# Living REFoRMS update 3 (REFoRMS LSR-3) report

## Updates to methods from LSR-2 (PROSPERO CRD42022380185)[1]

### Searches

For update 3, fewer bibliographic databases were searched. We limited the selection of databases to: Cochrane CENTRAL, Cochrane CDSR, the International HTA database, and Embase. For Embase only, searches were limited to conference abstracts. We also applied date limits of 2023 to current for these searches. We stopped searching the following databases which were shown to be finding no unique records in the previous updates: MEDLINE, and Science Citation Index–Expanded.

PROSPERO and clinical trial registries will continue to be searched, in addition to searches of OpenAlex (auto-update searches, custom searches, and network graph searches). Snowball citation searching will continue. In this update, machine learning - based on decisions we have made from previous screening - will be used to discard records that are very unlikely to be eligible. This is expected to reduce title and abstract screening at each update by 20-30%, with minimal risk of missing eligible reports among them. Database searches were run on 16th November 2023 and OpenAlex searches on 20th November 2023.

### Screening

The eligibility criteria for the studies was the same as the criteria set out in the original review and is as listed on PROSPERO.[1] Study selection was conducted using EPPI reviewer software. Screening was performed in line with LSR-1 methods.

Following discussions with our clinical advisory group, in this update we have stopped tracking CTR records that had an estimated study completion date of >10 years from the point in which we reviewed the CTR records for updates or new outputs.

### Data extraction and quality assessment

Data extraction was performed in line with baseline review methods.

A modified Downs and Black Checklist was used, as described in LSR-1.[2] Alongside this, a new quality assessment tool, the methodological index for non-randomised studies (MINORS) was assessed.[3] This 12-item list (eight relevant for single-arm studies) was considered to be a potentially more appropriate quality assessment tool to use for early phase studies, although one question regarding the consecutive enrolment of patients was not deemed appropriate for early-phase trials, and therefore was not included. The outcome of these two assessments were compared and the most suitable tool for future updates considered (see Summary section for further information).

### Study selection

From 3,340 studies identified from the searches, 98 were eligible at title and abstract screening. A detailed flow sheet of the LSR-3 process can be found in Figure 1. A simplified flowsheet of studies included in the REFoRMS project (baseline review and all updates) can be found in Figure 2.

**Figure 1:** LSR-3 flowsheet

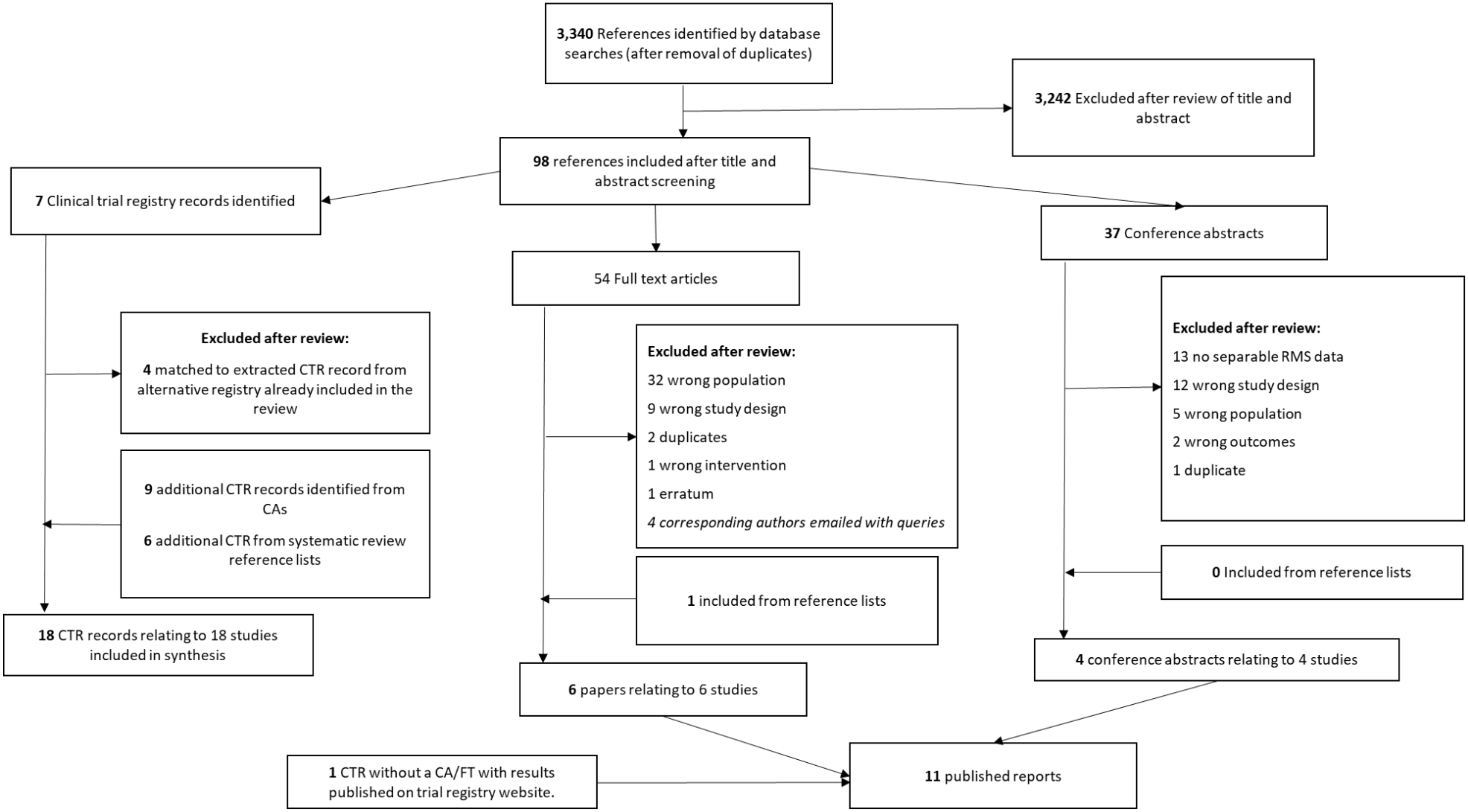
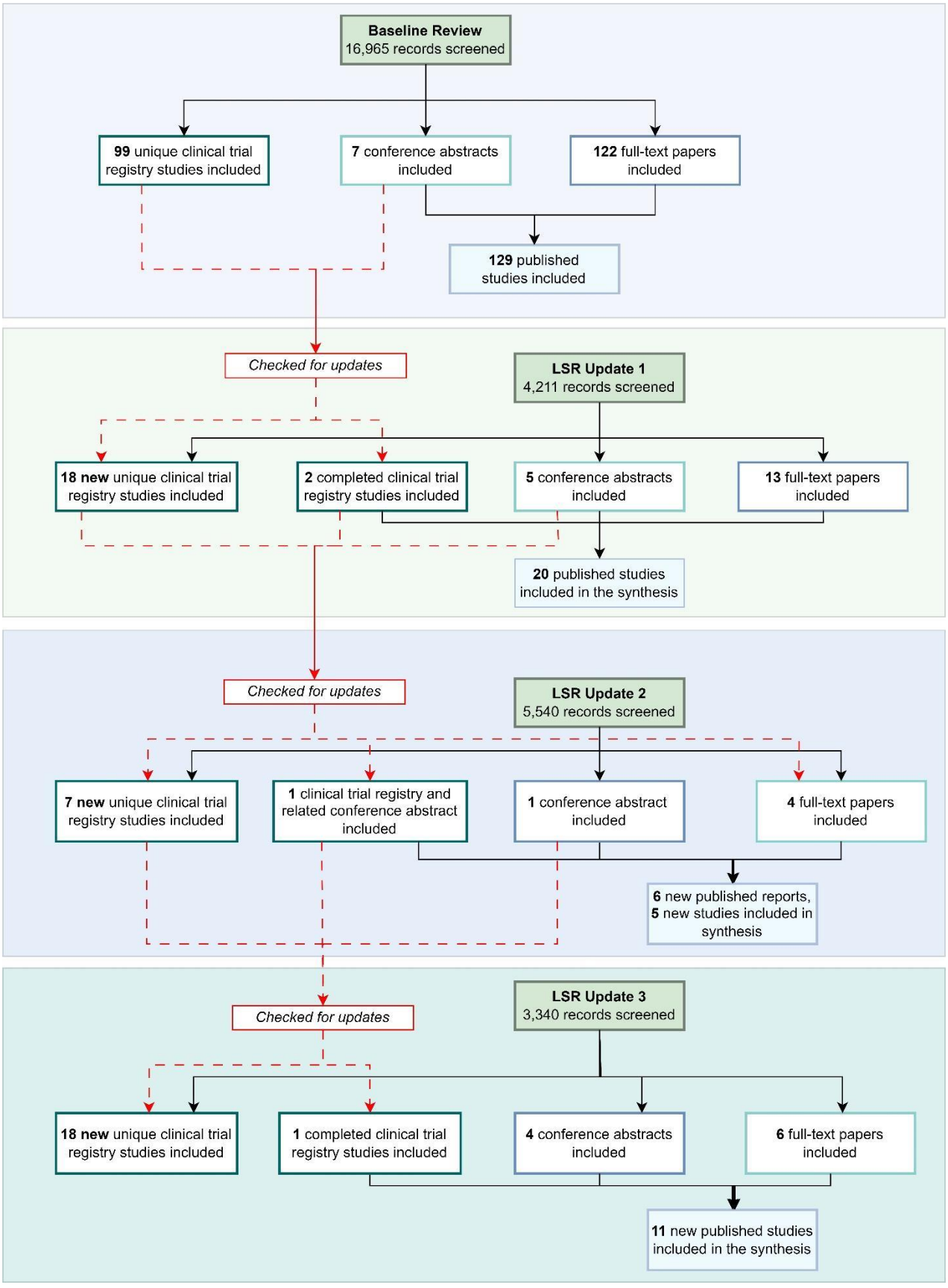


**Figure 2:** Flowsheet of included studies in REFoRMS



Following full-text screening, 11 studies providing results were included, including four conference abstracts [CAs][4] (three of which were extracted alongside associated clinical trial registry records [CTRs][5-7]) and six full-text papers[8-13], including one that was identified during reference list searching[11], as well as one study that provided study results on their CTR record.[14]

Seven authors were contacted for further information to determine eligibility for inclusion in this review (including four queries relating to texts identified in the database searches, and three queries relating to papers identified by reference list searching, from a relevant systematic review (n=1) and from the CA checking). We have received one reply at the time of preparing this report; which was not eligible as there were no RMS patients. Any responses received following the publication of this report will be included in the next update (LSR-4).

