Living REFoRMS update 1 (REFoRMS LSR-1) report.

Updates to methods from baseline review (PROSPERO CRD42022380185)[1]

Searches

The first update evaluated two types of search strategies: the use of standard database searches (as per the baseline REFoRMS study) compared with automated searches of the OpenAlex dataset (using OpenAlex Browser tools in EPPI-Reviewer Web software).

The standard searches were conducted in line with the original review on 26th and 27th October 2022, with minor changes only. The DARE database was not searched as it is no longer updated. Update searches used identical search strategies except for the word 'teen' which was truncated to 'teen*' in the strategies for Medline, Embase, Cochrane CDSR and Cochrane CENTRAL. In the OpenAlex searches, a network graph search retrieved all OpenAlex records connected to a specified set of 'seed' records (made of the 127 records included in the baseline review). The results of the standard database searches and the automated OpenAlex searches were compared.

Screening

The eligibility criteria for the studies as part of Living REFoRMS review was the same as the criteria set out in the original review and is as listed on PROSPERO.[2] Study selection was conducted using EPPI reviewer software. Screening was performed in line with baseline review methods.

Data extraction and quality assessment

Data extraction and quality assessment was performed in line with baseline review methods. Following a review of the data extraction used for the original systematic review, changes were made to the extraction tool to aid analysis. No new data fields were extracted.

Despite evaluation of other risk of bias tools, none were sufficiently relevant for early phase trials, so a modified Downs and Black Checklist was used.[3] Following the baseline review, two questions regarding the external validity of the studies that were not deemed relevant for early phase studies were removed (Questions 11 and 12).

Study selection

From 4,211 studies identified from the database searches, 76 were eligible at title and abstract screening. A detailed flowsheet of the LSR-1 process can be found in Figure 1. A simplified flowsheet of studies included in the REFoRMS project (baseline review and LSR-1) can be found in Figure 2.

Following full-text screening, 20 studies providing results were included, including two CTR records, five conference abstracts (three of which were extracted alongside associated CTRs) and 13 full-text papers (including three[4-6] identified during reference list searching).[7-16]

Six authors were contacted for further information. We received replies from three authors (50% response rate), two of which were eligible for inclusion.[7,16]

