront standard of care therapy. Presence of a suitable related HLA-haploidentical bone marrow donor | 1-50 years |
| NCT02076906[181] | MR-guided High Intensity Focused Ultrasound (HIFU) on Pediatric Solid Tumors | USA; Academic | 14 (E) | 01/04/2014* to 01/06/2022 | MR-HIFU ablative therapy | Response rates, Adverse events, Immune Markers, Patient Reported Outcomes/quality of life | Relapsed, Refractory, All solid tumours, Children, Young adults, Target lesion(s) must be located in bone or soft tissue in close proximity to bone | Up to 30 years old |
| NCT02536183[169] | A Phase I Study of Lyso-thermosensitive Liposomal Doxorubicin and MR-HIFU for Pediatric Refractory Solid Tumors | USA; Academic | 34 (E) | 01/10/2016* to 01/10/2021* | Part A: LTLD + MR-HIFU ablation<br>Part B: LTLD at dose determined from Part A + MR-HIFU | Response rates, Adverse events, Maximum Tolerated Dose, Feasibility, Social Impact of Treatment, PKs | Relapsed, Refractory, All solid tumours, Children, Young adults, Patient must have at least one tumour located in areas accessible to HIFU | Up to 30 years |
| NCT03455140 (ISRCTN21727048[228]) | A Study Evaluating the Safety and Activity of Pegylated Recombinant Human Arginase (BCT-100) (PARC) | Australia, UK; Academic | 64 (E) | 28/08/2018 to 01/04/2021* | PEG- BCT-100 | Response rates, Adverse events, Overall Survival, Progression Free Survival, RP2D, PKs | Relapsed, Refractory, Children, Young adults, Evidence of disease progression; Includes leukemia, neuroblastoma, sarcoma or High Grade Glioma | 1-25 years |
| **Recruitment status: Ongoing** | | | | | | | | |
| 2020-003733-38[243] | TEMOkids study (ORP-TMZ-I- b): A Population pharmacokinetic, | France, Germany, Netherlands, Spain, UK; | 40 (E) | NR | Temozolomide | Response rates, Adverse events, PKs, Acceptability | Children, Young adults, Glioblastoma, | 1 to less than 18 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
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| | acceptability and safety study for KIMOZO, a paediatric oral suspension of temozolomide | Pharmaceutical company | | | | | Neuroblastoma, RMS and Medulloblastoma | |
| 2019-000987-80[235] | COTESARC - A multicentre Phase I-II study evaluating the combination of a MEK inhibitor and a PDL1 inhibitor in pediatric and adult patients with locally advanced and/or metastatic soft tissue sarcoma | France; Academic | 80 (E) | NR | Atezolizumab & Cobimetinib | Response rates, Adverse events, Overall Survival, Progression Free Survival, Duration of Response | Soft-tissue sarcomas only, All ages | Paediatric Cohort: 6 months to 11 years. Adult Cohort: 12+ years |
| **Recruitment status: Active, not yet recruiting** | | | | | | | | |
| NCT02639546 (2014-004685-25[239]) | Safety and Pharmacokinetics of Cobimetinib in Pediatric and Young Adult Participants With Previously Treated Solid Tumors (iMATRIXcobi) | USA, France, Germany, Israel, Italy, Spain, UK; Pharmaceutical company | 56 (A) | 20/05/2016 to 21/02/2023 | Cobimetinib | Response rates, Adverse events, Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Dose Limiting Toxicities, RP2D, Duration of response, PKs | Relapsed, Refractory, Children, Young adults, Tumour with known or expected RAS/RAF/MEK/ERK pathway involvement | Dose-escalation is 6 months to 18 years; Expansion cohort is 6 months to 30 years |
| NCT00788125[149] | Dasatinib, Ifosfamide, Carboplatin, and Etoposide in Treating Young Patients With Metastatic or Recurrent Malignant Solid Tumors | USA; Academic | 143 (E) | 03/09/2008 to 31/12/2021 | Dasatinib with Ifosfamide, Carboplatin, Etoposide | Response rates, Adverse events, Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Exploratory correlative studies | Relapsed, Refractory, Solid tumours (excluding CNS tumours), Children, Young adults | 1-25 years |
| NCT00445965[154] | Iodine I 131 Monoclonal Antibody 3F8 in Treating Patients With Central Nervous System Cancer or Leptomeningeal Cancer | USA; Academic | 78 (A) | 01/01/2006* to 01/01/2023* | 131I-3F8 (10mCi intrathecal 131I-3F8 per week). Pre-medicated with dexamethasone, liothyronine and SSKI, acetaminophen and diphenhydramine | Response rates, Adverse events, Overall Survival | Refractory, All ages, Tumours known to express GD2, Leptomeningeal disease | All ages |