## Updates of previously identified CTRs

One hundred and seven CTRs were checked for updates. Eleven had newly identified CAs, five had posted data on the trial registry website, and four CTRs had newly identified full-text publications. None of the newly identified outputs provided data that was relevant to LSR-3. Eighteen CTR records were no longer tracked, as their study completion date was over 10 years ago.

Of the 52 CTRs identified to be currently open at the time of the last update, 40 continue to be reported as currently open. Since the last update, nine CTRs have finished recruitment (and are currently 'active not recruiting'), one study is now reported to be completed (but no outputs have been reported), and two studies are now suspended or terminated. Of the eighteen CTRs identified as completed but not yet reported at the time of the last update, three (16.7%) have newly identified information available.[14–16]

### Newly identified CTRs

Eighteen new CTRs were identified and extracted for LSR-3. Three were identified in the update search,[17–19] nine were included after being identified from new CAs,[20–28] and six were identified during citation searching of relevant systematic reviews identified in the database searches of LSR-3[29–34].

## Published studies

### Demographics of new studies

Eleven studies contributed thirteen new cohorts to REFoRMS LSR-3.[4-14] The reported countries of recruitment were: USA (6 studies[5-7,9,10,14]), Japan (4[5,11-13]), France (3[5,8,10]), Italy (3[5,8,10]), Spain (3[5,8,10]), Canada (3[5,9,10]), United Kingdom (2[8,10]), Australia (2[5,10]), Puerto Rico (2[6,7]), as well as Belgium[10], Austria[10], Faroe Islands[10], Germany[10], and the Netherlands[10] (1 each). One study did not report the countries of recruitment.[4] For studies which reported their location, most were completed in multiple countries (n=8, 73%).[4-10,14]

Five studies contributing seven cohorts evaluated multi-agent novel therapies,[4,5,8,9,14] one evaluated a novel-agent monotherapy,[10] three studies looked at biomarker-driven

monotherapies (one of which was evaluated as part of a molecular registry study),[6,7,13], and two evaluated vaccine therapies[11,12].

As expected, most studies identified by the update were published in 2023 (n=8[4-10,13]), while two studies were published before 2023 (one in 2021[12], and one in 2010[11]). Hashii et al. (2010) was identified during citation searching, and while it had been identified and excluded in searches in baseline REFoRMS, further analysis of the population determined that it was eligible for inclusion albeit it being unclear as to whether the patients had active disease when receiving therapy for relapse (See Table 4 for further details).[11] The results of one study have been posted on the CTR record only (2023).[14]

### Demographics of participants in new studies

At least 63 children and young people with relapsed and refractory rhabdomyosarcoma were included in the newly identified studies. Seven cohorts from six studies included five or fewer patients with relapsed/refractory rhabdomyosarcoma.[6,8,11-13] In one study, at least one patient with relapsed/refractory rhabdomyosarcoma was included, but the exact cohort size is unknown.[4] All of the studies recruited patients with a variety of tumour types. Where reported (n = 10), eight studies included children as young as one year old[5-12], but few (n = 4) studies included those under one[5,8,11,12]. Despite having lower age limits, three studies required participants to be able to take tablets/capsules, and this may limit the inclusion of the youngest patients in a study.[6,7,9]

Six cohorts reported the sex of included patients (two for rhabdomyosarcoma patients only[9,14], and four for the whole study population[8,13]), three cohorts reported gender (two for rhabdomyosarcoma patients only,[11,12] one for the whole study population[10]), and four reported neither sex nor gender (all conference abstracts)[4-7]. Sex/gender was reported as a binary characteristic in all studies included in the review, although one study only reported the number of males included.[8] Where sex/gender was reported for rhabdomyosarcoma patients specifically, 21 (66%) participants were male and eleven (34%) were female.

Two cohorts reported both the ethnicity and race of the rhabdomyosarcoma patients.[9,14] In these cohorts, the race of patients were white (n = 25), black (n = 1) or unknown (n = 4); and the ethnicity was hispanic (n = 8), non-hispanic (n = 20), or unknown (n = 2). Eleven cohorts (9 studies) reported neither race or ethnicity for any of the included patients.[4-8,10-13]

### Quality assessment of new studies

In this update, we compared the Downs and Black[2] and MINORS quality assessment tool[3]. Owing to the lack of available tools used to measure the quality of early phase trials, we have used a modified version of the Downs and Black tool to assess quality of included studies since the baseline systematic review. The MINORS checklist is another quality assessment tool that is used to assess the quality of non-randomised studies. Following the completion of the MINORS checklist, the reviewers deemed that one question “Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)” was not relevant in the case of early phase trials, and therefore was removed.

Table 1 and 2 present the quality of each study using the modified Downs and Black checklist and the MINORS checklist for the studies included in this LSR update. As shown in the tables, the MINORS checklist seems to be more sensitive to differences in study quality. For example, the 'unbiased assessment of endpoints' - whereby only two study reported using external assessors to evaluate response; or the 'prospective collection of data' - where some studies did not report corresponding clinical trial registrations or details of protocols.

Overall, when comparing the two checklists, for items on the Downs and Black and MINORS that were similar (for example questions regarding whether aims were clearly described, whether subjects lost to follow-up were described and prospective sample size collection), answers were the same. Both assessment tools were able to accurately reflect poorer quality studies that reviewers deemed were at a higher risk of bias. While the Downs and Black quality assessment tool included some questions that the MINORS study did not cover (i.e. adverse events), the MINORS checklist was deemed to be easier to understand and was more user friendly.

**Table 1:** Modified Downs and Black Quality Assessment for Included Studies

| | Reporting | | | | | | | | | External Validity | Internal Validity | | | | Power |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Author, Year** | **1** | **2** | **3** | **4** | **6** | **7** | **8** | **9** | **10** | **13** | **16** | **18** | **19** | **20** | **27** |
| Casanova, 2023[8] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | N/A | Yes | Yes | Yes | Yes | Yes | Yes |
| Cole, 2023[9] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Eisai, 2023[14] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | N/A | Yes | Yes | N/A | Yes | No | Yes |
| Gatz, 2023*[4] | Yes | No | Yes | Yes | Yes | Yes | No | Yes | N/A | Yes | Yes | N/A | Yes | UTD | Yes |
| Geoerger, 2023[10] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | N/A | Yes | Yes | Yes | Yes | Yes | Yes |
| Hashii, 2010[11] | No | Yes | Yes | Yes | Yes | N/A | No | Yes | N/A | No | Yes | N/A | Yes | Yes | No |
| Lassaletta, 2023*[5] | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | N/A | Yes | Yes | N/A | Yes | UTD | UTD |
| Lee, 2023*[6] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | UTD | N/A | Yes | Yes | N/A | Yes | UTD | UTD |
| Macy, 2023*[7] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | N/A | Yes | Yes | N/A | Yes | UTD | UTD |
| Oda, 2023[12] | Yes | Yes | Yes | Yes | Yes | N/A | No | No | N/A | No | Yes | N/A | Yes | Yes | No |
| Tao, 2023[13] | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | UTD | Yes | Yes | Yes | Yes | N/A |

*Studies labelled with a "*" are conference abstracts, so it would be anticipated that the level of reporting would be reduced, owing to limited word counts. N/A: not applicable; UTD: unable to determine. *1. Aims/Objective reported? 2. Main outcomes reported? 3. Subject eligibility criteria reported? 4. Interventions described? 6. Findings clearly described? 7. Random variation of data described? 8. Adverse events described? 9. Subjects lost to follow-up described? 10. Are p-values reported? 13. Were facilities where subjects were treated representative? 16. Have unplanned analyses been indicated? 18. Were statistical tests appropriate? 19. Compliance with intervention reliable? 20. Main outcome measures reliable? 27. Were sample size methods reported?*