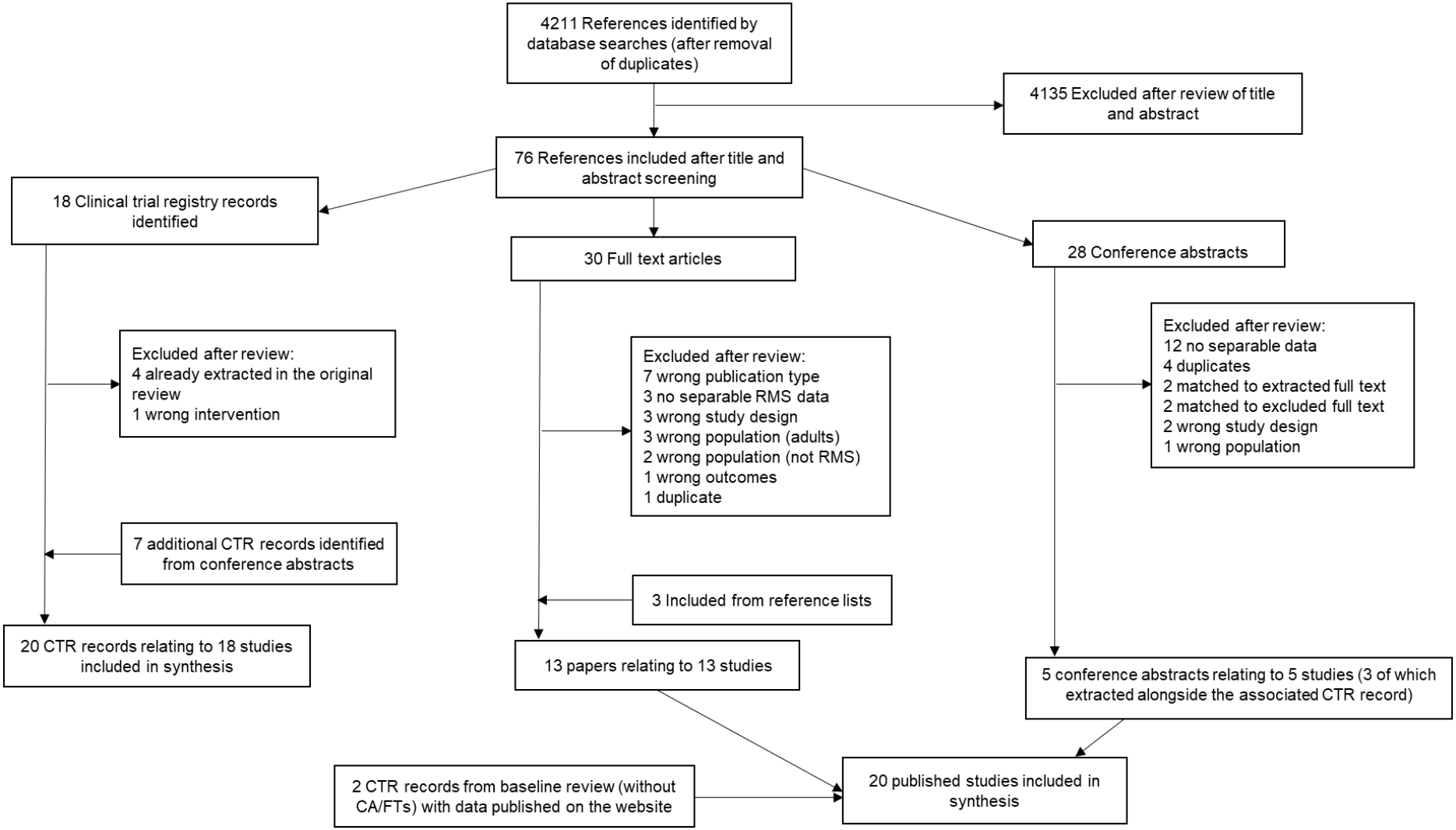

Figure 1: LSR-1 flowsheet

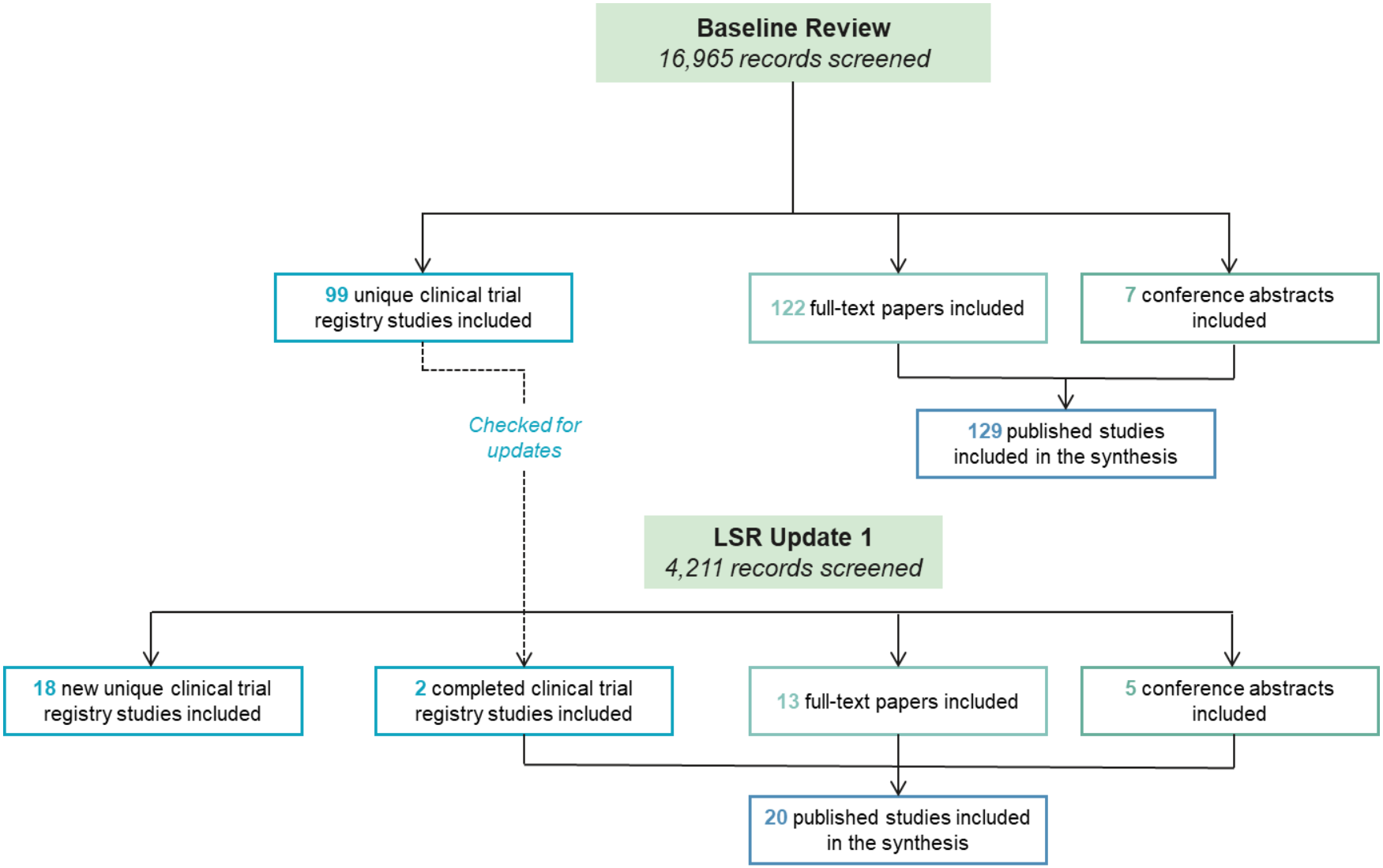

Figure 2: Flowsheet of included studies in REFoRMS

Updates of previously identified CTRs

Of the 99 unique CTRs identified in the baseline review, six had newly identified CAs[17-22] (three of which contributed relevant data to LSR-1[20-22]), and three[23-25] had newly identified full text publications. Of these, two new full text publications did not include evaluable rhabdomyosarcoma patients so these studies will no longer be tracked going forward.[24,25] The other full text publication did not include rhabdomyosarcoma patients but the paper only represented a subset of patients from the overarching trial (30/131 patients) so this trial will still be tracked to see if any future publications present the data for the whole cohort.[23]

Two of the original CTRs now provided extractable data on the trial registry website but had no identifiable conference abstracts or full texts available.[26,27] The CTR data has been extracted and included within the update, and records flagged for monitoring for conference abstracts and full texts in future updates.

Of the 63 CTRs identified to be currently open at the time of the baseline review, 55 (87%) continue to be reported as currently open. Six CTRs were now reported as completed (four with no identifiable outputs yet). Of the 19 CTRs identified as completed but not yet reported at the time of the baseline review, five (26%) have newly identified information available.[28-32]

Newly identified CTRs

Eighteen new CTRs were identified and extracted for LSR-1. Eleven were identified in the update search[33-43] and seven included after being identified from new conference abstracts.

Published studies

Demographics of new studies

