# Living REFoRMS update 5 (REFoRMS LSR-5) report

## Updates to methods from LSR-4 (PROSPERO CRD42022380185)[1]

### Searches

For LSR-5, the same standard database searches were conducted, with the exception of PROSPERO which was removed as per the LSR-4 report.[2] We applied a date limit of 2024 to current for the database searches. For OpenAlex searches, we adjusted the percentage of records imported from these searches from the top 1% to the top 0.75%, as well as rebuilding the machine learning classifier to improve searching efficiency (see PROSPERO for further details).[1] Database searches were run on 25th October 2024 and OpenAlex searches on 28th October 2024.

### Screening, data extraction and quality assessment

The eligibility criteria for the studies, data extraction and quality assessment processes were unchanged.[1] There were two minor changes to screening/tracking methods implemented in LSR-5:

1. During screening, the code 'Systematic Review' is used to exclude any systematic reviews that are then checked for additional references; for LSR-5, we used this code more broadly for any paper that didn't fit the eligibility criteria but could be useful for checking for additional eligible studies, not just systematic reviews.
2. Any clinical trial record (CTR) with a withdrawn, terminated or unknown trial status that recruited zero participants was no longer tracked.

## Results of LSR-4

### Study selection

From 1,713 records identified from the searches, 88 were eligible after title and abstract screening (see Figure 1). A simplified flowsheet of studies included in the REFoRMS project (baseline review and all updates) is shown in Figure 2.

Following full-text screening and tracking of previously included conference abstracts (CAs) and CTRs, ten full text papers[3-12] (including one pre-print[10]) and one CTR[13] with outcome data reported on the website, were included. Of these, one paper was identified from tracking a previous CA[10], and two from checking the reference lists of systematic reviews identified in LSR-5[8,12]. One paper was originally identified in LSR-4 but further information was provided from the corresponding author for LSR-5.[5] Three of the full-texts identified in LSR-5 related to previously extracted studies[6,7,12], meaning full data were now available. These publications are classed as new full-text papers, but not new studies. Therefore, 11 new publications including eight new studies were included in the synthesis.

Six authors (including three from additional searches) were contacted for further information to determine eligibility for inclusion in LSR-5. We received a reply regarding one paper which provided additional information to be able to include it in the synthesis.[8] Any further responses received following the publication of this report will be included in the next update (LSR-6).