| NCT02162732[163] | Molecular-Guided Therapy for Childhood Cancer | USA, Lebanon; Academic | 184 (A) | 01/06/2014* to 01/06/2026* | Guided therapy (combination of therapies with four agents). Actual guided therapies used not clearly described | Response rates, Adverse events, Progression Free Survival, Duration of Response, Feasibility of using tumour samples to assess genomic sequencing to make treatment decisions for children with cancer, PKs | Relapsed, Refractory, Children, Young adults | 13 months to 21 years |
| NCT03441360[212] (2018-001282-17) | Study to Assess Safety and Preliminary Activity of Eribulin Mesylate in Pediatric Participants With Relapsed/Refractory Rhabdomyosarcoma (RMS), Non-rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS) and Ewing Sarcoma | USA; Pharmaceutical company | 23 (A) | 17/04/2018 to 31/12/2021 | Eribulin Mesylate | Response rates, Adverse events, Overall Survival, Progression Free Survival, Duration of response, Change in Lansky play performance scale, Change in Karnofsky | Relapsed, Refractory, Soft-tissue sarcomas only, Children, Young adults | 12 months to 18 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | (EWS) | | | | | performance status | | |
| NCT02239861[213] | TAA-Specific CTLS for Solid Tumors (TACTASOM) | USA; Academic | 16 (A) | 01/04/2015* to 01/12/2024* | Tumour Associated Antigen (TAA)-Specific Cytotoxic T-Lymphocytes (CTLs) | Response rates, Dose Limiting Toxicities | Relapsed, Refractory, All solid tumours, Children, Young adults, Express the following antigens: PRAME, SSX2, MAGEA4, NY-ESO1-1 and/or Survivin | 2-80 years |
| NCT00638898[176] | Busulfan, Melphalan, Topotecan Hydrochloride, and a Stem Cell Transplant in Treating Patients With Newly Diagnosed or Relapsed Solid Tumor | USA; Academic | 25 (E) | 26/02/2007 to 30/12/2022 | High-dose chemotherapy (Topotecan hydrochloride, Busulfan & Melphalan) with Autologous HSCT | Overall Survival, Progression Free Survival, Treatment Feasibility, PKs and incidence of myeloid and platelet engraftment | All solid tumours, Children, Young adults, Either relapsed who achieved at least PR to prior treatment, or newly diagnosed patients for poor risk solid tumours | 6 months to 40 years |
| NCT04095221[216] | A Study of the Drugs Prexasertib, Irinotecan, and Temozolomide in People With Desmoplastic Small Round Cell Tumor and Rhabdomyosarcoma | USA; Academic | 21 (A) | 17/09/2019 to 01/09/2022* | Prexasertib, Irinotecan & Temozolomide | Response rates, RP2D | Relapsed, Refractory, Children, Young adults, RMS or desmoplastic small round cell tumour | 12 months and older |
| NCT03213665[159] | Tazemetostat in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With EZH2, SMARCB1, or SMARCA4 Gene Mutations (A Pediatric MATCH Treatment Trial) | USA, Puerto Rico; Academic | 49 (E) | 24/07/2017 to 31/03/2022 | Tazemetostat | Response rates, Progression Free Survival, Biomarkers predictors of response, Tumour genomic changes | Relapsed, Refractory, Children, Young adults, Presence of an actionable mutation, Radiographically measurable disease at the time of study enrolment. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to Molecular Analysis for Therapy Choice (MATCH) to APEC1621C based on the presence of an actionable mutation. | 12 months to 21 years |
| NCT03698994[184] | Ulixertinib in Treating Patients With Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With MAPK Pathway Mutations (A Pediatric MATCH Treatment Trial) | USA, Puerto Rico; Academic | 49 (E) | 01/10/2018 to 31/03/2022 | Ulixertinib | Response rates, Adverse events, Progression Free Survival, PKs, Biomarkers predicting response, Changes in tumour genomics | Relapsed, Refractory, Children, Young adults, Presence of an actionable mutation. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621J based on the presence of an actionable mutation. | 12 months to 21 years |
| NCT03220035[164] | Vemurafenib in Treating Patients With Relapsed or Refractory Advanced Solid | USA, Puerto Rico; Academic | 49 (E) | 24/07/2017 to 31/12/2023 | Vemurafenib | Response rates, Adverse events, Progression Free | Relapsed, Refractory, Children, Young adults, BRAF | 12 months to 21 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With BRAF V600 Mutations (A Pediatric MATCH Treatment Trial) | | | | | Survival, Changes in tumour genomics | V600 mutation, Radiographically measurable disease at the time of study enrolment. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to Molecular Analysis for Therapy Choice (MATCH) to APEC1621G based on the presence of a BRAF V600 mutation | |