**Table 2:** MINORS Quality Assessment Tools for Included Studies

| Author, Year | 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 |
|---|---|---|---|---|---|---|---|
| Casanova, 2023[8] | Reported and adequate | Reported and adequate | Reported and adequate | Reported but inadequate | Reported and adequate | Reported and adequate | Reported and adequate |

| Author, Year | 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 |
|---|---|---|---|---|---|---|---|
| Cole, 2023[9] | Reported and adequate | Reported and adequate | Reported and adequate | Reported and adequate | Reported and adequate | Reported and adequate | Reported and adequate |
| Eisai, 2023[14] | Reported and adequate | Reported and adequate | Reported and adequate | Reported but inadequate | Reported and adequate | Reported and adequate | Reported and adequate |
| Gatz, 2023*[4] | Reported and adequate | Not reported | Reported but inadequate | Not reported | Reported and adequate | Reported and adequate | Reported and adequate |
| Geoerger, 2023[10] | Reported and adequate | Reported and adequate | Reported and adequate | Reported but inadequate | Reported and adequate | Reported and adequate | Reported and adequate |
| Hashii, 2010[11] | Reported but inadequate | Not reported | Reported and adequate | Not reported | Reported and adequate | Reported and adequate | Not reported |
| Lassaletta, 2023*[5] | Reported and adequate | Reported and adequate | Reported but inadequate | Not reported | Not reported | Reported and adequate | Not reported |
| Lee, 2023*[6] | Reported and adequate | Reported and adequate | Reported but inadequate | Reported and adequate | Reported and adequate | Not reported | Not reported |
| Macy, 2023*[7] | Reported and adequate | Reported and adequate | Reported but inadequate | Not reported | Reported and adequate | Reported but inadequate | Not reported |
| Oda, 2023[12] | Reported and adequate | Reported and adequate | Reported and adequate | Not reported | Reported and adequate | Not reported | Not reported |
| Tao, 2023[13] | Reported and adequate | Not reported | Reported and adequate | Not reported | Reported and adequate | Reported and adequate | Not applicable |

**Studies labelled with a "*" are conference abstracts, so it would be anticipated that the level of reporting would be reduced, owing to limited word counts*

## Outcomes of new studies

Overall, data on outcomes was available for 60 patients with relapsed/refractory rhabdomyosarcoma. The number of evaluable rhabdomyosarcoma patients was clear for most studies (the number in two studies was unclear, but was at least one[4,5]). The majority of cohorts (62%) reported outcome data for only one patient with relapsed and refractory rhabdomyosarcoma.[4-6,8,11-13]

### *Survival*

One cohort reported Progression Free Survival (PFS); the median PFS was 22 days (15-57 days).[10] Three cohorts reported overall survival (OS).[10-12] The two vaccine studies reported an OS of over three years, however both of these studies included participants who had no active disease when the treatment was administered.[11,12] The other study reported a median OS of 73 days (range 15-234).[10]

### *Response rate*

Most cohorts showed no objective responses.[6-10,12,13] Most responses were seen in the study of vincristine, irinotecan and regorafenib, when an objective response rate of 66% was seen.[8] One study including 20 patients with rhabdomyosarcoma found a response rate of 10%.[14] In two studies, each including one patient with RMS, responses were seen.[5,11]

All cohorts reported combined results for relapsed and refractory rhabdomyosarcoma patients and thus 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. One study (a conference abstract) did not report any AE data.[4] Twelve cohorts contributed new AE data.[5-14] Within these studies, over 220 participants were evaluable for toxicities. Most AEs were haematological. Additional specific AEs varied by study treatment. No study explicitly reported treatment related or potentially treatment related deaths. One study reported deaths caused by adverse events, but none of these were considered to be treatment-related.[29]

## New CTRs

Eighteen new CTR studies were identified.[15-32] Reported start dates of the studies ranged between 2010 and 2023.

Thirteen studies were reported as having an academic sponsor,[15-18,20,22-24,27-29,31,32] and five a pharmaceutical sponsor[19,21,25,26,30].

We identified 13 currently open studies[15,17-22,24,26-29,32], two studies had closed recruitment [25,31] and two studies were reported as completed with no identified published results[16,23]. One study was now terminated.[30]

Sixteen studies were single-arm and evaluated a range of therapies, including novel single agent therapies (one study),[27] novel multi-agent therapies (three studies),[15,16,24] biomarker driven therapies (four studies),[25,30-32] molecular registry studies (four studies),[17,18,21,28] standard multi-agent therapies (one study),[16] radioimmunotherapy (one study),[19] CAR-T cell therapy (one study)[29] and vaccine therapy (one study)[22]. Two studies including four cohorts were non-comparative multi-arm studies; 1) a biomarker driven study alone or in combination with other chemotherapies[26] and 2) CAR-T cell therapy in combination with two different chemotherapies[20].

Three studies restricted eligibility to participants with sarcoma[15,20,22], and 15 included a wider range of malignancies[16-19,21,23-32]. One study included newly diagnosed patients (if they were in remission or had achieved a partial response at first- or second-line therapy).[22] Eligible ages varied: upper age limits were varied and ranged from 18 years to 75 years. Seven studies had no upper age limit.[19,21,25,26,28,30,32] In this update, eleven studies were open to infants and young children.[16-18,20-24,29,31,32] Seven studies were limited to those over the age of 10-16 years.[15,19,25-28,30]

The countries where studies were open included the USA (n=12),[16,18-20,23-26,28,30-32] Canada (n = 3),[16,26,32] China (n = 3),[15,27,29] United Kingdom (n = 2),[17,30] France (n = 2),[17,30] Germany (n = 2), [17,22] as well as Australia,[32] Austria,[30] Denmark,[17] Israel,[26] Italy,[17] Japan,[21] the Netherlands,[17] Puerto Rico[31] and Spain[17] (1 in each).

## Summary of new studies

The REFoRMS LSR-3 update identified eleven new published studies (13 cohorts) of 63 children and young adults with relapsed and refractory rhabdomyosarcoma. This means that **overall**, the REFoRMS systematic review has identified **165** published early phase studies

of interventions, including **over 1,300** children and young people with relapsed/refractory rhabdomyosarcoma.

In the LSR-3 update, we found a larger number of studies than in the previous update. This was most notable for the number of CAs. One reason this could be is because the time of year in which this update was conducted was at a similar time to when conference proceedings are published. This led to a larger number of studies being identified during searches and being eligible for inclusion. We also found a significant number of CTRs during this update. These were identified from reviews identified in the database searches that were then reviewed. Many of these studies included older children/younger adults only, hence why they may not have been captured in previous searches. The identification of additional studies through citation searching, and checking CAs and CTR records for update highlights the importance of using multiple methods to identify new relevant literature.

One study identified in this update shows promising results for children and young people with relapsed/refractory rhabdomyosarcoma.[8] In the study including eleven patients with relapsed and refractory rhabdomyosarcoma, regorafenib, in combination with vincristine and irinotecan showed an overall response rate of 63% and a disease control rate (CR, PR and SD) of 91%. Based on the results from this study, regorafenib is now being evaluated further in a phase II/III trial in patients with relapsed rhabdomyosarcoma. The FAR-RMS trial, which is currently recruiting, opened in 2020 with an estimated completion date of 2030.[33,34]

Overall, 52 clinical trials are reported to be open for recruitment. The number of newly identified clinical trials evaluating biomarker-driven therapies is increasing, highlighting the emerging drive to evaluate targeted therapies within the field of childhood cancer.

During this update, we have seen an increase in the number of compassionate-use studies in our searches. Compassionate use programmes allow select patients to access investigational drugs when enrollment on a clinical trials board is not possible - often owing to stringent eligibility criteria.[35] While these are not eligible for inclusion in Living-REFoRMS as they are not early phase studies, it is important to highlight that the reporting (and potentially practice) of compassionate use pathways is increasing.[36]

### Suggestions for new adaptations/changes for next update

In this update, we compared two quality assessment tools: the Downs and Black, and the MINORS checklist. As described above, we consider that the MINORS quality assessment tool is more sensitive to differences in assessing study quality, and is more user-friendly, and so this quality assessment checklist will be used henceforth. One question regarding the consecutive recruitment of patients will not be used in quality assessments as we do not deem it to be appropriate in the assessment of quality in early phase trials in childhood cancer.

## Tables

### Table 3 Demographic characteristics of new studies

| Author, date | Countries performed | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range)) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| **Novel agents - single agents** | | | | | | | | | | | | |
| Geoerger, 2023[10] | United Kingdom, USA, Canada, France, Australia, Belgium, Austria, Faroe Islands, Germany, Netherlands, Italy, Spain | Phase 1 + Expansion Study | Multi | May 2015 - Aug 2020 | Relapsed, refractory, all solid tumours, measurable disease. | Part 1: 2 to <18 years<br>Part 2: 1 to <18 years | For part 2, patients must have at least two of the following: 1) EGFR or 2) HER2 protein expression 3) EGFR or 4) HER2 gene amplification | **Afatinib**<br>*Starting at 18 mg/m2 PO OD.*<br>*Part 1 - received Dose Escalation; Part 2 - received MTD* | 7 (56) | WP: 11.5 years (2-18) | See comments | 564 patients were screened, 63 were positive for ≥2 biomarkers; and 56 received afatinib.<br><br>20% had received no chemotherapy (CT), 20% had received 1L CT and 61% had received 2L+ CT. 14% had received no radiotherapy (RT); 46% had received 1L of RT, and 39% had received 2L+ of RT |
| **Novel agents - multi-agents** | | | | | | | | | | | | |
| Casanova (2023)[8] | United Kingdom, France, Italy, Spain | Phase 1b + Expansion Study | Multi | Jan 2018 - Feb 2019 | Relapsed, refractory, all solid tumours, measurable disease. | 6 months to 18 years | | Regorafenib (Consecutive)<br>*72 mg/m2 PO given concomitantly on days 1-14 of 21 day cycles*<br>Vincristine<br>*50 mg/m2 IV on days 1-8*<br>Irinotecan<br>*1.5 mg/m2 IV on days 1-5*<br>*Max 12 cycles* | 1 (2) | WP: 14 years (10-17) | WP: 3.5 (range NR) | 1 embryonal RMS |
| | | | | | | | | Regorafenib (Sequential)<br>*72 mg/m2 PO given concomitantly on days 8-21 of 21 day cycles*<br>Vincristine<br>*50 mg/m2 IV on days 1-8*<br>Irinotecan<br>*1.5 mg/m2 IV on days 1-5*<br>*Max 12 cycles* | 1 (6) | WP: 12 years (5-15) | WP: 2 (range NR) | 1 RMS NOS |