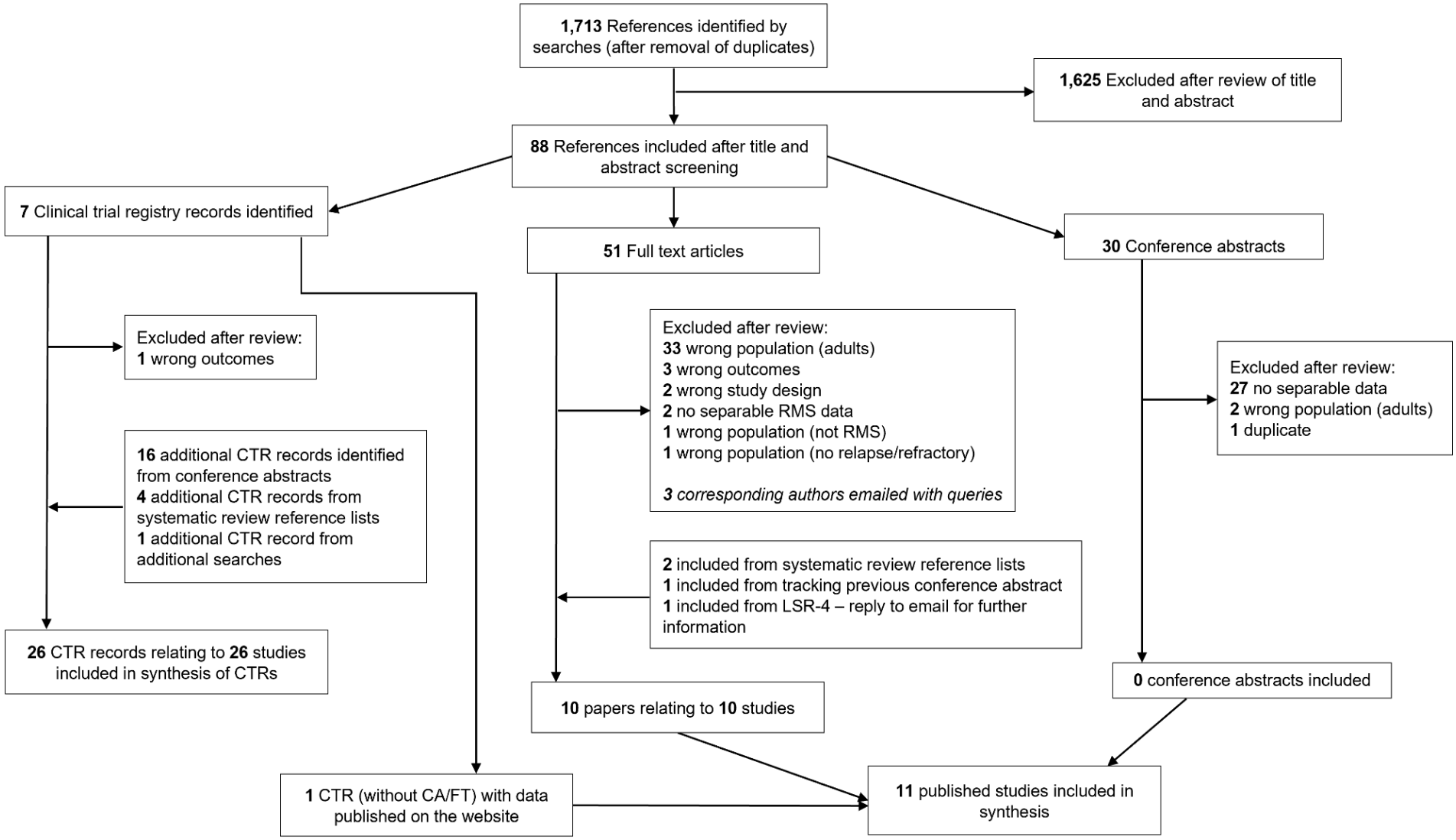


**Figure 1.** LSR-5 flowsheet

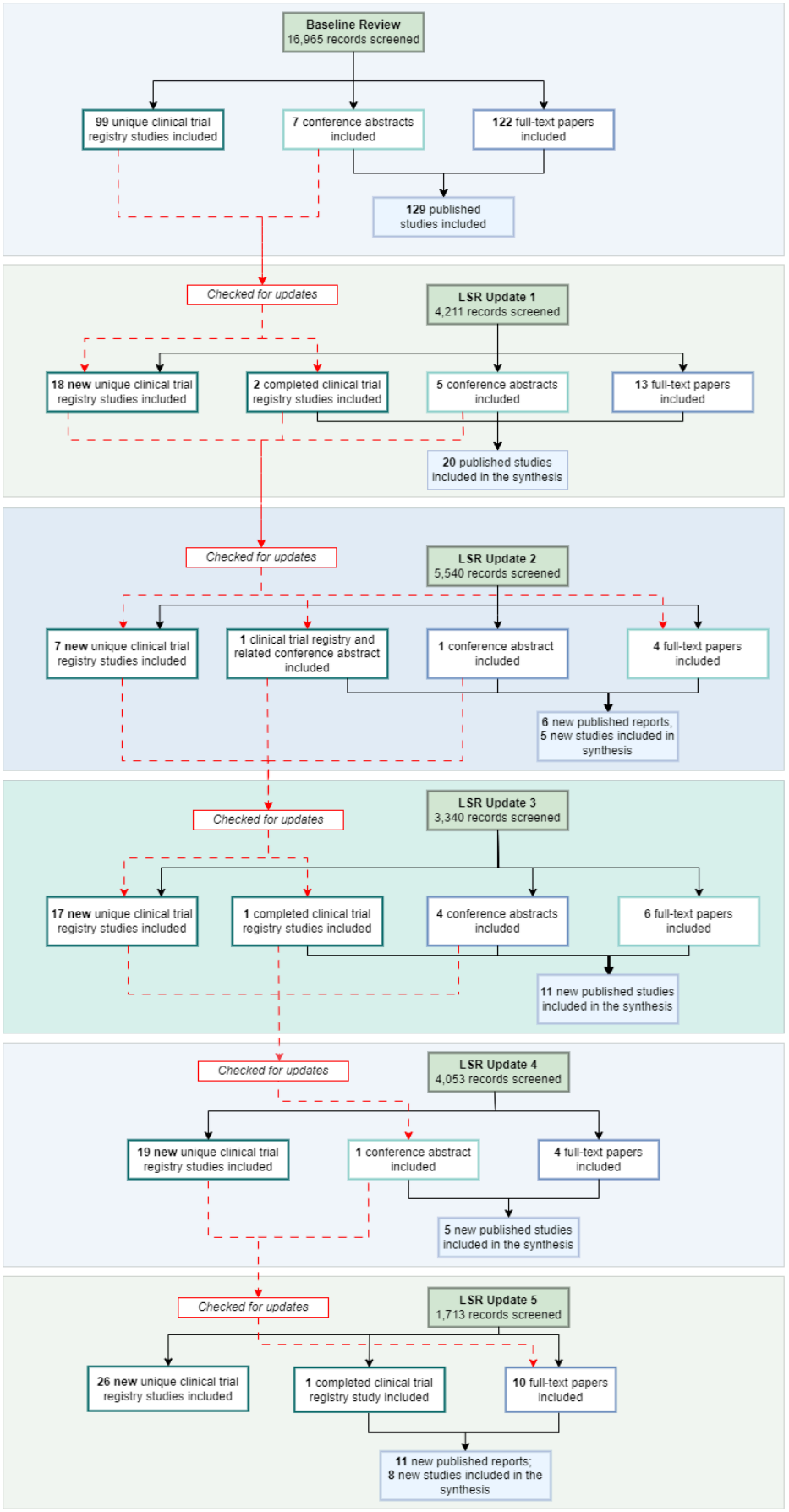


**Figure 2.** Flowsheet of included studies in REFoRMS

### Updates of previously identified CTRs

One hundred and twenty-six CTRs were checked for updates. Five CTRs had newly identified CAs, two had posted data on the trial registry website, and nine CTRs had newly identified full-text publications. Two newly identified outputs provided data that was relevant to LSR-5.[3,6] Ten CTR records were no longer tracked.

Of the 53 CTRs identified to be currently open (i.e. recruiting) at the time of the last update, 47 continue to be reported as currently open. One continues to be not yet recruiting. Since LSR-4, two CTRs have opened recruitment, three have finished recruitment (currently 'active not recruiting'), five are reported as completed, one terminated, one unknown and one has re-opened recruitment (previously suspended). Of the 22 CTRs identified as completed but not yet reported at the time of the last update, one (4.5%) has new information available but not related to children and young people (CYP) with rhabdomyosarcoma.

### Newly identified CTRs

Twenty-six new CTRs were included in LSR-5.[14-39] Five were identified in the update search[14,17-19,29], 16 from new CAs[15,21-27,30,32-37,39], four during citation searching of systematic reviews[16,20,31,38], and one from additional searches[28].

## Published studies

### Demographics of included studies

Eleven studies contributed 13 cohorts to LSR-5. Countries of recruitment included: USA (six studies)[4,6,7,10,12,13], Australia[5,11,13] and Puerto Rico[4,6,7] (three studies each), and Canada (two studies)[4,9]. Twenty-one other countries were reported as recruitment sites (see Table 2). One study did not report recruitment location.[8] Where reported, five studies (50%) were completed in multiple countries.[4-7,13]

Six studies evaluated single novel therapies[4-8,13], one evaluated standard multi-agent therapy[3], three were molecular registry studies where CYP received individualised treatment matched to the mutations within their tumour[9-11], and one investigated cellular therapies[12].

Almost all studies identified by the update were published in 2024 (n=10, 91%).[3-7,9-13] One study published in 2012 had not been identified in previous updates.[8]

### Demographics of participants in included studies

Sixty-six CYP with relapsed and refractory rhabdomyosarcoma were included in the studies. Eight studies of ten cohorts included fewer than five CYP with relapsed/refractory rhabdomyosarcoma.[4,5,7-12] All of the studies recruited CYP with a variety of tumour types. Two studies included infants younger than one years old.[9,10]

Ten studies reported the sex of included CYP[3,4,6-13] (six for CYP with rhabdomyosarcoma specifically[6,7,10-13]), while one study did not report sex or gender[5]. Sex was reported as a binary characteristic in all studies included in the review. Where sex was reported for CYP with rhabdomyosarcoma specifically, the male to female ratio was equal (1:1).

Only two studies (18 CYP) reported both the ethnicity and race of the CYP with rhabdomyosarcoma.[10,13] In these studies, ten participants were white (56%), three Asian

(17%), one Native Hawaiian or other Pacific Islander (6%), and four not reported (22%). Two of these 18 CYP were Hispanic or Latino (11%), 12 non-Hispanic/non-Latino (67%), and four unknown/not reported (22%). Three studies provided race and ethnicity data for the whole population[4,6,7], while six provided no race/ethnicity data[3,5,8,9,11,12].

Histopathology of the rhabdomyosarcoma was infrequently reported (17% of CYP). Where given, eight CYP had embryonal disease[3,8-11], and three had alveolar[3,8]. Seven studies reported the molecular characteristics of tumours.[3,4,6,7,9,11,12] Of these studies, three evaluable CYP with rhabdomyosarcoma were reported to have a PAX:FOXO1 fusion positive tumour.[3] A range of other mutations and genetic alterations were identified (see Table 2).

## Quality assessment of included studies

Studies reported adequate information in relation to most MINORS tool assessment criteria[40], but only one study provided adequate information on all domains[3] (see Table 1). All studies provided a clearly stated aim, used an appropriate follow-up period (frequently to death of the participant), and had minimal loss to follow-up. In contrast, most studies did not include adequately assessed endpoints, as response rates were not independently evaluated, or did not report who assessed response.

## Outcomes of included studies

Outcome data were available for 59 CYP with relapsed/refractory rhabdomyosarcoma.

### *Survival*

Six studies (of seven cohorts) reported Progression Free Survival (PFS) or Time to Progression (TTP).[6,7,10-13] PFS for any individual across these cohorts ranged from 20 days to 17 months, with the majority of CYP experiencing progression in less than three months. Two CYP, both treated with different interventions, experienced PFS of 12 months or more[11,12].

Five cohorts reported overall survival (OS).[6,7,11,12] Three cohorts reported median OS across five patients, with a median 17.4 months (range 6.4- >72).[11,12] Two cohorts reported a proportion OS, which was 50-60% at six months.[6,7] Whilst the duration of survival was not reported for all CYP, of 17 where the outcome at last follow-up was known[6,7,9-12], one CYP was still alive[12] and the remaining 16 had died.

### *Response rate*

Most cohorts (n=8; 62%) showed no objective responses.[4-11] In four cohorts, responses were seen.[3,9,12,13] Two cohorts reported a response rate >30% in fewer than five CYP with rhabdomyosarcoma, therefore the results should be interpreted cautiously.[9,12] One cohort, including 18 evaluable CYP with rhabdomyosarcoma, reported a response rate of 56% at six weeks and best overall response of 72%.[3] This study used standard multi-agent chemotherapy and has been filled in blue in Table 3.

Due to limited data, it was not possible to examine outcomes for separate groups (refractory, first relapse, subsequent relapse).