| NCT03233204[178] | Olaparib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With Defects in DNA Damage Repair Genes (A Pediatric MATCH Treatment Trial) | USA, Puerto Rico; Academic | 49 (E) | 24/07/2017 to 30/09/2024 | Olaparib | Response rates, Adverse events, Progression Free Survival, PKs, Tumour genomic profile | Relapsed, Refractory, All solid tumours, Children, Young adults, Presence of an actionable mutation. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to Molecular Analysis for Therapy Choice (MATCH) to APEC1621H based on the presence of an actionable mutation. | 12 months to 21 years |
| NCT02085148[147] | A Phase I Dose Finding Study in Children With Solid Tumors Recurrent or Refractory to Standard Therapy **Full-text paper with a subset of patients from dose escalation stage of this trial has also been extracted (Geoerger 2021)** **Conference abstract paper with a subset of patients from full trial has also been extracted (Casanova 2020)** | France, Italy, Spain, UK; Pharmaceutical company | 62 (A) | 11/04/2014 to 28/12/2024 | Vincristine, Irinotecan & Regorafenib | Response rates, Adverse events, Overall Survival, Maximum Tolerated Dose, RP2D, Time to progression, PKs | Relapsed, Refractory, Children, Young adults, Dose escalation phase was for all solid malignancies including CNS tumours. Dose expansion was RMS or other solid malignancies (EWS, hepatoblastoma, neuroblastoma, Wilms tumour) in which treatment with vincristine/irinotecan is considered backbone chemotherapy at relapse | 6 months to < 18 years |
| NCT00089245[153] | Radiolabeled Monoclonal Antibody Therapy in Treating Patients With Refractory, Recurrent, or Advanced CNS or Leptomeningeal Cancer | USA; Pharmaceutical company | 120 (E) | 01/07/2004* to 01/07/2025 | Radiolabeled Monoclonal Antibody Therapy - 2 mCi 131I-Omburtamab | Adverse events | Relapsed, Refractory, All ages, 8H8 reactive malignancy. CNS/Leptomeningeal disease which is refractory or recurrent brain tumours with | All ages |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | a predilection for leptomeningeal dissemination | |
| NCT02100891[198] | Phase 2 STIR Trial: Haploidentical Transplant and Donor Natural Killer Cells for Solid Tumors (STIR) | USA; Academic | 15 (A) | 01/03/2014* to 31/12/2021 | HLA-haploidentical bone marrow transplant preceded by reduced-intensity chemotherapy and radiation therapy followed by donor NK cells | Overall Survival, Disease-control rate, Non-relapse mortality | Relapsed, Refractory, All ages, Sarcoma, CNS tumours and Neuroblastoma. Only subjects who are not appropriate candidates for autologous or HLA-matched sibling HSCT | All ages |
| NCT02867592[192] | Cabozantinib-S-Malate in Treating Younger Patients With Recurrent, Refractory, or Newly Diagnosed Sarcomas, Wilms Tumor, or Other Rare Tumors | USA; Academic | 109 (A) | 08/05/2017 to 01/07/2022 | Cabozantinib s-malate | Response rates, Adverse events, Progression Free Survival, PKs | Relapsed, Refractory, All solid tumours, Children, Young adults, Includes newly diagnosed disease with no known curative therapy. Tumours included: EWS, RMS, NRSTS, osteosarcoma, Wilms, rare tumours (medullary thyroid carcinoma, renal cell carcinoma, hepatocellular carcinoma, hepatoblastoma, adrenocortical carcinoma) and any paediatric solid tumours with known molecular alterations in the targets of XL184 | 2-30 years |
| NCT03245151[144] | Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including Central Nervous System Tumors | USA, Canada; Pharmaceutical company | 120 (E) | 16/11/2017 to 31/05/2022 | Phase 1: Lenvatinib & Everolimus<br>Phase 2: RP2D of Lenvatinib & Everolimus | Response rates, Adverse events, Maximum Tolerated Dose, RP2D, Disease Control Rate, Clinical Benefit Rate, PKs | Relapsed, Refractory, Children, Young adults, Solid tumours (Phase 1), RMS cohort (Phase 2) | 2-21 years |