Twenty studies contributed 27 cohorts to REFoRMS LSR-1. The countries of recruitment were: USA (10 studies),[5,11,15,16,20-22,26,32,44-47] Canada (2),[7,44,47] Japan (1),[14] France (1),[6] and multiple European countries (1)[13]. Five studies did not report the countries of recruitment. Most studies were completed in one country (60%).[4,8-10,12]

Three studies, contributing nine cohorts, included in REFoRMS LSR-1 were molecular registry studies, where patients with an identified mutation within the rhabdomyosarcoma cells were enrolled on to an open clinical trial.[5,6,13] Although these studies' primarily collect data on the feasibility of molecular profiling in paediatric oncology, they do collect data on the clinical outcomes of the patients with an actionable mutation who are matched to a targeted therapy. Within these studies the majority of interventions were biomarker-driven therapies, alone or in combination with systemic therapy agents (n= 6[5,6,13] and 1[13] respectively); one cohort included a novel single-agent intervention[13], and one cohort evaluated multi-agent standard anti-systemic therapies[6].

An additional four studies (five cohorts) looked at biomarker-driven therapies with or without additional anticancer systemic therapies (n = 3 and 1 cohort respectively).[4,9,10,15] In the non-precision medicine studies, the main interventions were single-agent novel therapies (6 cohorts),[14,22,26,27,45,46] multi-agent novel therapies (4 cohorts),[8,20,21,32,44,47] multi-agent standard

systemic therapies (1 cohort)[11], immunotherapy (1 cohort)[12] and metronomic chemotherapy (1 cohort) [7].

Most studies identified by the update were published in 2021 (n=7)[8-10,13,16,22,44] or 2022 (n=10)[7,11,12,14,15,20,21,26,27,32,45-47] as expected. Three studies were identified prior to this (one in 2016[5], two in 2017[4,6]), which were identified during reference list searching.