*Quality of Life*

No new study reported quality of life data.

*Adverse Events (AEs)*

Adverse events were variably reported. Three studies (all molecular registry studies) did not report any AE data.[9-11] Eight studies contributed new AE data[3-8,12,13], although one did not provide details of the severity/grade of adverse events[13]. Within the studies that reported Grade 3/4 AEs, 187 participants (including 42 with rhabdomyosarcoma) were evaluable for toxicities.[3-8,12] Most AEs were haematological. Additional specific AEs varied by study treatment (see Table 4). No study explicitly reported treatment-related or potentially treatment-related deaths.

## New CTRs

Twenty-six new CTR studies were identified.[14-39] Reported start dates ranged between 2018 and 2025. Fifteen studies were reported as having an academic sponsor[14,16,17,19-21,25,27-30,33,35-37], and 11 studies with a pharmaceutical company as sponsor[15,18,22-24,26,31,32,34,38,39]. We identified 14 currently open studies[17-30], three studies pending recruitment[14-16], seven studies had closed recruitment[31-37], and one completed with no identified published results[38]. One study had been terminated (due to sponsor decision).[39]

Four studies included all solid tumours in their eligibility criteria[14,16,22,26], two studies included a smaller selection of solid tumours[17,29], two studies were restricted to soft-tissue sarcoma only[19,30] and one study restricted to sarcoma only[20], whilst a further 17 studies included a wider range of malignancies[15,18,21,23-25,27,28,31-39]. Two studies included newly diagnosed CYP.[19,28] Eligible ages varied: upper age limits ranged from 17 to 40 years, with 18 or 21 years being the most common cut-offs. Seven studies had no upper age limit.[21,22,26,30,34,36,37] Twenty studies were open to infants and young children[14-20,22-25,27-29,31-33,35,38,39], two studies were restricted to patients ≥12 years[26,34] and four studies restricted to patients ≥16 years[21,30,36,37].

Twenty-one studies were single-arm and evaluated a range of therapies including: nine novel single agent therapies[23,24,28,32,35-39], six novel multi-agent therapies[17,26,27,29-31], one standard multi-agent therapy[33], four cellular therapies[14,16,18,20], and one targeted nuclear medicine[15]. Five studies were multi-arm including three molecular registry studies[21,22,25], one non-comparative multi-arm study evaluating a novel agent alone or in combination with other therapies[34], and one RCT study comparing two different standard multi-agent therapies[19]. Thirteen CTR studies restricted their eligibility criteria to CYP with specific genetic mutations/alterations[15,20,23,24,26-29,32,34-37] (see Table 5 for details).

Thirteen studies provided a single recruitment country[16-21,27,30,33,35-37,39] and 11 studies provided multiple recruitment countries[22-26,28,29,31,32,34,38]. Common reported recruitment locations included the USA (n=13)[17,18,22-24,26,27,31,32,34,35,38,39], France[22-24,28,29,31,32,34,38] and Spain[16,20,22-24,29,31,34,38] (9 in each), United Kingdom[22-24,26,29,31,32,38] and Canada[22-26,32,34,38] (8 in each), Australia[22-26,32,34] (7), Germany[22-24,29,31,32], Italy[22-24,29,31,32] and Republic of Korea[22-24,26,32,34] (6 in each), China[19,22,23,30,33] and Netherlands[22,28,29,31,38] (5 in each). Other recruitment locations are provided in Table 5. Two studies have not provided recruitment location information.[14,15]

## Summary of new studies

The REFoRMS LSR-5 update identified data from 11 published studies (13 cohorts) of 66 children and young people with relapsed and refractory rhabdomyosarcoma. This means that **overall**, the REFoRMS systematic review has identified **174** published early phase studies of interventions, including **over 1,350** children and young people with relapsed/refractory rhabdomyosarcoma.

Survival outcomes were provided by six of the 11 studies, whilst all studies provided response rates. Eleven cohorts were small (≤5 CYP with rhabdomyosarcoma) and thus, caution should be taken when interpreting the effectiveness of these interventions as generalisability to other CYP with rhabdomyosarcoma is likely to be limited. Although duration of survival was not reported, one study shows promising results in terms of response rates reporting a 72% overall response rate and 100% disease control rate for CYP with rhabdomyosarcoma receiving vincristine combined with pegylated liposomal doxorubicin and cyclophosphamide.[3]

Overall, **64** clinical trials are reported to be open for recruitment. The number of newly identified clinical trials evaluating targeted therapies in individuals with particular genetic alterations is still increasing.

During screening in LSR-5, we experienced challenges due to a change in the website infrastructure of clinicaltrials.gov. The changes made it difficult to identify previous records that had been screened as duplicate records. Thankfully, the experienced REFoRMS team were quick to identify the issue and thus prevent duplicate reporting. However, this issue increased the human resource needed to resolve duplicates in LSR-5, and thus resulted in delays in identifying new CTRs. Given the clinicaltrials.gov website is unlikely to undergo another major update soon, we don't expect this issue to impact future updates.

Although not eligible for inclusion in REFoRMS, we acknowledge the recent publication by Owens et al. (2024)[41] which provides a cost estimation for implementing precision medicine programmes for CYP with cancer. As seen in Living-REFoRMS, programmes dedicated to testing tumour genetics and then providing a matched treatment are becoming increasingly available, especially in high income countries. Studies of these programmes are usually designed to test the feasibility of giving tailored treatments, and therefore, other outcomes including adverse events and associated costs are under-reported. Future research needs to continue investigating the feasibility of these types of trials and whether they make a difference to patient outcomes compared to standard early phase trials.

## Tables

### Table 1. Quality assessment of included studies using the MINORS tool

| Author, Year | MINORS assessment criteria | | | | | | |
|---|---|---|---|---|---|---|---|
| | Clearly stated aim | Prospective collection of data | Appropriate endpoints | Unbiased assessment of endpoint | Appropriate follow-up | Loss to follow-up <5% | Prospective sample size calculation |
| Lu, 2024[3] | Reported and adequate | Reported and adequate | Reported and adequate | Reported and adequate | Reported and adequate | Reported and adequate | Reported and adequate |
| Laetsch, 2024[4] | Reported and adequate | Reported and adequate | Reported and adequate | Not reported | Reported and adequate | Reported and adequate | Reported and adequate |
| Fenwick, 2024[5] | Reported and adequate | Reported and adequate | Reported and adequate | Not reported | Reported and adequate | Reported and adequate | Reported and adequate |
| Macy, 2024[6] | Reported and adequate | Reported and adequate | Reported and adequate | Reported but inadequate | Reported and adequate | Reported and adequate | Reported and adequate |
| Vo, 2024[7] | Reported and adequate | Reported and adequate | Reported and adequate | Reported but inadequate | Reported and adequate | Reported and adequate | Reported and adequate |
| Geoerger, 2012[8] | Reported and adequate | Reported and adequate | Reported and adequate | Not reported | Reported and adequate | Reported and adequate | Reported and adequate |
| Deyell, 2024[9] | Reported and adequate | Reported but inadequate | Reported and adequate | Reported but inadequate | Reported and adequate | Reported and adequate | Reported but inadequate |
| Vasquez, 2024[10] | Reported and adequate | Reported and adequate | Reported but inadequate | Reported but inadequate | Reported and adequate | Reported and adequate | Not reported |
| Lau, 2024[11] | Reported and adequate | Reported and adequate | Reported and adequate | Reported but inadequate | Reported and adequate | Reported and adequate | Not reported |
| Hegde, 2024[12] | Reported and adequate | Reported and adequate | Reported and adequate | Not reported | Reported and adequate | Reported and adequate | Reported and adequate |
| NCT04447755 last updated 2024[13] | Reported and adequate | Reported and adequate | Reported and adequate | Reported but inadequate | Reported and adequate | Reported and adequate | Reported but inadequate |