| JPRN-UMIN000003002[221] | Randomized phase II study of two cross-over sequences comprising outpatient chemotherapies, vinorelbine/cyclophosphamide (R1) and temozolomide/etoposide (R2), for relapsed or refractory solid tumors in children and young adults | Japan; Group for "Cross-over rPII of outpatient chemotherapies for refractory pediatric solid tumors" | 45 (E) | 01/01/2010 to NR | Vinorelbine and Cyclophosphamide (Comparator: Temozolomide and Etoposide) | Response rates, Adverse events, Overall Survival, Progression Free Survival, Time to treatment failure, Quality of life, Number of days attending school/work and number of days not attending hospital | Relapsed, Refractory, All solid tumours, Children, Young adults, Neuroblastoma, RMS, undifferentiated sarcoma, Ewing's sarcoma family of tumours, retinoblastoma, Wilm's tumour, hepatoblastoma, osteosarcoma, other bone or soft tissue sarcoma, primary CNS tumours, germ cell tumours | 3-30 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| **Recruitment status: Completed** | | | | | | | | |
| JPRN-UMIN000017453[224] | Clinical trial to evaluate the safety of Temsirolimus combined with Vincristine and Irinotecan in children with recurrent/refractory solid tumors | Japan; Academic | 6 (E) | 09/07/2013 to 30/04/2015 | Vincristine, Irinotecan & Temsirolimus | Response rates, Adverse events, Dose Limiting Toxicities | Relapsed, Refractory, All solid tumours, Children, Young adults | 1 day old to 18 years |
| NCT03041701[217] | Insulin-like Growth Factor 1 Receptor (IGF-1R) Antibody AMG479 (Ganitumab) in Combination With the Src Family Kinase (SFK) Inhibitor Dasatinib in People With Embryonal and Alveolar Rhabdomyosarcoma | USA; Academic | 14 (A) | 07/07/2017 to 16/10/2021 | Phase 1: Ganitumab & Dasatinib<br>Phase 2: Ganitumab at the maximum tolerated dose & Dasatinib | Response rates, Adverse events, Progression Free Survival, Maximum Tolerated Dose | RMS only, Children, Young adults, No curative or life prolonging treatments available | 2 years and older |
| NCT00055939[211] | Exatecan Mesylate in Treating Children With Relapsed or Refractory Rhabdomyosarcoma | USA, Canada; Pharmaceutical company | 13-27 (E) | 01/01/2003* to 01/04/2006* | Exatecan mesylate | Response rates, Adverse events, Overall Survival, Time to progression, PKs, Pain | Relapsed, Refractory, RMS only, All ages | All ages |
| NCT00002543[201] | Gallium Nitrate in Treating Children With Brain Tumor, Neuroblastoma, Rhabdomyosarcoma, Non-Hodgkin's Lymphoma, or Refractory Solid Tumors | USA; Academic | 3 (E) | 01/02/1995* to 01/10/2004* | Gallium Nitrate | Adverse events | Refractory, All solid tumours, Children, Young adults | Up to 21 years |
| NCT00006234[203] | Holmium Ho 166 DOTMP Followed by Peripheral Stem Cell Transplantation in Treating Patients With Metastatic Ewing's Sarcoma or Rhabdomyosarcoma That Has Spread to the Bone | USA; Academic | 4 (E) | 01/11/2001* to 01/03/2006* | Holmium Ho 166 DOTMP. Autologous peripheral blood stem cells | Adverse events, Dosimetry, PKs, Change in tumour cell content | Refractory, Children, Young adults, EWS or RMS, Responsive to conventional therapy with osseous metastases at diagnosis | 12 years and older |
| NCT00019630[155] | Liposomal Doxorubicin in Treating Children With Refractory Solid Tumors | USA; Academic | 21-36 (E) | 01/07/1999 to NR | Doxorubicin HCl liposome (Lipodox) | Adverse events, Dose Limiting Toxicities, Feasibility, Maximum Tolerated Dose, PKs | Refractory, All solid tumours, Children, Young adults | Up to 21 years |
| NCT00007813[150] | Peripheral Stem Cell Transplantation Plus Chemotherapy in Treating Patients With Malignant Solid Tumors | USA; Academic (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins) and Pharmaceutical company (Amgen, Baxter Healthcare Corporation, Nexell Therapeutics Inc) | 21 (A) | 31/05/1997 to 01/02/2005 | High-dose Carboplatin & Etoposide + stem cell rescue | Response rates, Adverse events, Feasibility of leukapheresis, Activity of CD34+ PBSC (multiple outcomes) | All solid tumours, Children, Young adults, Metastatic disease or has failed at least first-line therapy - recurrent | Up to 35 years |