| Author, date | Countries performed | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range)) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| | | | | | | | | Regorafenib (Sequential)<br>*82 mg/m2 PO given concomitantly on days 8-21 of 21 day cycles*<br>Vincristine<br>*50 mg/m2 IV on days 1-8*<br>Irinotecan<br>*1.5 mg/m2 IV on days 1-5*<br>*Max 12 cycles* | 10 (13) | WP: 10 years (1.5-16) | WP: 2 (range NR) | 8 alveolar RMS, 2 embryonal RMS |
| Cole (2023) [9] | USA, Canada | Phase 2 | Multi | Oct 2016 - May 2020 | Relapsed, refractory, measurable disease; RMS, NB and MB/other CNS embryonal tumours | <21 years (FT), 1-21 years (CTR record) | Able to swallow tablets, body surface area >0.49m2 | Adavosertib (capsules):<br>*85 mg/m2 PO for 5 days every 21 days*<br>Irinotecan (solution, mixed with cranberry juice):<br>*90mg/m2 PO for 5 days every 21 days.*<br><br>*Max 18 cycles* | 10 (39) | RMS: 14 years (4-19) | RMS: 3 (1-7) | 5 Alveolar RMS, 3 Embryonal RMS, 2 RMS NOS; 9/10 patients have previously received irinotecan |
| Eisai Inc. (2023) (NCT03245151) [14] | USA,Canada | Phase 1/2 | Multi | Nov 2017 - Sept 2022 | Relapsed, refractory, all solid tumours, measurable disease | ≥2 to <18 years for Phase 1. ≥2 to ≤21 years for Phase 2. | No evidence of untreated CNS metastases, body surface area > 0.6m2 | Lenvatinib (oral capsules or extemporaneous suspension)<br>*11mg/m2 OD (for phase 2, RMS patients)*<br>Everolimus (tablets for oral suspension)<br>*3mg/m2 OD*<br>28-day cycles. Max 7 cycles. | 20 (64) | RMS:<br>2-11 yrs: 9<br>12-17 yrs: 6<br>18-64 yrs: 5 | NR | |
| Gatz (2023)[4] | NR | Phase 2 | NR | NR | Relapsed, refractory, advanced malignancies | 'Paediatric' | | Olaparib<br>*90 mg/m2 PO bd on days 1-10 of 21 day cycle*<br>Irinotecan<br>*20 mg/m2 IV on days 4-8 of 21 day cycle* | ≥1 (70) | WP: 14 years (5-23) | NR | Median (range) number of treatment cycles for WP: 2 (1-51) |
| Lassaletta (2023)[5] | USA, France, Italy, Japan, Spain, Australia, Canada | Phase 1b | Multi | Nov 2020 - Jun 2022 (data-cut off in CA; study still recruiting) | Relapsed, refractory, all solid tumours, measurable disease | ≤ 18 years | Body weight ≥10kg and body surface area ≥0.5. | Abemaciclib<br>*55-115 mg/m2 PO bd*<br>Irinotecan<br>*50 mg/m2 IV, on days 1-5 of 21 day cycle;*<br>Temozolomide<br>*100 mg/m2 IV/PO, on days 1-5 of 21 day cycle* | 3 (20) | NR | NR | |
| **Biomarker driven studies** | | | | | | | | | | | | |
| Lee (2023)[6] | USA, Puerto Rico | Phase 2 | Multi | Jun 2018 - Jul 2022 | Relapsed, refractory, all solid tumours (inc lymphoma or histiocytic disorders), measurable disease | 1-21 years | Activating alterations in FGFR 1/2/3/4; must be able to swallow tablets | Erdafitinib<br>*4.7 mg/m2 PO daily in 28-day cycles*<br>*Max 26 cycles* | 1 (20) | WP: 15 years (NR) | NR | |

| Author, date | Countries performed | Study design | | Patient enrolment dates | Inclusion/exclusion criteria | | | Intervention(s) | Number of R+R RMS patients (total) | Age (median (range)) | Median prior lines of therapy (range) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Phase | Single/ multi centre | | Disease | Age | Other | | | | | |
| Macy (2023) [7] | USA, Puerto Rico | Phase 2 | Multi | Aug 2018 - May 2022 | Relapsed, refractory, all solid tumours (inc lymphoma or histiocytic disorders), measurable disease | 1-21 years | Amplification of CDK4, CDK6, CCND1, CCND2, or CCND3; positive Rb expression, able to swallow capsules | Palbociclib<br>*75mg/m2 PO daily on days 1-21 of 28-day cycles. Max:2 years* | 6 (23) | WP: 15 years (9-21) | NR | |
| **Molecular Registry Studies** | | | | | | | | | | | | |
| Tao (2023)[13] | Japan | PM | Single | Aug 2016 - Dec 2021 | Relapsed, refractory, all solid tumours | >1 year at enrollment; and <18 at diagnosis | | Palbociclib<br>*Dose, method of administration and frequency NR* | 1 (13) receiving targeted therapy | WP: 12 years (1-28) of 142 enrolled pts | NR | Tumour sample collected at diagnosis, no germline alterations, RMS patient had alveolar RMS & CDK4 amplification. |
| **Vaccine Therapy** | | | | | | | | | | | | |
| Oda (2021)[12] | Japan | Phase 2 | NR | Oct 2016 - Mar 2017 | Relapsed, refractory, all solid tumours | <17 years | | Personal Peptide Vaccines<br>*Subcutaneously into thigh, thorax or abdomen.*<br><br>*Maximum 4 peptides (1 mg/each peptide in 0.5 ml for 4-11 year olds and 2 mg for 12-17 year-olds) - selected based on the results of human leukocyte antigen (HLA)-class IA typing and peptide-specific IgG titers.*<br><br>*Cycle 1: weekly for 6 consecutive weeks. Cycle 2+ every 2-6 weeks.* | 1 (4) | RMS: 5 years | RMS: 2 prior LOT | 1 Alveolar RMS; GU primary; metastatic at presentation and at relapse.<br><br>RMS patient was disease-free at time of commencing vaccinations. RMS patient received peptide vaccination 22 times.<br><br>One additional patient was treated with intervention for secondary osteosarcoma (primary tumour had been RMS). |
| Hashii (2010)[11] | Japan | Phase 1/2 | Single | March 2006 - Feb 2009 | All solid tumours or leukaemia, resistant to conventional multimodal therapy | <20 years | WT1 protein overexpression in solid cancer tissues, HLA-A*2402-positive | WT1 peptide vaccine<br>*O.5mg for patients <10kg, 1mg for 10-20kg, 2mg for 20-30kg, and 3mg for >30kg. Weekly for 23 weeks or longer.* | 1 (5) | RMS: 7 years | RMS: 2 | 1 Alveolar RMS, Patient had VGPF response to pretreatment but small residual disease at end of multimodal therapy (UTD if active disease at start of vaccine therapy). |

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

bd = twice daily; CNS = central nervous system; CTR = clinical trial record; DL = dose level; HIPEC = hyperthermic intraperitoneal chemotherapy; IV = intravenous; NOS = not otherwise specified; NR = not reported; od = once daily; PM = precision medicine; po = orally; RMS = rhabdomyosarcoma; SD = standard deviation; SG = subgroup; UK = United Kingdom; USA = United States of America; WP = whole population