## Table 2. Demographic characteristics of new studies

| Author, Year | Countries performed | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | No. of R+R RMS patients (total) | Median age (range) | Median prior lines of therapy (range) | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single / multi centre | | Disease | Age | Other | | | | | |
| **Standard agents - multiple agents** | | | | | | | | | | | | |
| Lu, 2024[3] | China | Phase 1 | Single | 7 January 2020 to 18 November 2021 | Relapsed, refractory, all solid tumours, evaluable disease | 1-18 years | | Vincristine *1.5mg/m$^2$ (max 2mg)* Pegylated Liposomal Doxorubicin *Escalating dose from 30-50mg/m$^2$* Cyclophosphamide *1500mg/m$^2$ 2-12 cycles Frequency and method of administration NR* | 24 (34) | WP: 6 (1-18) years | WP: 2 (1-5) | At least 1 embryonal and 1 alveolar RMS. 3 RMS *PAX-FOXO1* fusion positive. Additional information on somatic mutations is reported in the paper |
| **Novel agent - single agents** | | | | | | | | | | | | |
| Laetsch, 2024[4] | USA, Puerto Rico, Canada (info from CTR) | Phase 2 | Multi | 28 November 2017 to 12 April 2023 | Relapsed, refractory, all solid tumours. Included lymphomas, CNS tumours & histiocytosis disorders. Measurable disease | 1-21 years | Had to have an actionable tumour alteration in the P13K/ mTOR pathway without a resistance mutation in the MAPK pathway. Excluded if ARAF, BRAF, NRAS, KRAS, HRAS, MAP2K1, GNA11, GNAQ, NF1 variants | Samotolisib *Starting dose 80mg/m$^2$/dose up to 115mg/m$^2$/dose, bd, po in continuous 28-day cycles for up to 2 years* | 1 (17) | WP: 15 (7-20) years (only focused on the treated pop) | NR | 1 RMS with *PIK3CA c.1636C>A, p.Gln546Lys (0.41) (*additional tumour *GNAS c.602G>A, p.Arg201His (0.46))* |
| Fenwick, 2024[5] | UK, Australia, Netherlands | Phase 1/2 | Multi | August 2018 to July 2022 | Relapsed, refractory. Four | <25 years | No prior treatment with an arginine depleting drug | BCT-100 *1600U/kg IV over 1 hr on days 1,8,15,22 of* | 3 (45) | Exact age NR but reported | NR | WP = total patients treated. 3 RMS included - confirmed via email correspondence |

| Author, Year | Countries performed | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | No. of R+R RMS patients (total) | Median age (range) | Median prior lines of therapy (range) | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single / multi centre | | Disease | Age | Other | | | | | |
| | | | | | cohorts: ALL/AML, NB, HGG, sarcoma | | | *28-day cycle* | | as CYP | | |
| Macy, 2024[6] | USA, Puerto Rico | Phase 2 | Multi | June 2018 to May 2022 | Relapsed, refractory, all solid tumours. Includes CNS tumours, lymphomas and histiocytic disorders. Measurable disease | 1-21 years | Amplification of CDK4, CDK6, CCND1, CCND2, or CCND3; positive Rb expression. Able to swallow capsules | Palbociclib *75mg/m$^2$ od, po on days 1-21 in 28-day cycles, max 2 years* | 5 (20) | RMS: 15* (13-16) years | NR | All RMS had *CDK4 amplification*;1 also had *MYCN amplification* |
| Vo, 2024[7] | USA, Puerto Rico (info from CTR) | Phase 2 | Multi | November 2018 to March 2021 | Relapsed, refractory, all solid tumours. Includes NHL and histiocytic disorders. Measurable disease | 1-21 years | Actionable alterations were defined in ARAF, BRAF, HRAS, NRAS, KRAS, MAPK1, MAP2K1, GNA11, GNAQ, NF1 | Ulixertinib *260 or 350mg/m$^2$ per dose, po, bd. 28-day cycles, max 2 years* | 4 (20) | RMS: 11* (8-14) years | NR | 1 RMS with *NRAS* mutation, 2 RMS with *NRAS* and *PIK3CA* mutations, 1 RMS with *NF1, FGFR4, CREBBP* mutations |
| Geoerger, 2012[8] | NR | Phase 1 | Multi | March 2004 to November 2007 | Relapsed, refractory, all solid tumours | 1-18 years | Excluded if previous doxorubicin >400mg/m$^2$ | Plitidepsin *Escalating dose from 4mg/m$^2$, IV every 2 weeks* | 3 (41) | WP: 10 (2-17) years | WP: 3 (1-10) | Note only 38 CYP treated, including 2 alveolar RMS. One embryonal RMS not treated |
| NCT04447755, 2024[13] | See comments | Phase 2 | Multi | 30 July 2020 to 16 September 22 | Relapsed, refractory, all solid tumours, measurable diseases | 2-21 years | Excluding osteosarcoma | Lenvatinib *14mg/m$^2$ od, po* | 17 (127) | RMS: mean (SD): 13.1 (4.7) years | NR | Performed in: USA, Argentina, Australia, Belgium, Croatia, Czechia, France, Guatemala, Hungary, Israel, Italy, Republic of Korea, New |

| Author, Year | Countries performed | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | No. of R+R RMS patients (total) | Median age (range) | Median prior lines of therapy (range) | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single / multi centre | | Disease | Age | Other | | | | | |
| | | | | | | | | | | | | Zealand, Peru, Russian Federation, Serbia, South Africa, Spain, Sweden, Turkey |
| **Molecular Registry Studies** | | | | | | | | | | | | |
| Deyell, 2024[9] | Canada | Feasibility study | Multi | September 2013 to July 2019 | Relapsed, refractory, or cancers with poor prognosis (<30% overall survival) | Exact age NR but paediatric | Had to provide a tumour sample | Temsirolimus (matched treatment) + Vinorelbine, Cyclophosphamide *Dose, frequency and method of administration NR for all study cohorts* | 2 (79 with somatic sequencing) | WP: 8.8 (0.3-20.7) years at diagnosis<br><br>13.8 (0.5-21.2) years at enrollment | NR | 2 embryonal RMS. 1 RMS with *P13K SNV (GoF)* target, and 1 RMS with *FGFR4 SNV (GoF)* target |
| | | | | | | | | Palbociclib (matched treatment) + Irinotecan, Temozolomide | 1 (79) | | NR | 1 embryonal RMS with *CDK4 CNV* (gain), *CDK4/6* outlier expression high |
| Vasquez, 2024[10] | USA | NR | Single | March 2018 to August 2020 | Relapsed, refractory, all solid tumours, relapsed leukaemia, newly diagnosed high-risk cancer with no standard of care | <30 years | Had to undergo tumour sampling as part of their standard care | Trametinib *Dose, frequency and method of administration NR* | 1 (33 enrolled) | RMS: 0-5 years at diagnosis | RMS: 4 | Patient had second relapse embryonal RMS |
| Lau, 2024[11] | Australia | NA | Multi | September 2017 to December 2020 | Relapsed, refractory, all solid tumours, any high risk | <21 years (see comment box) | | Trametinib *Dose, frequency and method of administration NR for all study cohorts* | 1 (110 received PGT) | RMS: 4.8 years | RMS: 1 | Age: Patients > 22y with paediatric-type cancers included if approved by study chair. 1 embryonal RMS with first relapse and |

| Author, Year | Countries performed | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | No. of R+R RMS patients (total) | Median age (range) | Median prior lines of therapy (range) | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single / multi centre | | Disease | Age | Other | | | | | |
| | | | | | malignancy at diagnosis (<30% probability of cure) | | | | | | | *NRAS* mutation |
| | | | | | | | | Nivolumab | 1 (110) | RMS: 10.2 years | RMS: 1 | 1 embryonal RMS with *high TMB* - had prior relapse but NED at study enrollment |
| **Cellular therapies** | | | | | | | | | | | | |
| Hegde, 2024[12] | USA | Phase 1 | Multi | 1 July 2015 to 18 October 2019 | Relapsed, refractory | Paediatric and adults | HER2 positive sarcoma (at least grade 1 (1-25% positive) and intensity score 1+ for HER2 staining | Lymphodepleting chemotherapy (fludarabine or fludarabine + cyclophosphamide) followed by HER2 CAR-T cells | 3 (8) | RMS: 10* (8-17) years | RMS prior chemo: 2 (2-3)* | Cohort B was the only cohort with RMS patients. One RMS patient re-enrolled on to this study. All RMS had metastatic disease |