| NCT00005952[148] | Temozolomide Plus Peripheral Stem Cell Transplantation in Treating Children With Newly Diagnosed Malignant Glioma or Recurrent CNS or Other Solid Tumors | USA; Academic | 30 (E) | 01/08/2000* to 01/11/2005* | Temozolomide + stem cell rescue | Response rates, Adverse events, Disease-free survival, Engraftment related to autologous marrow or PBSC | All solid tumours, Children, Young adults, Recurrent, Newly diagnosed malignant glioma also included | 18 years and under |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| JPRN-UMIN000030767 | A study of haploidentical transplantation with post-transplant cyclophosphamide and prophylactic donor lymphocyte infusions | Japan; Academic | 8 (E) | 01/01/2018 to 03/12/2018 | Haploidentical HSCT | Response rates, Adverse events, Overall Survival, Engraftment, Acute and chronic GVHD, Complete chimerism, event free survival, Treatment related mortality (at 100 days), Relapse rate at 1 year, Relapse rate at 100 days. | Children, Young adults, AML, ALL, MDS, NHL, CML Neuroblastoma, RMS, EWS | 1 month to 192 months old (up to 16 years) |
| JPRN-UMIN000020144[227] | Phase I/II Study of Irinotecan and Gemcitabine in Pediatric, adolescent and Young Adult Patients with Relapsed or Refractory Solid Tumors | Japan; Group for "combination chemotherapies for refractory Adolescent and Young Adult solid tumors" | 40 (E) | 11/12/2015 to 05/02/2019 | Irinotecan & Gemcitabine | Adverse events, Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Tolerability of 4+ courses chemo at recommended dose | Relapsed, Refractory, All solid tumours, Children, Young adults | 1-40 years old |
| JPRN-UMIN000001037[220] | Phase I/II Study of Topotecan and Ifosfamide in Pediatric Patients with Relapsed or Refractory Solid Tumors | Japan; Group for "making evidence for the drugs which are available in clinical practice in Europe and USA but not available in Japan" | 40 (E) | 01/02/2008 to NR | Topotecan & Ifosfamide | Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Dose Limiting Toxicities, Probability of patients who can tolerate more than 4 courses of chemo at the recommended dosage | Relapsed, Refractory, All solid tumours, Children, Young adults, Neuroblastoma, RMS, undifferentiated sarcoma, Ewing's sarcoma family of tumours, retinoblastoma, Wilm's tumour, hepatoblastoma, osteosarcoma, other bone or tissue malignant tumour, medulloblastoma. | 1-30 years |
| NCT02982941[193] | Enoblituzumab (MGA271) in Children With B7-H3-expressing Solid Tumors | USA; Pharmaceutical company | 25 (A) | 01/12/2016* to 22/05/2019 | Enoblituzumab | Response rates, Adverse events, PKs, Proportion of patients who develop antibodies | Relapsed, Refractory, All solid tumours, Children, Young adults, B7-H3 expression | 1-35 years |
| NCT03139331[246] | PAZIT Study for Children and Young Adults With Relapsed or Refractory Sarcoma | USA; Academic | 16 (A) | 06/06/2017 to 30/09/2020 | Pazopanib, Irinotecan and Temozolomide (PAZIT) | Response rates, Adverse events, Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Dose Limiting Toxicities | Relapsed, Refractory, Children, Young adults, EWS/PNET, osteosarcoma, RMS, NRSTS, desmoplastic small round cell tumour. Patients who previously received irinotecan and/or temozolomide will be eligible as long as they didn't progress while receiving these treatments | 6-30 years |
| NCT00436657[175] | Continuous Hyperthermic Peritoneal Perfusion (CHPP) With Cisplatin for | USA; Academic | 10 (A) | 01/02/2007* to 01/04/2011* | Abdominal surgery & Cisplatin | Maximum Tolerated Dose | Relapsed, Refractory, Children, Young adults, | 3-18 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | Children With Peritoneal Cancer | | | | | | Peritoneal or retroperitoneal tumour | |
| NCT03245450[202] | Study Evaluating the Safety and Efficacy of Eribulin Mesilate in Combination With Irinotecan Hydrochloride in Children With Refractory or Recurrent Solid Tumors | France, Germany, Greece, Italy, Poland, Spain, Switzerland, UK; Pharmaceutical company | 40 (A) | 22/02/2018 to 16/05/2021 | Eribulin mesilate & Irinotecan hydrochloride | Response rates, Adverse events, Progression Free Survival, Maximum Tolerated Dose, RP2D, PKs, Clinical benefit rate | Relapsed, Refractory, All solid tumours, Children, Young adults | 6 months to 25 years |
| NCT02748135[208] | A Study of TB-403 in Pediatric Subjects With Relapsed or Refractory Medulloblastoma | USA; Academic (Beat Childhood Cancer) and Pharmaceutical company (Oncurious) | 18 (A) | 01/05/2016* to 06/10/2020 | TB-403 | Maximum Tolerated Dose, Dose Limiting Toxicities, PKs | Relapsed, Refractory, Children, Young adults, Medulloblastoma, Neuroblastoma, EWS or Alveolar RMS | 6 months to 18 years |