Demographics of participants in new studies

One hundred and four children and young people with relapsed and refractory rhabdomyosarcoma were included in the newly identified studies. The majority of studies recruited patients with a variety of tumour types (95%),[4-16,20,22,26,27,44-47] and three also included newly diagnosed patients.[5,13,22,46] Most studies recruited only patients under 18 or 21 years of age.[4,6-12,14-16,20,21,26,32,44,45,47]

Fourteen studies reported the sex of included patients (nine for rhabdomyosarcoma patients only[6,8,12,13,15,21,22,26,32,44,46,47], one for a subgroup population[14] and four for the whole study population[7,9,11,16]), two reported gender (one for rhabdomyosarcoma participants only[8], and one for a subgroup population[10]), two did not specify whether they had reported sex or gender [4,45], and two reported neither sex nor gender[5,20]. Sex/gender was reported as a single binary characteristic in all studies included in the review. Where sex/gender was reported (for rhabdomyosarcoma patients only), 51 (65%) participants were male and 28 were female.

Eight studies reported both the ethnicity and race of included patients (five for rhabdomyosarcoma patients only[12,21,22,32,44,46,47] and three for the whole study population[11,15,16]). One study reported the race of rhabdomyosarcoma patients only.[12] Eleven studies reporter neither race or ethnicity.[4-10,13,14,20,45] Where race was reported (for rhabdomyosarcoma patients only), 38 (66%) participants were White, two were Black or African American (3%), nine were Asian (16%), six participants were unknown (10%) and the race of three rhabdomyosarcoma patients was not reported in these studies (5%). Where ethnicity was reported (for rhabdomyosarcoma patients only), eight participants were Hispanic or Latino (15%), 43 were non-Hispanic or non-Latino (78%), and the ethnicity of four participants was not reported or unknown in these studies (7%).

Quality assessment of new studies

Quality assessment of new studies was similar to that within the baseline review (Figure 3). The included molecular registry studies were difficult to assess using the Downs and Black criteria,[3] particularly around the adverse events of interventions, which were often intentionally not evaluated. We considered this question not to be applicable for these study designs.