* data has been calculated for CYP with RMS specifically

ALL = acute lymphocytic leukaemia; AML = acute myeloid leukaemia; bd = twice daily; CAR-T = chimeric antigen receptor-T cells; CNS = central nervous system; CNV = copy number variation; CTR = clinical trial record; CYP = children and young people; GoF = gain of function; HGG = high grade glioma; IV = intravenous; NA = not applicable; NB = neuroblastoma; NED = no evidence of disease; NHL = non-Hodgkin's lymphoma; NR = not reported; od = once daily; PGT = precision-guided therapy; po = orally; RMS = rhabdomyosarcoma; R+R = relapsed and refractory; SNV = single nucleotide variant; TMB = tumour mutational burden; UK = United Kingdom; USA = United States of America; WP = whole population

## Table 3. Outcome data for new studies

| Regimen | Author, Year | Total no. of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median survival (range) | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| **Standard agents - multiple agents** | | | | | | | | | | |
| Vincristine, Pegylated Liposomal Doxorubicin, Cyclophosphamide | Lu, 2024[3] | 18 R+R RMS at 6 weeks | 2 | 8 | 8 | 0 | 56%* | NR | NR | |
| | | 18 R+R RMS best response | 9 | 4 | 5 | 0 | 72%* | | | |
| **Novel agent - single agents** | | | | | | | | | | |
| Samotolisib | Laetsch, 2024[4] | 1 R+R RMS | 0 | 0 | 0 | 1 | 0%* | NR | NR | |
| BCT-100 | Fenwick, 2024[5] | 3 R+R RMS | 0 | 0 | | 2 | 0%* | NR | NR | 2 RMS with PD at 8 weeks, 1 RMS had response assessment at 4 weeks but outcome NR (info provided via email) |
| Palbociclib | Macy, 2024[6] | 5 R+R RMS | 0 | 0 | 0 | 5 | 0%* | 0%* at 6 months | 60%* at 6 months | All CYP with RMS died by time of last follow-up |
| Ulixertinib | Vo, 2024[7] | 4 R+R RMS | 0 | 0 | 0 | 4 | 0%* | 0%* at 3 months | 50%* at 6 months | All CYP with RMS died by time of last follow-up |
| Plitidepsin | Geoerger, 2012[8] | 2 R+R RMS | 0 | 0 | 0 | 2 | 0%* | NR | NR | |
| Lenvatinib | NCT04447755, 2024[13] | 17 R+R RMS | | | | | 11.80% (1.5-36.4) | 2.6 (95% CI 1.2- 5.6) months | NR | DOR in 2 RMS median 4.6 months<br>Up to approx 21 months, DCR 52.9% (27.8-77), CBR 29.4% (10.3-56) |
| **Molecular Registry Studies** | | | | | | | | | | |
| Temsirolimus, Vinorelbine, Cyclophosphamide | Deyell, 2024[9] | 2 R+R RMS | 2 | 0 | 0 | 0 | 100%* | NR | NR | Both CYP relapsed after CR and had died at the end of follow-up |
| Palbociclib, Irinotecan, Temozolomide | | 1 R+R RMS | 0 | 0 | 1 | 0 | 0%* | NR | NR | |
| Trametinib | Vasquez, 2024[10] | 1 2nd relapse RMS | 0 | 0 | 0 | 1 | 0%* | 20 days | NR | Patient DOD after treatment discontinuation |
| Trametinib | Lau, 2024[11] | 1 1st relapse RMS | 0 | 0 | 0 | 1 | 0%* | 1.7 months | 6.4 months | PFS measured from the point of receiving PGT<br>OS measured from point of enrolment |

| Regimen | Author, Year | Total no. of relevant CYP$ | Responses (number of CYP) | | | | Response rate % (95% CI) CR+PR | Median survival (range) | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | SD | PD | | PFS/TTP | OS | |
| Nivolumab | | 1 1st relapse RMS | NA | NA | NA | NA | NA | 12.4 months | 39.6 months | PFS/OS measured as described above.<br>This patient had one prior relapse at study entry but had NED at the point of receiving PGT. Also received UGT and had PD after 1.9 months, although it is not clear if this was before or after PGT |
| **Cellular therapies** | | | | | | | | | | |
| Lymphodepleting chemotherapy followed by HER2 CAR-T cells | Hegde, 2024[12] | 3 R+R RMS | 1 | 0 | 1 | 1 | 33.3%* | 3.7 (1.9-17) months | 17.4 (8.5->72) months | 1 initially had CR then progressed at 17 months but re-enrolled and then in CR for over 6 years at follow-up |

$ = evaluable CYP with RMS; *calculated from provided information; Blue highlight = study with more than 10 CYP where response rate was >30%

CAR-T = chimeric antigen receptor-T cells; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; CYP = children and young people; DCR = disease control rate; DOD = died of disease; DOR = duration of response; NA = not applicable; NED = no evidence of disease; NR = not reported; OS = overall survival; PD = progressive disease; PFS = progression free survival; PGT = precision-guided therapy; PR = partial response; R+R = relapsed and refractory; RMS = rhabdomyosarcoma; SD = stable disease; TTP = time to progression; UGT = unguided therapy; WHO = World Health Organisation

## Table 4. Adverse Event data

| Intervention | Author, Year | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| **Standard agents - multiple agents** | | | | | | |
| Vincristine, Pegylated Liposomal Doxorubicin, Cyclophosphamide | Lu, 2024[3] | 34 (24) | 2P | 20E | 20E | DLTs: 2P with G4 **neutropenia** ≥7 days (both in DL2 - 40mg/m$^2$ of pegylated liposomal doxorubicin)<br>G3 AEs: 7P anaemia, 7P **neutropenia**, 2P **thrombocytopenia**, 4P **febrile neutropenia**<br>G4 AEs: 14P **neutropenia**, 3P **thrombocytopenia**, 3P **febrile neutropenia** |
| **Novel agent - single agents** | | | | | | |
| Samotolisib | Laetsch, 2024[4] | 17 (1) | | 6E in 4P | | 6 ≥G3 TRAEs in 4P (1P at DL1, 3P at DL2). 2 G3 lymphocyte count decrease (both DL2), 2 G3 hypokalemia (1 at DL1, 1 at DL2), 1 G3 **mucositis** (DL2), 1 G3 pneumonitis (DL1). 1P discontinued due to TRAEs |
| BCT-100 | Fenwick, 2024[5] | 45 (3) | 0 | | | No G3+ treatment-related AE or SAEs<br>Non treatment-related SAEs<br>G3: 1P **vomiting**, 1P upper respiratory infection, 1P urinary tract infection, 1P headache, 1P seizure. |