| NCT02390843[162] | Simvastatin With Topotecan and Cyclophosphamide in Relapsed and/or Refractory Pediatric Solid and CNS Tumors (AflacST1402) | USA; Academic | 13 (A) | 01/02/2015* to 22/09/2019 | Simvastatin, Topotecan & Cyclophosphamide | Response rates, Adverse events, Maximum Tolerated Dose, Dose Limiting Toxicities, Cholesterol and biomarker levels | Relapsed, Refractory, All solid tumours, Children, Young adults | 1-29 years |
| NCT00001564[205] | A Pilot Study of Tumor-Specific Peptide Vaccination and IL-2 With or Without Autologous T Cell Transplantation in Recurrent Pediatric Sarcomas | USA; Academic | 30 (A) | 23/12/1996 to 25/10/2007 | Peptide vaccine with IL-2 therapy + autologous T cell transplantation (Comparator: Peptide vaccine with IL-2 therapy (NO T-cell transplantation)) | "Safety, feasibility and efficacy" | Relapsed, Children, Young adults, Alveolar RMS and Ewing's sarcoma family of tumours. Presence of a tumour-specific fusion protein which corresponds to one of the tumour-specific fusion peptide vaccines available. Weight greater than 10kg | Up to 30 years |
| NCT00093821[219] | Tanespimycin in Treating Young Patients With Recurrent or Refractory Leukemia or Solid Tumors | USA; Academic | 70 (A) | 01/09/2004* to 01/08/2007* | Tanespimycin | Dose Limiting Toxicities, Maximum Tolerated Dose, PKs, Change in Hsp90 client protein levels | Relapsed, Refractory, Children, Young adults, Leukaemia or select solid tumours (neuroblastoma, EWS, osteosarcoma, desmoplastic small round cell tumour, RMS) | Up to 21 years |
| **Recruitment status: Terminated** | | | | | | | | |
| NCT00002863[151] | Cryosurgery in Treating Patients With Soft Tissue Sarcoma **(Terminated due to insufficient accrual)** | USA; Academic | 19 (A) | 01/06/1996* to 01/07/2000* | Cryoablation with systemic chemotherapy followed by surgery | NR | Soft-tissue sarcomas only, All ages | All ages |
| NCT00623077[152] | MT2004-30: Tomotherapy for Solid Tumors **(Terminated after being replaced by another study)** | USA; Academic | 23 (A) | 01/08/2005* to 01/10/2016* | TMI given prior to alkylator intensive conditioning regimen. Conditioning includes Busulfan, Melphalan | Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Change in bone marrow density, | Relapsed, All solid tumours, All ages, High-risk metastatic | Up to 70 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | | | | | & Thiotepa. Stem Cell transplantation with Ifosfamide, Etoposide and Mesna + Filgrastim. Whole lung radiation | Treatment related mortality in non-TMI patients, Primary neutrophil engraftment, % of PET scans and spot radiation to PET-positive lesions after transplant | | |
| **Recruitment status: Suspended** | | | | | | | | |
| NCT03213678[160] | Samotolisib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With TSC or PI3K/MTOR Mutations (A Pediatric MATCH Treatment Trial) **(Suspended due to agent expiry issue)** | USA, Puerto Rico; Academic | 144 (E) | 31/07/2017 to 30/09/2024 | Samotolisib | Response rates, Adverse events, Progression Free Survival, PKs, Biallelic loss of function Frequency, Predictive biomarker identification, Change in genomic profile of tumour | Relapsed, Refractory, All solid tumours, Children, Young adults, Presence of an actionable mutation. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to Molecular Analysis for Therapy Choice (MATCH) to APEC1621D based on the presence of an actionable mutation | 12 months to 21 years |
| NCT03213652[179] | Ensartinib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With ALK or ROS1 Genomic Alterations (A Pediatric MATCH Treatment Trial) **(Suspended pending release of next amendment)** | USA, Puerto Rico; Academic | 98 (E) | 24/07/2017 to 30/09/2024 | Ensartinib | Response rates, Adverse events, Progression Free Survival, PKs, Biomarkers predicting response, Changes in tumour genomic profile | Relapsed, Refractory, Children, Young adults, Presence of an actionable mutation, Radiographically measurable disease at the time of study enrolment. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to Molecular Analysis for Therapy Choice (MATCH) to APEC1621F based on the presence of an actionable mutation | 12 months to 21 years |