## Table 4 Outcome data for new studies

| Regimen | Author, date (Reference) | Total no. 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 | |
| **Novel agents - single agents** | | | | | | | | | | |
| Afatinib | Geoerger, 2023[10] | 7 R+R RMS | 0 | 0 | 0 | 4 | 0% | 22 days (15-57) | 73 days (15-234) | 3 additional patients had unconfirmed PD. Median (range) time on treatment: 19 days (8-57). PFS and OS data included censored patients |
| **Novel agents - multiple agents** | | | | | | | | | | |
| Regorafenib (consecutive) with Irinotecan and Vincristine | Casanova, 2023[8] | 1 R+R RMS | 0 | 1 | 0 | 0 | 100% | NR | NR | ORR across all arms: 58.3% (27.7-84.8) and DCR: 91.7% (61.5-99.8).<br><br>ARM 1: Pt with PR experienced PD > 300 days; ARM 2: Pt with non-CR/non-PD experienced PR > 150 days; ARM 3: 2 pt (1 PR and 1 CR) terminated treatment at ~100 days; 1 pt with PR terminated treatment at ~200 days, 1 pt with PR experienced PD >450 days; 2 pts (1 PR and 1 CR) remained on treatment after 650 days and 850 days.<br><br>Responses were seen in:<br>● 5/8 patients with A-RMS and 2/3 with E-RMS;<br>● 3/4 patients with refractory disease and 4/7 with relapsing disease<br>● 3/6 pt who had previously had irinotecan, and in 4/6 who did not.<br><br>An additional patient with metastatic RMS refractory to frontline therapy achieved and sustained a CR after the data cut-off. |
| Regorafenib (sequential, 72mg/m2) with Irinotecan and Vincristine | Casanova, 2023[8] | 1 R+R RMS | 0 | | | 0 | 0% | NR | NR | |
| Regorafenib (sequential, 82mg/m2) with Irinotecan and Vincristine | Casanova, 2023[8] | 9 R+R RMS | 2 | 4 | 3 | 0 | 66% | NR | NR | |
| Adavosertib and Irinotecan | Cole, 2023[9] | 10 R+R RMS | 0 | 0 | 5 | 5 | 0% | NR | NR | 2 of the patients with SD had prolonged stable disease lasting eight and ten cycles |
| Lenvatinib and Everolimus | Eisai Inc., 2023 (NCT03245151)[14] | 20 R+R RMS | NR | NR | NR | NR | 10% (1.2-31.7) | NR | NR | Disease control rate (SD+PR+CR): 40% (95% CI, 19.1-63.9)<br>Clinical benefit rate (prolonged SD+PR+CR): 10% (95% CI, 1.2-31.7%)<br>Duration of response - 2.4 months (95% CI 2.1 to NA) |
| Olaparib and Irinotecan | Gatz, 2023[4] | *1#* R+R RMS | | | | | NR | NR | NR | 1 RMS pt had unconfirmed partial response for 6 cycles |
| Abemaciclib with Temozolomide and Irinotecan | Lassaletta, 2023[5] | *1#* R+R RMS | 1 | 0 | | | UTD | NR | NR | Outcomes of two patients not reported<br>CR was achieved at 55mg/m2 |
| **Biomarker driven therapies** | | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Erdafitinib | Lee, 2023[6] | 1 R+R RMS | 0 | 0 | 0 | 1 | 0% | NR | NR | |
| Palbociclib | Macy, 2023[7] | 6 R+R RMS | 0 | 0 | | ≥5 | 0% | NR | NR | 1 pt with sarcoma had SD for 3 cycles but came off therapy due to toxicity - UTD whether this patient had RMS |
| **Molecular Registry Studies** | | | | | | | | | | |
| Palbociclib | Tao, 2023[13] | 1 R+R RMS | 0 | 0 | 0 | 1 | 0% | NR | NR | Pt with RMS received palbociclib for 1.9 months |
| **Vaccine therapies** | | | | | | | | | | |
| Personalised peptide vaccine | Oda, 2018[12] | 1 (see comment) | 0 | 0 | 1 | 0 | 0% | NR | 37+ months | ***Patient was disease-free prior to receiving the vaccine.*** |
| WT1 peptide vaccine | Hashii, 2010[11] | 1 (see comment) | 1 | 0 | 0 | 0 | 100% | NR | 42+ months | ***UTD whether the patient had active disease prior to receiving the vaccine.***<br>Patient still receiving therapy at time of publication |

*calculated from provided information, # plus italicised indicates studies where exact number of evaluable RMS patients is unknown but is definitively >1

CI = confidence intervals; CR = complete response; CYP = children and young people; HIPEC = hyperthermic intraperitoneal chemotherapy; NR = not reported; OS = overall survival; PR = partial response; PD = progressive disease; PFS = progression free survival; RFS = relapse free survival; RMS = rhabdomyosarcoma; SD = stable disease; TTP = time to progression; UTD = unable to determine

## Table 5 Adverse Event data

| Intervention | Author, year (reference) | Number evaluable for toxicity | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| **Novel agents - single agents** | | | | | | |
| Afatinib | Geoerger, 2023[10] | 56 | 11P (6P in C1) | 35 G3+ | | DLTs: 1P G3 **Diarrhoea** (18mg/m2/day); 2P **decreased appetite** considered serious due to hospitalisation, associated with moderate **diarrhoea** (23mg/m2/day); 1P G4 hypernatremia, G4 dehydration, G4 **diarrhoea**, G3 decreased appetite, G3 hypokalemia, G3 cheilitis, G3 rash (23mg/m2/day). Other DLTs not reported.<br><br>G3+ AEs: 3P **Diarrhoea**, 1P stomatitis, 2P paronychia, 1P chelitis, 1P rash, 2P hypokalemia, 1P hyponatremia, 1P ALT increase, 2P decreased appetite.<br><br>5P experienced G3+ AEs leading to afatinib dose reduction; 3P experienced G3+ AEs leading to discontinuation of afatinib; 10P experienced G3+ treatment-related AEs.<br><br>Death (not considered treatment-related): 1 hydrocephalus, 1 respiratory distress, 1 respiratory arrest. |
| **Novel agents - multiple agents** | | | | | | |
| Regorafenib (consecutive) with Irinotecan and Vincristine (ARM 1) | Casanova, 2023[8] | 2 | 2P (C1) | 20 G3+ | | DLTS: 1P G3 peripheral sensory neuropathy, hepatic pain, ALT increase, AST increase, drug-induced liver injury; 1P G3 abdominal pain, **vomiting**, **febrile bone marrow aplasia**.<br><br>G3+ AEs: 2P **Neutropenia**, 2P abdominal pain, 2P **vomiting**, 1P **decreased appetite**, 1P **thrombocytopenia**, 1P **nausea**, 2P ALT increase , 2P AST increase, 1P hypokalemia, 1P leukopenia, 1P weight decrease, 1P GGT increase, 1P hypophosphatemia, 1P **febrile neutropenia**, 1P peripheral sensory neuropathy.<br><br>ALL ARMS: Treatment-related AEs led to dose modification of ≥1 of the three study drugs in 18P (86%), and permanent discontinuation of ≥1 study drug was required for 3P(14%). 8P (38%) experienced serious AEs. No treatment-related G5 AEs occurred. |
| Regorafenib (sequential, 72mg/m2) with Irinotecan and Vincristine (ARM 2) | Casanova, 2023[8] | 6 | 1P (C1) | 29 G3+ | | DLTS: 1P G3 maculopapular rash, AST increase<br><br>G3+ AEs: 1P **diarrhoea**, 1P anaemia, 6P **neutropenia**, 1P abdominal pain, 2P **thrombocytopenia**, 1P **nausea**, 2P ALT increase, 2P AST increase, 3P leukopenia, 1P GGT increase, 1P hypophosphatemia, 1P hyponatremia, 1P rash maculopapular, 1P **febrile neutropenia**, 1P clostridium difficile infection, 1P lipase increase, 1P neck pain, 1P pain of skin, 1P HSFR |
| Regorafenib (sequential, 82mg/m2) with Irinotecan and Vincristine (ARM 3) | Casanova, 2023[8] | 13 | 1P (C1) | 43 G3+ | | DLTs: 1P G3 **thrombocytopenia** >7 days<br><br>G3+ AEs: 3P **diarrhoea**, 6P anaemia, 7P **neutropenia**, 1P abdominal pain, 1P pyrexia, 2P **vomiting**, 1P decreased appetite, 4P **thrombocytopenia**, 1P ALT increase, 3P hypokalemia, 3P leukopenia, 1P hypophosphatemia, 1P pain, 1P hypocalcemia, 1P asthenia, 1P blood creatine increase, 1P **febrile neutropenia**, 1P lymphopenia, 1P acute kidney injury, 2P hypotension, 1P lipase increase. |
| Adavosertib and Irinotecan | Cole, 2023[9] | 30 | 0 | 31 | 8 | 12P **neutropenia** (G3: 8P, G4: 4P), 4P **thrombocytopenia** (G3: 2P, G4: 2P), 3P G3 anaemia, 4P G3 leukopenia, 7P lymphopenia (G3: 5P, G4: 2P), 2P G3 nausea, 3P G3 **vomiting**, 1P G3 diarrhoea, 1P G3 anorexia, 1P G3 dehydration, 1P G3 hypokalemia |