| Intervention | Author, Year | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | G4: 1P sepsis, 1P distress due to fluid overload, 5E in 3P dyspnea, 1P respiratory arrest<br>G5: 1P cardiac arrest<br>Data on non treatment-related AEs provided in manuscript. |
| Palbociclib | Macy, 2024[6] | 20 (5) | 4P | 25E | 9E | 17P ≥1 G3+ AE. 5P had dose modifications due to AEs but remained on therapy.<br>G3 AEs: 5P anemia, 1P GGT increase, 1P lymphocyte count decrease, 8P **neutrophil count decrease**, 5P **platelet count decrease**, 5P WBC decrease.<br>G4 AEs: 2P lymphocyte count decrease, 2P **neutrophil count decrease**, 3P **platelet count decrease**, 2P WBC decrease |
| Ulixertinib | Vo, 2024[7] | 20 (4) | 15E | | | DLTs: in C1: 1 G3 **diarrhoea**, 1 G4 hypernatremia, 2 G3 hypoalbuminemia, 2 G3 fatigue (1 RMS P), 1 G2 and 2 G3 **nausea**, 1 G3 dehydration, 1 G2 rash acneiform, 1 G2 **vomiting** (RMS P), 1 G3 anorexia. In C3: 1 G3 creatine increase. In C5: 1 G3 hip fracture.<br><br>G3+ AEs: 1P ALT increase (DL2), 3P anemia (1 DL1, 2 DL2), 1P anorexia (DL1), 1P AST increase (DL1), 1P cholecystitis (DL1), 1P creatinine increase (DL1), 2P dehydration (1 DL1, 1 DL2), 1P **diarrhoea** (DL1), 2P fatigue (1 DL1, 1 DL2), 1P hip fracture (DL2), 1P hypernatremia (DL2), 3P hypoalbuminemia (2 DL1, 1 DL2), 1P lipase increase (DL1), 2P lymphocyte count decrease (1 DL1, 1 DL2), 4P **nausea** (3 DL1, 1 DL2), 1P **platelet count decrease** (DL1), 2P rash maculo-papular (2 DL1), 1P sepsis (DL1), 1P Stevens-Johnson syndrome (DL1), 1P urinary retention (DL1), 1P **vomiting** (DL1) |
| Plitidepsin | Geoerger, 2012[8] | 38 (2) | 14E in 11P | | | 35C delayed in 14P. 16 delays due to plitidepsin-related toxicity: 7 CPK increase, 6 transaminase increase, 1 transaminase and CPK increase, 1 QTc segment prolongation, 1 G2 **thrombocytopenia**<br><br>DLTs: 1 G2 myalgia (DL1), 1 G4 CPK increase (DL3), 2 G3 ALT increase (1 DL3, 1 CE), 2 G3 **nausea** (DL2, 1 CE), 2 G3 **vomiting** (DL2, 1 CE), 1 G3 myalgia (CE), 1 G3 dysaesthesia (CE), 4 G3 CPK increase (all CE)<br><br>TRAEs: G3: 1P abdominal pain, 4P hypersensitivity (all 5mg/m$^2$ dose), 1P myalgia, 2P **nausea**, 1P pyrexia, 3P **vomiting**. 4P withdrawn from study - 2P due to hypersensitivity AEs, 2 to disease progression<br><br>On-treatment laboratory abnormalities:<br>G3: 2P haemoglobin, 5P lymphocytes, 2P **neutrophils**, 12P ALT, 3P Alkaline phosphatase, 2P AST, 5P CPK<br>G4: 1P haemoglobin, 1P WBC, 1P **neutrophils**, 1P **platelets**, 1P AST, 1P CPK |
| Lenvatinib | NCT04447755, 2024[13] | 127 (17) | | | | All P ≥1 AE. 8P (no RMS) discontinued due to AE. 94P all-cause mortality (15/17 RMS). 63P ≥1 SAE (5/17 RMS).<br><br>SAEs (grade NR): 1P pericardial effusion, 1P inappropriate antidiuretic hormone secretion, 4P abdominal pain, 1P anal fistula, 1P colitis, 1P **constipation**, 2P **diarrhoea**, 1P enterocolitis, 1P gastritis haemorrhagic, 1P gastrointestinal obstruction (RMS), 1P ileus, 1P intestinal obstruction, 1P intra-abdominal haemorrhage, 1P pneumoperitoneum, 2E in 1P **vomiting**, 2P asthenia, 1P complication associated with device, 1P fatigue, 4P pyrexia (1 RMS), 2P cholecystitis, 1P bronchitis, 1P bronchopulmonary aspergillosis, 1P covid-19, 1P device related infection, 1P device related sepsis, 1P gastroenteritis, 1P pneumonia, 8E in 3P pneumonia aspiration, 3P sepsis, 1P |

| Intervention | Author, Year | Number evaluable for toxicity (RMS) | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| | | | | | | soft tissue infection, 1P upper respiratory tract infection, 4P urinary tract infection (1 RMS), 1P accidental overdose, 1P ligament sprain, 1P overdose, 1P pneumothorax traumatic, 1P subdural haematoma (RMS), 2P wound dehiscence, 2P blood bilirubin increase, 1P **weight decrease**, 2P decrease appetite, 1P arthralgia, 1P arthritis, 1P back pain, 1P muscle weakness, 1P musculoskeletal pain, 1P pain in extremity, 1P tumour associated fever, 1P tumour pain, 1P depressed level of consciousness, 1P haemorrhage intracranial, 4P headache, 1P hemiparesis, 1P hydrocephalus, 3P intracranial pressure increase, 1P posterior reversible encephalopathy syndrome, 3E in 2P seizure, 1P device dislocation, 1P hallucination, 2P acute kidney injury, 1P neurogenic bladder, 1P aspiration, 1P atelectasis, 1P laryngeal fistula, 11E in 7P pneumothorax, 3P hypertension, 1P hypotension<br><br>Further information on non-serious AEs can be found on trial website. |
| **Molecular Registry Studies** | | | | | | |
| Multiple interventions, see Table 2 | Deyell, 2024[9] | No AE data reported | | | | |
| Trametinib | Vasquez, 2024[10] | No AE data reported | | | | |
| Trametinib | Lau, 2024[11] | No AE data reported | | | | |
| **Cellular therapies** | | | | | | |
| Lymphodepleting chemotherapy followed by HER2 CAR-T cells | Hegde, 2024[12] | 13 (3) | 2 | | | CRS in 11P ( 2 RMS). 1 G3 and 1 G4 CRS with respiratory involvement in 2P (not RMS) - both considered DLTs.<br><br>G3-4 TRAEs: 2P dyspnea (1 cohort B, 1 cohort C). 1P hypoxia (cohort C), 1P respiratory failure (cohort C), 1P hypercapnia (cohort C), 1P sinus tachycardia (cohort C), 2P hypotension (1 cohort A, 1 cohort C), 1P fever (cohort C).<br><br>Note: 1 patient was re-enrolled, it's unclear if their AEs were counted twice |

AEs written in **bold** text represent the AEs most important to the parent group.

AE(s) = adverse event(s); ALT = alanine aminotransferase; AST = aspartate aminotransferase; C = cycle(s); CAR-T = chimeric antigen receptor-T cells; CE = cohort expansion; CPK = creatine phosphokinase; CRS = cytokine release syndrome; DL = dose level; DLT = dose limiting toxicity; E = event(s); G = grade; GGT = gamma-glutamyl transferase; INR = international normalised ratios; NR = not reported; P = patient(s); RMS = rhabdomyosarcoma; SAE(s) = serious adverse event(s); TRAE = treatment-related adverse events; WBC = white blood cells