| NCT04320888[187] | Selpercatinib for the Treatment of Advanced Solid Tumors, Lymphomas, or Histiocytic Disorders With Activating RET Gene Alterations, a Pediatric MATCH Treatment Trial **(Suspended pending release of next amendment)** | USA, Puerto Rico; Academic | 49 (E) | 14/09/2020 to 30/09/2027 | Selpercatinib | Response rates, Adverse events, Progression Free Survival, Profile changes in tumour genomics | Relapsed, Refractory, All solid tumours, Children, Young adults, Presence of an actionable mutation. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621N based on the presence of an actionable | 12 months to 21 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | mutation | |
| NCT03210714 | Erdafitinib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With FGFR Mutations (A Pediatric MATCH Treatment Trial) **(Suspended pending release of next amendment)** | USA, Puerto Rico; Academic | 49 (E) | 06/11/2017 to 31/12/2024 | Erdafitinib | Response rates, Adverse events, Progression Free Survival, PKs, Change in tumour genomic profile | Relapsed, Refractory, Children, Young adults, Presence of an actionable mutation. Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to molecular analysis for therapy choice (MATCH) to APEC1621B based on the presence of an actionable mutation | 12 months to 21 years |
| **Recruitment status: Withdrawn** | | | | | | | | |
| NCT04906876[158] | A Phase 2 Study of 9-ING-41 Combined With Chemotherapy in Adolescents and Adults With Advanced Sarcomas **(Withdrawn due to IND withdrawal)** | USA; Academic (Brown University) and Pharmaceutical company (Actuate Therapeutics) | 0 (A) | 01/09/2021* to 01/07/2025* | 9-ING-41, Gemcitabine &, Docetaxel | Response rates, Progression Free Survival, Disease control rate (based on response rates) | Soft-tissue sarcomas only, No more than 3 lines of prior systemic therapy (prev untreated patients can be enrolled), Locally advanced and unresectable, or metastatic STS. | 10 years and older |
| NCT02689336[173] | Erlotinib in Combination With Temozolomide in Treating Relapsed/Recurrent/Refractory Pediatric Solid Tumors **(Withdrawn due to being unable to recruit participants)** | NR but sponsor/ contact in USA; Academic | 0 (A) | 06/08/2016 to 31/05/2020 | Erlotinib & Temozolomide | Response rates, Adverse events, Time to progression | Relapsed, Refractory, All solid tumours, Children, Young adults | 1-21 years |
| NCT02011126[194] | Imetelstat Sodium in Treating Younger Patients With Relapsed or Refractory Solid Tumors **(Withdrawn due to IND not being available)** | NR but sponsor/ contact in USA; Academic | 0 (A) | 30/06/2014 to 25/03/2016 | Imetelstat sodium | Response rates, Adverse events, Progression Free Survival, Telomerase length | Relapsed, Refractory, Children, Young adults, Osteosarcoma, EWS, PNET, RMS, Neuroblastoma or Hepatoblastoma | 1-30 years |
| NCT02557854[223] | HIFU Hyperthermia With Liposomal Doxorubicin (DOXIL) for Relapsed or Refractory Pediatric and Young Adult Solid Tumors **(Withdrawn due to lack of enrolment)** | USA; Academic | 0 (A) | 01/12/2016* to 16/03/2019 | Liposomal Doxorubicin (Doxil) + MR-HIFU | Response rates, Adverse events, Dose Limiting Toxicities, PKs, Percentage of patients who are able to receive hyperthermia to greater than 75% of predetermined treatment volume for 75% of the planned treatment duration | Relapsed, Refractory, Children, Young adults, Histologically confirmed malignant extra-cranial solid tumor or demoid fibromatosis | 1-40 years |
| NCT03111069[214] | Study of Doxorubicin and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) | NR but sponsor/ contact in USA; | 0 (A) | 01/08/2018* to 01/08/2021* | Resectable Tumours: Surgical tumour resection followed by | Maximum Tolerated Dose, Progression of Disease | Children, RMS or undifferentiated sarcoma of | 1-6 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | and Intraoperative Brachytherapy for Unresectable or Refractory Pelvic and Abdominal Rhabdomyosarcoma and Undifferentiated Sarcomas in Children **(Withdrawn by Principle Investigator)** | Academic | | | hyperthermic intra-peritoneal chemotherapy with Doxorubicin Unresectable Tumours: Debulking surgery, followed by intra-operative radiation (brachytherapy) | | pelvis/abdomen | |