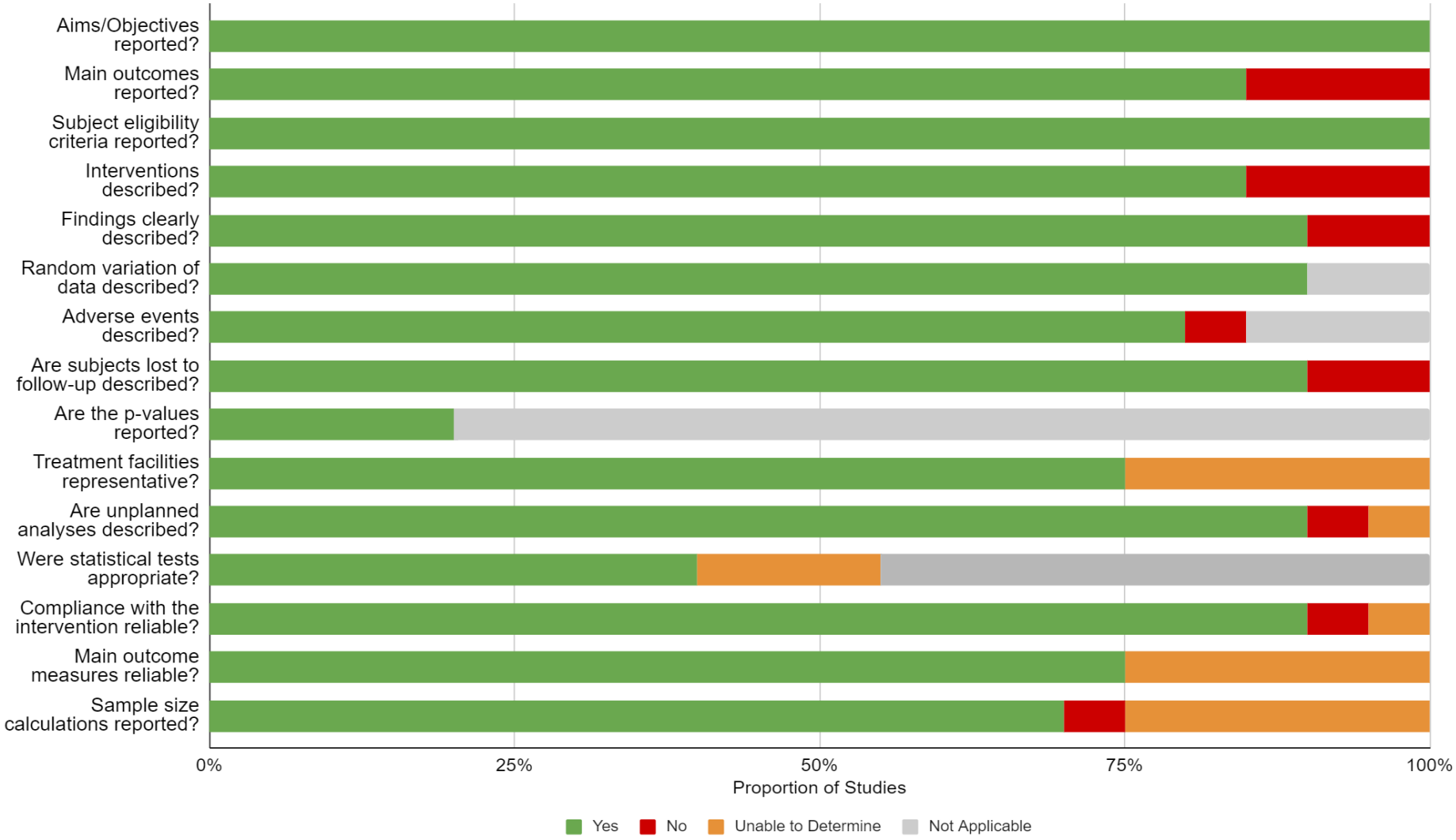

Figure 3: Graphical representation of the quality assessment of newly identified studies (all single arm studies)

Outcomes of new studies

Twenty new studies reporting 27 cohorts contributed data to the outcome synthesis. The number of evaluable rhabdomyosarcoma patients was clear for most studies, with just one cohort where the evaluability of a single patient was unclear [45]. The majority of cohorts (81%) reported outcome data for five or fewer patients with relapsed and refractory rhabdomyosarcoma.[4-16,20,45]

Survival

Seven studies (contributing 12 cohorts) reported Progression Free Survival (PFS) or Time to Progression (TTP).[8,13,15,21,22,26,27,32,46] This was ≤6 months for eight cohorts[8,13,15,21,26,27,32], with the remaining cohorts reporting only one participant each. Two patients (in two separate cohorts of the same study) received ponatinib (+/- ruxolitinib) with both having a PFS over 22 months.[13] These are small numbers which need interpretation with caution.

Five studies (contributing 10 cohorts) reported Overall Survival.[8,13,15,22,26,27,46] Similarly, Overall Survival times were short for most cohorts.

Response rate

No CRs were reported within the new studies. Three PRs were reported in 44 children and young people with relapsed and refractory rhabdomyosarcoma where the RECIST response was known. Additionally, one patient was reported to have an objective response (i.e CR or PR) but the exact response was not reported.[27]

Most 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).

Only one cohort containing more than one participant with relapsed and refractory rhabdomyosarcoma had an objective response rate of greater than 10%.[27]

Quality of Life

No new study reported quality of life data.

Adverse Events (AEs)

Adverse events were variably reported. Three molecular registry studies did not report any AE data.[5,6,13] Seventeen studies (with 18 cohorts) contributed new AE data.[4,7-12,14-16,20-22,26,27,32,44-47] Within these studies, over 400 participants were evaluable for toxicities (some studies did not clearly report the number evaluable).

As expected, the most commonly reported AEs were haematological, but specific AEs varied by study treatment.

All-cause mortality was reported by five studies, with the cause of death not being clearly reported.[21,22,26,27,32,44,46,47] No study explicitly reported treatment related or potentially treatment related deaths.

New CTRs

Eighteen new CTR studies were identified. Reported start dates of the studies were mostly in 2021 (n=4[37,38,40,41]), and 2022 (n=6[33-36,42,43]). Seven studies reported a start date prior to 2020 (1 in 2015[48], 1 in 2016[49], 1 in 2017[50], 3 in 2019[51-53] and 1 in 2020[54]). One study did not report a start date. [39]

Seven studies were reported as having an academic sponsor [34,37,40,43,49,51,52], five a pharmaceutical sponsor[36,38,48,53,54] and six both academic and pharmaceutical sponsors[33,35,39,41,42,50].