| Intervention | Author, year (reference) | Number evaluable for toxicity | Total number AEs | | | AE details provided by manuscript |
|---|---|---|---|---|---|---|
| | | | DLT | G3 | G4 | |
| Lenvatinib and Everolimus | Eisai Inc. , 2023 (NCT03245151) [14] | 64 | NR | NR | NR | G3/4 AEs not reported; 2P experienced treatment-emergent serious adverse event (TESAE) at 8mg/m2 lenvatinib + 3mg/m2 everolimus; 12P experienced TESAE at 11mg/m2 lenvatinib + 3mg/m2 everolimus<br><br>Phase 1 SAEs: 1 pain, 1 headache; Phase 1/2 SAEs: 1 **febrile neutropenia**, 1 hypothyroidism, 1 eyelid oedema, 1 abdominal pain, 1 dysphagia, 2 **nausea**, 2 **vomiting**, 1 **diarrhoea**, 1 mouth haemorrhage, 1 oral cavity fistula, 2 pancreatitis, 1 pneumatosis intestinalis, 3 pain, 1 face oedema, 4 pyrexia, 1 aspiration pneumonia, 1 sepsis, 2 URTI, 1 pneumonia, 1 tendon rupture, 1 increased alanine aminotransferase, 1 increase aspartate aminotransferase, 2 dehydration, 1 hypophosphatemia, 2 back pain, 1 MSK pain, 1 muscular weakness, 1 MSK chest pain, 1 myalgia, 1 malignant pleural effusion, 1 tumour haemorrhage, 1 cancer pain, 1 dysarthria, 2 headache, 1 nystagmus, 5 seizure, 1 CSF leakage, 1 depressed level of consciousness, 1 encephalopathy, 1 hydrocephalus, 1 optic neuritis, 1 paraesthesia, 1 mental status change, 5 hypoxia, 2 pneumothorax, 1 respiratory failure, 1 cough, 1 haemothorax, 3 pleural effusion, 1 hypotension, 1 deep vein thrombosis |
| Olaparib and Irinotecan | Gatz, 2023[4] | NR | NR | NR | NR | No AE data reported |
| Abemaciclib with Temozolomide and Irinotecan | Lassaletta (2023) [5] | NR | 4P | NR | NR | DLTS: at 70mg/m2: 3P **neutropenia**, 1P GGT increase; at 55mg/m2: 1P **thrombocytopenia**.<br>High grade AEs were mostly haematological. Discontinuations due to AEs occurred in 2 patients at 70mg/m2, and 0 at 55mg/m2 |
| **Biomarker driven therapies** | | | | | | |
| Erdafitinib | Lee, 2023[6] | 20 | NR | 1 | 1 | 1 G3 spinal cord compression; 1 G4 intracranial haemorrhage |
| Palbociclib | Macy, 2023[7] | 20 | NR | ≥30 G3+ | | G3+ **Neutropenia** (10P), G3/4 **thrombocytopenia** (8P), G3+ leukopenia (7P), and anaemia (5P).<br>Four patients came off study for toxicity (3P with prolonged **thrombocytopenia**, and 1P prolonged grade 4 **neutropenia**). |
| **Molecular Registry Studies** | | | | | | |
| Palbociclib | Tao, 2023[13] | 1 | NR | 1E | 4E | 1P leukopenia (G4), 1P **neutropenia** (G4), 1P lymphopenia (G4), 1P thrombocytopenia (G4), 1P anaemia (G3) |
| **Vaccine therapies** | | | | | | |
| Personalised peptide vaccine | Oda, 2018[12] | 4 | NR | 0 | 0 | No severe PPV related adverse events |
| WT1 peptide vaccine | Hashii, 2010[11] | 5 | 0 | 0 | 0 | Local injection site erythema was seen in all patients (no grade reported). No other Grade 3+ AEs reported |

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

AE = adverse event; C = cycle(s); CI = confidence interval; CTR = clinical trial record; DL = dose level; DLT = dose limiting toxicity; E = event(s)/episode(s); HIPEC = hyperthermic intraperitoneal chemotherapy; G = grade; NR = not reported; NOS = not otherwise specified; P = patient(s); RMS = rhabdomyosarcoma;SAE = serious adverse event