| NCT01697514[215] | A Study of LY2940680 in Pediatric Medulloblastoma or Rhabdomyosarcoma **(Withdrawn due to being unable to recruit participants)** | USA; Pharmaceutical company | 0 (A) | 01/07/2013* to 01/07/2016* | LY2940680 | Response rates, Maximum Tolerated Dose, PKs | Relapsed, Refractory, Children, Young adults, RMS or Medulloblastoma | 12 months to 21 years |
| **Recruitment status: Unknown** | | | | | | | | |
| NCT03868852[218] | Efficacy and Safety of Radiotherapy Combined With Apatinib Mesylate in the Treatment of Rhabdomyosarcoma in Children | China; Academic | 48 (E) | 01/01/2019 to 01/04/2020 | Radiotherapy & Apatinib mesylate | Response rates, Adverse events, Overall Survival, Quality of Life, Disease Control Rate | RMS only, Children, Young adults | 3-18 years |
| NCT02409576[204] | Pilot Study of Expanded, Activated Haploidentical Natural Killer Cell Infusions for Sarcomas (NKEXPSARC) | Singapore; Academic | 20 (E) | 01/02/2015* to 01/09/2020* | NK donor cells. Chemotherapy + Radiation | Adverse events, Disease response (radiological response), Persistence/ phenotype of NK cells, Performance status, Acute/chronic GVHD | All ages, Metastatic, progressive or relapsed EWS or RMS | Up to 80 years |
| NCT01807468[197] | Haploidentical Stem Cell Transplantation and NK Cell Therapy in Patients With High-risk Solid Tumors | Republic of Korea; Academic | 12 (E) | 01/05/2013* to 01/06/2019* | Haploidentical stem cell transplantation and NK cell therapy | Adverse events, Overall Survival, Event free survival, Number of patients developing GVHD | Relapsed, All solid tumours, Children, Young adults, High risk, Stable disease with salvage chemotherapy after relapse, Suitable haploidentical donor | Up to 21 years |
| NCT01216839[207] | Phase II Study of Everolimus in Children and Adolescents With Refractory or Relapsed Rhabdomyosarcoma and Other Soft Tissue Sarcomas **Conference abstract paper with data from patients in this trial has also been extracted (Epelman, 2015)** | Brazil; Individual (Sidnei Epelman, Director of Pediatric Oncology, Hospital Santa Marcelina) | 20 (E) | 01/03/2011* to 01/12/2013* | Everolimus | Response rates, Everolimus toxicity | Relapsed, Refractory, Soft-tissue sarcomas only, Children, Young adults | Up to 21 years |
| NCT00750126[247] | Allogeneic Hematopoietic Stem Cell Transplantation (RICE) | France; Academic | 30 (E) | 01/04/2007* to 01/04/2009* | Reduced intensity conditioning (fludarabine, busulfan and thymoglobulin) followed by allogeneic hematopoietic stem cell transplantation | Response rates, Adverse events, Overall Survival, GvHD | Children, Young adults, Solid tumours or hematological malignancy. Having a HLA-identical sibling donor for HLA-A, HLA-B and HLA-DR antigens or a HLA mismatch on only one antigen, or | Up to 20 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | Number of participants | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | having a 10/10 pheno-identical donor, or compatible cord blood | |

* Where trials have only dates made up of months and years, we have selected the first day of the month, e.g. February 2004 would be 01/02/2004

A = actual enrolment; ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; CAR-T = chimeric antigen receptor T-cell; CML = chronic myeloid leukaemia; CNS = central nervous system; COG = Children's Oncology Group; DIPG = diffuse intrinsic pontine glioma; E = estimated enrolment; EWS = Ewing's sarcoma; G-CSF = granulocyte-colony stimulating factor; GPC3 = glypican-3; GVHD = graft-versus-host disease; HSCT = haematopoietic stem cell transplant; HIFU = high intensity focused ultrasound; HLA = human leukocyte antigen; IND = investigational new drug; LTLD = lyso-thermosensitive liposomal doxorubicin; MATCH = molecular analysis for therapy choice; MDS = myelodysplastic syndrome; MR-HIFU = magnetic resonance-guided high intensity focused ultrasound; NHL = non-Hodgkin lymphoma; NR = not reported; NRSTS = non-rhabdomyosarcoma soft tissue sarcoma; PET = positron emission tomography; PKs = pharmacokinetics; PNET = primitive neuroectodermal tumour; RMS = rhabdomyosarcoma; RP2D = recommended phase 2 dose; TMI = total marrow irradiation; UK = United Kingdom; USA = United States of America