## Table 5. New clinical trial registry records

| Clinical trial registry number | Planned locations; Sponsor | N | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|
| **Recruitment status: Not yet recruiting** | | | | | | | |
| NCT06625190 | No location data provided; Academic | 27 (E) | 01/02/24* - 01/02/30* | **Alpha/beta T cell** and **CD19+ B cell depleted stem cell graft** with **zoledronic acid** (IV days +28/56/84/112/140, initially 1.25mg/m$^2$, adjusted according to toxicity) | OS, PFS, rates of aGVHD | Relapsed, Refractory, All solid tumours, Excluded if allogeneic HSCT in last 6 months | ≤25 years |
| NCT06441331 | No location data provided; Pharmaceutical company | 20 (E) | 01/01/25* - 01/04/34* | **Lutetium Lu 177-Edotreotide** (IV, 2-6 cycles every 8 weeks) | Response rates, AEs, OS, PFS, Duration of response | Relapsed, Refractory, Solid tumours + CNS + lymphoma. If extensive bone/bone marrow involvement, must have PBSCs available. Dependent on previous RT doses. Excluded if previous CAR-T, vaccine therapy, or bulky CNS disease. Must have *positive SSTR protein expression* | 2 to 18 years |
| 2024-518417-25-00 | Spain; Academic | 24 (E) | 01/08/19 - 30/09/28 | **Alocelyvir** (Allogeneic bone marrow stem adult mesenchymal cells expanded Infected with Icovir-5), added to other therapy (chemotherapy, surgery, radiotherapy) | Response rates, AEs, OS, PFS, Dose Limiting Toxicities | Relapsed, Refractory, All solid tumours, Evaluable/measurable disease. Excluded if allergic to penicillin | 1 to 21 years |
| **Recruitment status: Recruiting** | | | | | | | |
| NCT06541262 | USA; Academic | 114 (E) | 30/10/24 - 01/11/35 | **Silmitasertib** 600mg/m$^2$ or 800mg/m$^2$ po bd plus **Vincristine**, **Irinotecan**, **Temozolomide** (dose and frequency NR) | Response rates, AEs, PFS, Dose Limiting Toxicities, (OS only in phase 2 which RMS not eligible for) | Relapsed, Refractory, Neuroblastoma, Ewing Sarcoma, Osteosarcoma (phase I only), RMS (phase I only), Liposarcoma (phase I only). Evaluable/measurable disease | <30 years at initial Dx |
| NCT06566092 | USA; Pharmaceutical company | 40 (E) | 28/03/24 - 01/07/28 | Biological: **LN-145/LN-144** (Autologous Tumour Infiltrating Lymphocytes) | Response rates, AEs, OS, PFS, Duration of response, Disease control rate | Relapsed, Refractory. RMS, Ewing sarcoma, primary CNS malignancies, melanoma. Must be >8kg. At least 1 resectable lesion & at least 1 other measurable lesion. Excluded if symptomatic brain metastases, or previous allogeneic HSCT | 6 months to 21 years |
| NCT06514313 | China; Academic | 110 (E) | 03/07/24 - 01/12/26 | **Mitoxantrone** + **Irinotecan** + **Vincristine**, IV, for 4 cycles (dose and frequency NR) | Response rates, OS, PFS, Disease Control Rate, ctDNA | Relapsed, Refractory, Soft-tissue sarcomas only, RMS must be 1st, 2nd or 3rd line only. Measurable disease. Excluded if prior mitoxantrone or prior VIT | 2 to 21 years |

| Clinical trial registry number | Planned locations; Sponsor | N | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|
| | | | | Comparator: **Vincristine** + **Irinotecan** + **Temozolomide** every 3 weeks (dose and frequency NR) | | | |
| NCT06087341 | Spain; Academic | 18 (E) | 10/01/24 - 01/04/28* | **NKG2D-CAR memory T cells**, IV +/- intratumoral | Response rates, Maximum Tolerated Dose, Dose Limiting Toxicities, PKs | Relapsed, Refractory, Sarcoma. Evaluable/measurable disease. *Positive NKG2DL expression* (positive expression defined as at least 2+ expression (0-4+ scale) in >50 percent of the tumor cells using anti-MICA and or anti-ULBP2) | Unclear - <30 years in one place in record, ≤40 years in another |
| NCT04817956 | Norway; Academic | 3000 (E) | 01/04/21 - 30/04/45 | Molecular registry study, multiple interventions available depending on mutational analysis | Response rates, OS, PFS, Access to drugs | Relapsed, Refractory, Solid tumours + CNS + haematological. Evaluable/measurable disease | ≥16 years |
| NCT04589845 | UK, USA, France, Germany, Canada, Australia, Belgium, Brazil, China, Denmark, Hong Kong, Israel, Italy, Japan, Republic of Korea, Netherlands, New Zealand, Poland, Portugal, Puerto Rico, Russian Federation, Singapore, South Africa, Spain, Switzerland, Taiwan; Pharmaceutical company | 920 (E) | 18/01/21 - 25/09/32 | Molecular registry study - multiple drugs dependent on mutations identified | Response rates, AEs, OS, PFS, PKs, Duration of response, Clinical benefit rate, Quality of Life | Relapsed, Refractory, All solid tumours, measurable disease | All ages |
| NCT04774718 | UK, USA, France, Germany, Canada, Australia, Brazil, China, Denmark, Italy, Republic of Korea, Spain; Pharmaceutical company | 42 (E) | 14/09/21 - 03/07/30 | **Alectinib** po bd in 28-day cycles | Response rates, AEs, OS, PFS, Dose Limiting Toxicities, PKs, Duration of response, Clinical benefit rate, time to response | Relapsed, Refractory, Solid tumours + CNS. Measurable/evaluable disease. Must have tumour tissue from current disease. Must have *ALK* gene fusion. Excluded if prior ALK inhibitors | <17 years |
| NCT03899792 | UK, USA, France, Germany, Canada, Australia, Denmark, Italy, | 50 (E) | 13/06/19 - 31/05/29 | **Selpercatinib** Starting dose 160mg bd for 28-day cycles | Response rates, AEs, OS, PFS, Dose Limiting Toxicities, PKs, Duration | Relapsed, Refractory, Solid tumours + CNS, measurable or non-measurable disease. Must have activating *RET gene alteration*. Excluded if prior RET inhibitors | 6 months to 21 years |

| Clinical trial registry number | Planned locations; Sponsor | N | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|
| | Japan, Republic of Korea, Spain; Pharmaceutical company | | | | of response, Clinical benefit rate, pain scores, Quality of life | | |
| NCT06208657 | Canada, Australia; Academic | 82 (E) | 10/07/24 - 01/12/35* | Arm A (only current registered arm): **Irinotecan** 50mg/m$^2$/day, IV, on days 1-5. **Temozolomide** 150mg/m$^2$/day, po, days 1-5. **Paxalisib** 21mg/m$^2$ po, daily. 28 day cycles, max 13 cycles<br><br>**Pimasertib** 28mg/m$^2$ po, bd, 28 day cycle, 26 cycles (unclear if separate arm or part of this intervention) | Response rates, AEs, PFS, PKs, Clinical benefit rate, RP2D | Relapsed, Refractory, Solid tumours + CNS + lymphoma, must be enrolled on a precision medicine study, Evaluable/measurable disease. Excluded if symptomatic CNS disease | <21 years |
| NCT05907304 | UK, USA, Canada, Australia, Republic of Korea; Pharmaceutical company | 115 (E) | 17/08/23 - 01/11/25* | **Naporafenib** 200mg bd + **Trametinib** 1mg od | Response rates, AEs, OS, PFS, PKs, Duration of response, time to response, disease control rate | Relapsed, Refractory, All solid tumours, archival tissue required (within 5 yrs of enrollment). Measurable disease. *RAS Q61X mutation*. Excluded if prior ERK-, MEK-, RAF-, or RAS-inhibitor, or symptomatic CNS metastases | ≥12 years |
| NCT05407441 | USA; Academic | 49 (E) | 10/08/23 - 01/02/29 | **Tazemetostat** (po bd) + **Nivolumab** (IV) + **Ipilimumab** (IV) | Response rates, AEs, OS, PFS, Maximum Tolerated Dose, Dose Limiting Toxicities, RP2D | Relapsed, Refractory, Solid tumours + CNS, Measurable disease. *INI1- or SMARCA4-deficient*. Excluded if prior allo HSCT, anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA4 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. OX40, CD137) | 6 months to 21 years |
| NCT04925609 | France, Netherlands; Academic | 65 (E) | 18/08/22 - 01/12/30* | **Brigatinib** po (dose NR) | Maximum Tolerated Dose, Dose Limiting Toxicities, PKs, RP2D | Relapsed, Refractory, All solid tumours, Includes ALCL and IMT (relapsed or newly diagnosed). ALK+ tumours. Able to swallow tablets. Weight >10kg | ≤18 years in phase 1 (RMS cohort); < 25 years for other cohorts |
| 2023-504880-18-00 | UK, France, Germany, Netherlands, Ireland, Spain, Denmark, Italy; Academic | 71 (E) | 18/04/18 - 01/01/30 | **Crizotinib** po + **Temsirolimus** IV | Response rates, AEs, OS, PFS, Dose Limiting Toxicities, PKs, Duration of response, time to response | Relapsed, Refractory, Neuroblastoma or RMS (Stratum 2). *ALK, ROS1, or MET* rearrangements, activating mutations, or ALK/MET amplification. Measurable and non-measurable disease. No prior therapy directly targeting ALK, ROS1 or MET | 1 to 21 years |