## Table 6 New clinical trial registry records

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | N | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| **Recruitment status: Recruiting** | | | | | | | | |
| NCT05857969 | Ex Vivo Drug Sensitivity Testing and Multi-Omics Profiling[18] | USA; Academic | 65 (E) | 22/02/23 - 31/12/28 | Functional precision medicine guided therapy | Overall Survival, Progression Free Survival, Percentage of patients receiving functional precision medicine guided treatment options, PFS 2/1 ratio | Relapsed, Refractory, All solid tumours, Children, Young adults, Tissue available for testing | 1 day to 21 years |
| NCT04995003 | HER2 Chimeric Antigen Receptor (CAR) T Cells in Combination With Checkpoint Blockade in Patients With Advanced Sarcoma[20] | USA; Academic | 25 (E) | 07/12/21 - 31/12/40 | **HER2 CAR-T cell therapy** (infusion): DL1- 1x10^8 cells/m2; DL-1: 5x10^7 cells/m2<br><br>**Pembrolizumab** (injection, route NR): 2mg/kg/dose every 3 weeks; max dose 200mg.<br><br>*and*<br><br>**HER2 CAR-T cell therapy** (infusion) - DL1: 1x10^8 cells/m2; DL-1: 5x10^7 cells/m2.<br><br>Nivolumab (route NR) 3mg/kg/dose, or 124mg (>= 40kg) every two weeks. | Response rates, Dose Limiting Toxicities | Relapsed, Refractory, Children, Young adults, HER2-positive sarcoma, Presence of bulky tumour at the primary or metastatic site | 1 to 25 years |
| NCT05355701 | A Study to Learn About the Study Medicine Called PF-07799933 in People With Advanced Solid Tumors.[26] | USA, Canada, Israel; Pharmaceutical Company | 174 (E) | 05/07/22 - 15/02/28 | **PF-07799933** PO (tablet)<br><br>and<br><br>**PF-07799933** PO (tablet) with **binimetinib** PO (tablet) or **cetuximab** (IV) | Response rates, Adverse events, Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Dose Limiting Toxicities, Duration of response, Disease control rate, PKs, TTR | Relapsed, Refractory, All solid tumours (including CNS tumours), qualifying BRAF alteration (V600 or non-V600 class II/III BRAF alteration) Exclusion: brain metastases > 4cm | 16 years+ |
| NCT02693535 | TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That | USA; Academic | 3791 (E) | 14/03/16 - 31/12/25 | One of the following, depending on tumour mutation profile: **Palbociclib** (CDKN2A, CDK4, CDK6); **Sunitinib** (CSF1R,PDGFR,VEGFR); **Temsirolimus** (mTOR, TSC); **Trastuzumab and Pertuzumab** (ERBB2), **Vemurafenib and** | Response rates, Overall Survival | Relapsed, Refractory, All solid tumours, Measurable disease. Mutations which can be | 12 years+ |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | N | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer (TAPUR)[28] | | | | **Cobimetinib** (BRAF V600E/D/K/R), **Regorafenib** (RET, VEGFR1/2/3, KIT, PDGFRβ, RAF-1, BRAF), **Olaparib** (BRCA1/2; ATM), **Pembrolizumab** (POLE, POLD1), **Nivolumab and Ipilimumab** (MSI-H, high mutational load), **Abemaciclib** (CDKN2A, CDK4, CDK6), **Talazoparib** (BRCA1/2, PALB2), **Atezolizumab and PHESGO** (ERBB2), **Atezolizumab and Talazoparib** (BRCA1/2, PALB2, ATM, and others), **Entrectinib** (ROS1 Fusion), **Larotrectinib** (NTRK amplification), **Tucatinib plus Trastuzumab** subcutaneous (ERBB2), and **Futibatinib** (FGFR1,2,3,4 fusion or mutation). | | matched to drugs. Leptomeningeal metastases excluded.<br><br>*Not all therapies available for those under 18.* | |
| NCT05130255 | GD2-SADA:177Lu-DOTA Complex in Patients With Solid Tumors Known to Express GD2[19] | USA; Pharmaceutical Company | 60 (E) | 17/11/22 - 01/01/25* | **Radioimmunotherapy**: GD2-SADA (IV infusion), followed by 177Lu-DOTA (IV infusion). 1 treatment cycle in Part A, 2 treatment cycles in Part B and up to 5 treatment cycles in Part C | Adverse events, Dose Limiting Toxicities, RP2D | SCLC, Melanoma, Sarcoma, Measurable disease; Relapsed/Refractory (only mentioned in title) | >= 16 years old |
| NCT04469530 | Sirolimus in Combination With Metronomic Chemotherapy in Children With High-Risk Solid Tumors (AflacST1903)[24] | USA; Academic | 50 (E) | 16/09/20 - 01/09/25* | **Sirolimus**: 2mg/m2 OD, oral solution/tablet. **Metronomic chemotherapy** including cyclophosphamide (po, od), etoposide ( po, od), celecoxib (po, od) - **MAINTENANCE CHEMOTHERAPY AFTER STANDARD TREATMENT** | Adverse events, Overall Survival, Progression Free Survival, number of patients who came off protocol therapy due to toxicity or non-compliance | Relapsed, All solid tumours (Primary CNS tumours and lymphomas not eligible), Cohort 2: recurrent solid tumour in SECOND COMPLETE REMISSION | 1 to 30 years |
| jRCTs031190104 | The prospective trial of patient-proposed healthcare services with multiple targeted agent based on the result of gene profiling by multigene panel test. (BELIEVE)[21] | Japan; Pharmaceutical Company | 1000 (E) | 03/10/19 - NR | Molecular targeted therapy | Response rates, Adverse events, Overall Survival, Progression Free Survival, Disease control rate | Relapsed, Refractory, All solid tumours, No leptomeningeal metastases or symptomatic brain metastases | No limits |
| NCT05286801 | Tiragolumab and Atezolizumab for the Treatment of Relapsed or Refractory SMARCB1 or SMARCA4 Deficient Tumors[32] | USA, Canada, Australia; Academic | 86 (E) | 17/11/22 - 30/09/25 | **Atezolizumab** IV over 30-60 mins on day 1; and **tiragolumab** IV over 30-90 mins on day 1 of each 21-day cycle. Max 5 years. Pts in part A start tiragolumab in cycle 2, pts in part B receive tiragolumab from cycle 1. | Adverse events, Overall Survival, Progression Free Survival, PKs, Duration of Response, DLTs | Relapsed, Refractory, SMARCB1 (INI1) or SMARCA4 deficient tumours; newly diagnosed with no known curative therapy; no known untreated CNS metastases | 12 months and older |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | N | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| NCT05106777 | Surufatinib in Patients With Osteosarcoma and Soft Tissue Sarcoma[27] | China; Academic | 47 (E) | 10/12/21 - 10/12/23 | **Surufatinib** (300mg) PO OD, on a 21-day cycle | Response rates, Overall Survival, Progression Free Survival, Disease Control Rate | Relapsed, Refractory, CNS metastases excluded, BSA greater than or equal to 1.5m2, >6 months since completion of therapy | 14 to 70 years old |
| NCT04025931 | Chidamide Combined With Toripalimab in Sarcoma[15] | China; Academic | 74 (E) | 19/01/20 - 30/12/24 | **Chidamide** (30mg orally twice a week) and **toripalimab** (240mg every three weeks) | Response rates, Disease Control Rate, Progression Free Survival, Overall Survival | Refractory, Sarcoma, brain metastases with symptoms excluded, measurable disease | 14 to 70 years |
| NCT04432649 | Targeting CD276 (B7-H3) Positive Solid Tumors by 4SCAR-276[29] | China; Academic | 100 (E) | 01/06/20 - 31/05/24 | **4SCAR-276 T cells** | Response rates, Adverse events, Overall Survival, Progression Free Survival | Relapsed, Refractory, Positive expression of CD276 antigen, weight >10kg, exclude patients with untreated CNS | 1 to 75 years |
| NCT06094101 | Personalized Vaccination in Fusion+ Sarcoma Patients (PerVision)[22] | Germany; Academic | 30 (E) | 19/09/23 - 01/09/27* | **Peptide vaccination**: Peptides will be administered subcutaneously together with the novel toll like receptor (TLR) 1/2 ligand XS15 emulsified in Montanide ISA 51 VG as adjuvant. Three vaccinations applied every 28 days | Adverse events, Overall Survival, Progression Free Survival, T-cell response, Quality of Life; Vaccine-induced response of cluster of differentiation (CD) 4+ and/or CD8+ T cells | Sarcoma (RMS, synovial or Ewings), in first or second complete remission or partial response after local therapy and intensive standard chemotherapy. Must be metastatic fusion positive. Excluded if prior HSCT. | 2 to 40 years |
| NCT02813135 | European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (ESMART)[17] | UK, France, Germany, Denmark, Spain, Netherlands, Italy; Academic | 460 (E) | 03/08/16 - 01/08/27 | ***#ARM A: Ribociclib + Topotecan and Temozolomide*** *(Topotecan iv QD and temozolomide capsules orally QD Days 1 to 5; Ribociclib capsules or oral solution orally QD from Day 6 to 20 of a 28 day cycle);* ***Arm B. Ribociclib + Everolimus*** *(Ribociclib capsules or oral solution orally QD for 21 days of each 28 day cycle; Everolimus orodispersible tablets orally QD for 28 days);* **ARM C. Adavosertib + Carboplatin** (Adavosertib capsules orally BID 3 days on / 4 days off in week 1; Carboplatin iv QD AUC 5 on Day 1 of a 21 day cycle.); ***Arm D. Olaparib + Irinotecan*** *(Olaparib tablets orally BID on Day 1-10 of a 21 day cycle Irinotecan iv QD on Day 4-8 of a 21 day cycle);* ***Arm E. Vistusertib single agent*** *(Vistusertib tablets orally BID 2 days on/5 days off per week of a 28 day cycle.);* ***Arm F. Vistusertib + Topotecan and Temozolomide*** *(Topotecan iv QD and temozolomide capsules orally QD Days 1 to 5; Vistusertib tablets orally BID 3 days on/4 days off per week of a 28 day cycle.);* ***Arm G. Nivolumab + Cyclophosphamide +/- Radiotherapy*** *(Nivolumab iv QD every 2 weeks* | Response rates, Progression Free Survival, Maximum Tolerated Dose, RP2D, PK, Duration of Response | Relapsed, Refractory, solid tumours and haematological malignancies, advanced molecular profiling, measurable disease, for oral medications patients must be able to swallow tablets (nasogastric/ gastrostomy feeding tube administration only allowed if indicated), exclude if symptomatic | up to 18 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | N | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | | | | | *of a 28 day cycle (Days 1 and 15); Cyclophosphamide tablets or oral solution orally BID, 1 week on/1 week off; Palliative irradiation/radiofrequency/cryotherapy starting 2 weeks after the first nivolumab injection.);* **Arm H. Selumetinib + Vistusertib** (Selumetinib capsules twice daily on a continous administration. Vistusertib orally twice daily on an intermittent schedule : 2 days on / 5 days off per week of a 28 day cycle.); **Arm I. Enasidenib** (Enasidenib tablets or sprinkle solution orally on a continuous dosing once daily (QD) per 28 day cycle.); **Arm J. Lirilumab + Nivolumab** (Nivolumab iv QD on Day 1 and 15 of a 28 day cycle; Lirilumab iv QD on Day 1 of a 28 day cycle); **Arm K. Fadraciclib (CYC065) + Temozolomide** (Fadraciclib iv QD on Day 1 (+/- 15) of a 28 day cycle Temozolomide capsules orally QD on Day 1-5 of a 28 day cycle); **Arm L. Fadraciclib (CYC065) + Cytarabine** (Fadraciclib iv QD on Day 1 (+/- 15) of a 28 day cycle Cytarabine iv or sc on Day 2-5 and Day 8-11 of a 28 day cycle); **Arm M. Ribociclib + Everolimus +/- Dexamethasone** (Ribociclib capsules or tablets orally QD on Day 1-21 of a 28 day cycle. Everolimus dispersible tablets orally QD on a continuous dosing per 28 day cycle.); **Arm N. Ceralasertib (AZD6738) + Olaparib** (Olaparib tablets orally BID per 28 days Ceralasertib tablets QD or BID per 28 day cycle); **Arm O. Futibatinib (TAS-120)** (Futibatinib tablets orally on a continuous dosing QD per 28 day cycle.); **Arm P. Capmatinib (INC280) + Everolimus** (Capmatinib tablets orally on a continuous dosing BID per 28 day cycle. Everolimus dispersible tablets orally QD on a continuous dosing per 28 day cycle.) | | CNS metastases | |
| **Recruitment status: Active, not recruiting** | | | | | | | | |
| NCT02428712 | A Study of FORE8394 as a Single Agent in Patients With Advanced Unresectable Solid Tumors[25] | USA; Pharmaceutical Company | 113 (A) | 01/04/15* - 01/04/24* | **FORE8394** | Response rates, Adverse events, Progression Free Survival, PKs, clinical benefit rate, RP2D, duration of response | Relapsed, Refractory, All solid tumours, presence of BRAF mutation; Participants with known co-occurring RAS-related mutations or RTK activation are not allowed. At least 30kg. | 10 years and older |
| NCT03213665 | 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)[31] | USA, Puerto Rico; Academic | 20 (A) | 13/11/17 - 22/09/24 | **Tazemetostat**: PO, BID days 1-28 of 28-day cycle: 520mg/m^2 for pts without CNS involvement, 1200 mg/m^2 for pts with CNS involvement. Max 2 years. | Response rates, Adverse events, Progression Free Survival | Relapsed, Refractory, All solid tumours (inc. CNS tumours, non-Hodgkin lymphoma, or histiocytic disorders). Measurable disease. gain of function mutations in EZH2, or loss of function mutations in the SWI/SNF complex | 12 months to 21 years |

| Clinical trial registry number(s) | Title of registered clinical trial | Planned locations; Sponsor | N | Start date to end date | Intervention (+/- comparator) | Outcomes to be collected | Conditions being studied | Ages eligible |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | subunits SMARCB1 or SMARCA4 | |
| **Recruitment status: Completed** | | | | | | | | |
| NCT01132911 | A Phase I Study of Vorinostat and Bortezomib in Children With Refractory of Recurrent Solid Tumors, Including CNS Tumors and Lymphomas[19] | USA; Academic | 5 (E) | 10/05/10 - 13/04/11 | **Vorinostat:** PO OD on days 1-5 and 8-12 of 21 day cycle; and **bortezomib**: IV on days 1, 4, 8 and 11 of a 21 day cycle. Doses NR in CTR record | Response rates, Adverse events, Maximum Tolerated Dose, RP2Ds, PKs | Relapsed, Refractory, All solid tumours, Measurable disease | 12 months to 21 years |
| NCT01294670 | Clinical Study of Vorinostat in Combination With Etoposide in Pediatric Patients < 21 Years at Diagnosis With Refractory Solid Tumors[21] | USA, Canada; Academic | 27 (A) | 09/02/11 - 08/12/20 | **Vorinostat** (escalating doses PO, OD for 4 days) and **Etoposide** (OD for 3 days, IV) - 3-week cycles.<br><br>In phase II, pts will be treated at the RP2D established in the Phase I component of the study, which was found to be 270 mg/m2/dose of vorinostat and 100 mg/m2/dose of etoposide | Response rates, Maximum Tolerated Dose, Dose Limiting Toxicities | Relapsed, Refractory, All solid tumours, Excluded if known brain mets, have undergone SCT (either allogeneic or autologous). Must be able to swallow capsules. Phase 2: restricted to relapsed/refractory sarcomas and may only have measurable disease. | 4 to21 years |
| **Recruitment status: Terminated** | | | | | | | | |
| NCT04770246 | TAS-117 in Patients With Advanced Solid Tumors Harboring Germline PTEN Mutations[23] | UK, USA, France, Austria; Pharmaceutical Company | 17 (A) | 31/03/21 - 06/03/23 | **TAS-117** (orally, either daily or intermittently on 21-day cycle) | Adverse events, Overall Survival, Progression Free Survival, Disease Control Rate, Duration of Response, PKs, MTD, RP2D, Response rates | All solid tumours, For 12-18 year olds, confirmed germline PTEN inactivating mutation, progressed after standard treatment; body weight >40kg, relapsed, refractory, measurable disease. Exclusion criteria: meningeal carcinomatosis, leptomeningeal carcinomatosis, spinal cord compression, or symptomatic or unstable brain metastasis. | 12 years and older |

* 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; #studies in italics have already been accounted for in previous LSR updates (LSR-1 and LSR-2)

A = actual enrolment; CNS = central nervous system; CT = computerised tomography; CTR = clinical trial registry; DOR = duration of response; E = estimated enrolment; HRQoL = health-related quality of life; MRI = magnetic resonance imaging; NR = not reported; PKs = pharmacokinetics; RMS = rhabdomyosarcoma; RP2D = recommended phase two dose; STS = soft tissue sarcoma; TTR = time to response; UK = United Kingdom; USA = United States of America

## References


1. Morgan JE, Evans C, Shepherd L, Bryan G, Fulbright H, Shemilt I. A living systematic review of early phase studies for children and young people with relapsed and refractory rhabdomyosarcoma (Living-REFoRMS) %U https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022380185. PROSPERO2023.
2. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of epidemiology and community health*. 1998;52(6):377-384.
3. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ journal of surgery*. 2003;73(9):712-716.
4. Gatz S, Berlanga P, Archambaud B, et al. Abstract CT088: Phase I/II study of the PARP inhibitor olaparib in combination with irinotecan in children with advanced malignancies: arm D of the AcSé-ESMART trial. *Cancer Research*. 2023;83(8):CT088-CT088 %U https://explore.openalex.org/works/W4365513182.
5. Lassaletta Á, Moreno L, Ogawa C, et al. Recommended phase 2 dose (RP2D) for abemaciclib in combination with irinotecan (IRN) and temozolomide (TMZ) in pediatric patients with relapsed/refractory solid tumors (JPCS Part A). *Journal Of Clinical Oncology*. 2023;41(16):10039-10039 %U https://explore.openalex.org/works/W4379281819.
6. Lee A, Alex C, er J, et al. Erdafitinb in patients with FGFR-altered tumors: Results from the NCI-COG Pediatric MATCH trial arm B (APEC1621B). *Journal Of Clinical Oncology*. 2023;41(16):10007-10007 %U https://explore.openalex.org/works/W4379339254.
7. Macy Margaret E, Mody R, Reid Joel M, et al. Palbociclib in solid tumor patients with genomic alterations in the cyclin D-CDK4/6-INK4a-Rb pathway: Results from NCI-COG pediatric MATCH trial Arm I (APEC1621I). *Journal Of Clinical Oncology*. 2023;41(16):10006-10006 %U https://explore.openalex.org/works/W4379340105.
8. Casanova M, Bautista F, Campbell-Hewson Q, et al. Regorafenib plus Vincristine and Irinotecan in Pediatric Patients with Recurrent/Refractory Solid Tumors: An Innovative Therapy for Children with Cancer Study. *Clinical Cancer Research*. 2023;29(21):4341-4351 %U https://explore.openalex.org/works/W4386046962.
9. Cole Kristina A, Ijaz H, Surrey Lea F, et al. Pediatric phase 2 trial of a WEE1 inhibitor, adavosertib (AZD1775), and irinotecan for relapsed neuroblastoma, medulloblastoma, and rhabdomyosarcoma. *Cancer*. 2023;129(14):2245-2255 %U https://explore.openalex.org/works/W4366603213.
10. Geoerger B, Marshall Lynley V, Nysom K, et al. Afatinib in paediatric patients with recurrent/refractory ErbB-dysregulated tumours: Results of a phase I/expansion trial. *European Journal Of Cancer*. 2023;188:8-19 %U https://explore.openalex.org/works/W4366496702.
11. Hashii Y, Sato E, Ohta H, Oka Y, Sugiyama H, Ozono K. WT1 peptide immunotherapy for cancer in children and young adults. *Pediatric Blood & Cancer*. 2010;55(2):352-355 %U https://onlinelibrary.wiley.com/doi/abs/10.1002/pbc.22522.
12. Oda K, Ito Y, Yamada A, Yutani S, Itoh K, Ozono S. Evaluation of the Immunological Response of Childhood Cancer Patients Treated with a Personalized Peptide Vaccine for Refractory Soft Tissue Tumor: A Four-Case Series. *The Kurume Medical Journal*. 2021;68(2):157-163 %U https://explore.openalex.org/works/W4376127223.
13. Tao K, Yamazaki F, Kubo T, et al. Pediatric Precision Medicine at the National Cancer Center Japan: Prospective Genomic Study of Pediatric Patients with Cancer as Part of the TOP-GEAR Project. *JCO Precision Oncology*. 2023;(7 %U https://explore.openalex.org/works/W4383314495)
14. Eisai I. Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including Central Nervous System Tumors %U https://clinicaltrials.gov/study/NCT03245151. *clinicaltrialsgov*. 2017;

15. University SY-s. Chidamide Combined With Toripalimab in Sarcoma %U https://clinicaltrials.gov/study/NCT04025931. 2019;
16. Center MSKC. Clinical Study of Vorinostat in Combination With Etoposide in Pediatric Patients < 21 Years at Diagnosis With Refractory Solid Tumors %U https://clinicaltrials.gov/study/NCT01294670. 2011;
17. Gutave Roussy Cancer Campus Grand P. European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (ESMART) %U https://clinicaltrials.gov/study/NCT02813135. *ClinicalTrialsgov*.
18. Florida International U, Nicklaus Children's Hospital f, a Miami Children's H, First Ascent Biomedical I, National Institute on Minority H, Health D. Ex Vivo Drug Sensitivity Testing and Multi-Omics Profiling %U https://classic.clinicaltrials.gov/show/NCT05857969. 2023;
19. Therapeutics Ym. GD2-SADA:177Lu-DOTA Complex in Patients With Solid Tumors Known to Express GD2 %U https://clinicaltrials.gov/study/NCT05130255. 2021;
20. Baylor College o, Medicine, Center f, et al. HER2 Chimeric Antigen Receptor (CAR) T Cells in Combination With Checkpoint Blockade in Patients With Advanced Sarcoma %U https://classic.clinicaltrials.gov/show/NCT04995003. 2021;
21. Hospital NCC. Patient-requested treatment for multiple molecular target treatments based on gene profiling through gene panel testing (NCCH1901) %U https://jrct.niph.go.jp/latest-detail/jRCTs031190104. 2019;
22. University H, Tuebingen, Deutsches Konsortium f, et al. Personalized Vaccination in Fusion+ Sarcoma Patients (PerVision) %U https://classic.clinicaltrials.gov/show/NCT06094101. 2023;
23. Institute NC. A Phase I Study of Vorinostat and Bortezomib in Children With Refractory of Recurrent Solid Tumors, Including CNS Tumors and Lymphomas %U https://clinicaltrials.gov/study/NCT01132911. 2010;
24. University E. Sirolimus in Combination With Metronomic Chemotherapy in Children With High-Risk Solid Tumors (AflacST1903) %U https://clinicaltrials.gov/study/NCT04469530. 2020;
25. Biotherapeutics F. A Study of FORE8394 as a Single Agent in Patients With Advanced Unresectable Solid Tumors %U https://clinicaltrials.gov/study/NCT02428712. 2015;
26. Pfizer I. A Study to Learn About the Study Medicine Called PF-07799933 in People With Advanced Solid Tumors. %U https://clinicaltrials.gov/study/NCT05355701. 2022;
27. University SY-s. Surufatinib in Patients With Osteosarcoma and Soft Tissue Sarcoma %U https://clinicaltrials.gov/study/NCT05106777. 2021;
28. Oncology ASoC. TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer (TAPUR) %U https://clinicaltrials.gov/study/NCT02693535. 2016;
29. Institute SG-IM. Targeting CD276 (B7-H3) Positive Solid Tumors by 4SCAR-276 %U https://clinicaltrials.gov/study/NCT04432649. 2020;
30. Inc TO. TAS-117 in Patients With Advanced Solid Tumors Harboring Germline PTEN Mutations %U https://clinicaltrials.gov/study/NCT04770246. 2021;
31. Institute NC. 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) %U https://clinicaltrials.gov/study/NCT03213665. 2017;
32. Institute NC. Tiragolumab and Atezolizumab for the Treatment of Relapsed or Refractory SMARCB1 or SMARCA4 Deficient Tumors %U https://clinicaltrials.gov/study/NCT05286801. 2022;
33. Chisholm J, Mandeville H, Adams M, et al. Frontline and Relapsed Rhabdomyosarcoma (FAR-RMS) Clinical Trial: A Report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). *Cancers (Basel)*. Feb 29 2024;16(5)doi:10.3390/cancers16050998

34. University of Birmingham. FaR-RMS: An Overarching Study for Children and Adults With Frontline and Relapsed RhabdoMyoSarcoma (FaR-RMS) https://classic.clinicaltrials.gov/ct2/show/NCT04625907. 2020;
35. Gerasimov E, Donoghue M, Bilenker J, Watt T, Goodman N, Laetsch TW. Before it's too late: multistakeholder perspectives on compassionate access to investigational drugs for pediatric patients with cancer. *American Society of Clinical Oncology Educational Book*. 2020;40:e218-e227.