| Clinical trial registry number | Planned locations; Sponsor | N | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|
| ChiCTR2300071221 | China; Academic | 26 | 10/05/23 - 31/12/25 | **Tislelizumab** with **Eribulin** and **Anlotinib** | Response rates, AEs, OS, PFS, Disease control rate | Relapsed, Refractory, Soft-tissue sarcomas only, Distant metastases or locally advanced unresectable STS failing at least 1st line therapy | ≥16 years |
| **Recruitment status: Active, not recruiting** | | | | | | | |
| NCT03837899 | UK, USA, France, Germany, Italy, Netherlands, Spain; Pharmaceutical company | 50 (A) | 07/03/19 - 30/12/24 | **Durvalumab** 20mg/kg. **Tremelimumab** 1mg/kg at cycles 2 to 5 only. Both drugs every 4 weeks as IV infusions | Response rates, AEs, OS, PFS, PKs, Duration of Response, Best Objective Response, Disease Control Rate | Relapsed, Refractory, Solid tumours + NHL. Excluded if previous allogeneic HSCT. Evaluable disease | <18 years |
| NCT04773782 | UK, USA, France, Germany, Canada, Australia, Austria, Italy, Republic of Korea; Pharmaceutical company | 37 (E) | 24/02/22 - 30/12/25 | **Avapritinib** po od in 28-day cycles | Response rates, AEs, PFS, PKs, Duration of response, RP2D, Disease Control Rate, Time to Response | Relapsed, Refractory, Solid tumours + CNS, measurable disease. Mutation in *PDGFRA* and/or *KIT*. Recent cellular therapies excluded. Must be able to swallow tablets | 2 to <18 years |
| NCT05620862 | China, Academic | 68 (E) | 25/10/22 - 01/06/25 | **Mitoxantrone** alone (Phase 1a: IV 16/20/24 mg/m$^2$; Phase 1b: 24mg/m$^2$) or with **Irinotecan** (50mg/m$^2$ d1-5) + V**incristine** (1.5mg/m$^2$ d1), 21d cycles, max 6 cycles | Response rates, AEs, PFS, Maximum Tolerated Dose, Dose Limiting Toxicities, PKs | Relapsed, Refractory, All solid tumours, + lymphoma. Measurable disease | 2 to 21 years |
| NCT04985604 | USA, France, Canada, Australia, Belgium, Republic of Korea, Spain; Pharmaceutical company | 168 (E) | 15/07/21 - 31/12/25 | **Tovorafenib (DAY101)** po (dose and frequency NR)<br><br>Comparator: **Tovorafenib** plus **pimasertib** po (dose and frequency NR) | Response rates, AEs, OS, PFS, PKs, Duration of response, time to response, RP2D | Relapsed, Refractory, All solid tumours + melanoma. Measurable disease. Substudy A *BRAF fusion, CRAF/RAF1 fusion, or CRAF/RAF1 amplification*; Substudy B *MAPK* pathway alteration (geno*mic alterations in* RAS, RAF, MEK, or NF1). Must have archival (<3 yrs old) or fresh tissue available. Excluded from substudy A if prior RAS- RAF-, MEK-, or ERK-directed inhibitor | ≥12 years |
| NCT03429803 | USA; Academic | 44 (A) | 27/02/18 - 31/12/24 | **Tovorafenib (DAY101),** 28 day cycle, po, once per week (dose NR) | Response rates, AEs, Dose Limiting Toxicities, PKs | Relapsed, Refractory, Solid tumours + CNS, Measurable disease. Activation of the *RAS/RAF/MEK/ER*K pathway. Must be able to swallow tablets. Patients with NF1 excluded | 1 to 25 years |
| jRCT2091220344 | Japan; Academic | 15 (E) | 20/04/18 - 30/09/24 | **Nivolumab** 240mg IV every other week | Response rates, AEs, OS, PFS, Disease control rate | Relapsed, Rare cancer or rare tissue subtype of common cancer which is MSI-high or dMMR - negative of at least one immunohistochemical staining markers MLH1, MSH2, MSH6, PMS2. Excluded if symptomatic brain metastases. Measurable disease. No prior immune checkpoint inhibitors | ≥16 years |
| jRCT2091220 | Japan; Academic | 54 | 20/04/18 | **Nivolumab** 240mg IV every | Response rates, AEs, | Relapsed, Rare cancer or rare histologic subtype of common | ≥16 years |

| Clinical trial registry number | Planned locations; Sponsor | N | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|
| 345 | | (E) | - 21/11/22 | other week | OS, PFS, Disease control rate | cancer with MSI-low or pMMR. Excluded if symptomatic brain metastases. Measurable disease. No prior immune checkpoint inhibitors. | |
| **Recruitment status: Completed** | | | | | | | |
| NCT04029688 | UK, USA, France, Canada, Netherlands, Spain; Pharmaceutical company | 38 (A) | 27/01/20 - 06/05/24 | **Idasanutlin** po od on days 1-5 of 28-day cycle | Response rates, AEs, OS, PFS, Dose Limiting Toxicities, PKs, Duration of response, Clinical benefit rate | Relapsed, Refractory, Solid tumours + haematological malignancies, Must have tumour tissue available from relapse | <18 years |
| **Recruitment status: Terminated** | | | | | | | |
| NCT03690869 | USA; Pharmaceutical company | 57 (A) | 24/09/18 - 10/05/23 | **Cemiplimab** IV (phase 1 only of interest) | Response rates, AEs, Dose Limiting Toxicities, PKs | Relapsed, Refractory, Solid tumours + CNS, Excluded if bulky CNS disease, previous allogeneic HSCT, prior PD-1/PD-L1/PD-L2 inhibitors | <18 years (phase 1) |

* 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; AE(s) = adverse event(s); aGVHD = acute graft-versus-host disease; ALCL = anaplastic large cell lymphoma; bd = twice daily; CAR-T = chimeric antigen receptor-T cells; CNS = central nervous system; ctDNA = circulating tumour DNA; dMMR = mismatch repair deficiency; Dx = diagnosis; E = estimated enrolment; HSCT = hematopoietic stem cell transplant; IMT = inflammatory myofibroblastic tumours; IV = intravenous; MSI = microinstability; N = number of participants; NHL = non-Hodgkin's lymphoma; NR = not reported; od = once daily; OS = overall survival; PBSC = peripheral blood stem cells; PFS = progression free survival; PKs = pharmacokinetics; pMMR = mismatch repair proficiency; po = orally; RMS = rhabdomyosarcoma; RP2D = recommended phase 2 dose; RT = radiotherapy; SSTR = somatostatin receptor; STS = soft tissue sarcoma; UK = United Kingdom; USA = United States of America

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