We identified 13 currently open studies including 10 studies reported as currently recruiting, [35-38,40-42,48,53,54] two not yet recruiting[34,43] and one expanded access study[39]. Two studies were reported as completed with no identified published results (both completed in Q4 of 2022).[50,52] One withdrawn study where no participants had been recruited was identified but the reason for withdrawal was not specified.[33] Additionally, we identified two studies with an unknown status, both studies ending in late 2020.[49,51]

Sixteen studies were single-arm and evaluated a range of therapies, including novel single agent therapies (2 studies),[41,50] novel multi-agent therapies (3),[33,38,54] biomarker driven therapies alone (3)[40,48,53] or in combination with other systemic therapies (1),[42] standard multi-agent systemic therapies (2),[34,51] and other therapies (2)[39,49]. Two CTR studies were evaluating systemic therapies alongside another intervention: one evaluated a standard single agent systemic therapy with radiotherapy,[37] and the other evaluated novel multi-agent therapies with cryoablation[35]. One CTR was a molecular registry study.[52] Two studies were multi-arm; one evaluated a biomarker driven therapy with standard multi-agent chemotherapy compared with standard multi-agent chemotherapy alone.[36] The other compared standard chemotherapy schedules.[43]

One study was designed for rhabdomyosarcoma patients only,[43] three for sarcomas[33,34,37], and 14 for a wider range of malignancies[35,36,38-42,48-54]. The majority (n=17) included relapsed and refractory patients,[33-38,40-43,48-54] with one study also including newly diagnosed patients[53]. Eligible ages varied. Most studies had a lower age limit of one to two years and therefore infants (<1 year old) were only eligible for five studies.[39,43,48,52,54]Upper age limits were very varied (from 17-75 years) but most were in early adulthood. Four studies had no upper age limit.[33,34,39,53] One study was open to recruiting patients of all ages.[39]

The counties where studies were open included USA (n=9),[33-35,38,39,41,49,52,54] Spain (n=1),[37] Japan (n=1),[50] and multiple countries (n=5) [36,40,42,48,53]. Two studies did not report the country, but for both the sponsor/contact details for the study were located in China.[43,51]

Summary of new studies

The REFoRMS LSR-1 identified 20 new published studies of 104 children and young adults with relapsed and refractory rhabdomyosarcoma. This means that **overall**, the REFoRMS systematic review has identified **149** published early phase studies of interventions, including **over 1,200** children and young people with relapsed/refractory rhabdomyosarcoma.

The studies included in LSR-1 more frequently reported survival outcomes (35% reported PFS, and 25% reported OS), compared to the baseline systematic review (21% reported PFS and 20% reported OS). The REFoRMS parent group considered survival outcomes to be more meaningful than RECIST response criteria, which does not necessarily correspond to duration of survival. The REFoRMS parent group, however, also considered quality of life to be an important outcome, which was not reported in any of the newly identified studies.

Interestingly, this update identified more precision medicine studies (both studies of biomarker driven therapies, and molecular registry studies), highlighting the shift towards targeted therapies within the field of oncology. This has presented new challenges for the REFoRMS team, as molecular registry studies are usually focused more on the feasibility of performing genomic testing and matching treatments to eligible participants, rather than on the effectiveness of the relevant treatments. While these studies do report outcomes for children with a particular mutation receiving a targeted therapy, data on efficacy and adverse effects are often limited and sample sizes are often small.

The number of currently open studies identified from CTRs continues to increase (n=68 total - 55 identified in baseline review and still reported as open in LSR-1, and 13 newly identified in LSR-1). The large number of available studies provides many options for families and clinicians which may be considered positively, but also brings challenges in decision making and in the recruitment into many studies.

Suggestions for new adaptations/changes for next update

During REFoRMS LSR-1, changes were made to the baseline review methods to improve the reporting and synthesis of results across studies. Reviewers found these changes to be helpful, and they will continue to be implemented in following REFoRMS updates. Minor changes to the current data fields will be made in the update to reflect changes to the evidence identified and improve ease of reporting.

In future updates, the modified Downs and Black checklist will be used, although the REFoRMS team will continue to review alternative, more suited quality assessment tools for early phase trials if they become available. Further considerations of how molecular registry studies should be assessed meaningfully will also be implemented.

Tables

Table 1 - Quality Assessment

	Reporting									External Validity	Internal Validity - Bias				Power
Author, Year	**1**	**2**	**3**	**4**	**6**	**7**	**8**	**9**	**10**	**13**	**16**	**18**	**19**	**20**	**27**
Full Texts															
Loeb, 2022[12]															
Takagi, 2022[14]															
Metts, 2022[11]															
Geoerger, 2017[4]															
Eckstein, 2022[15]															
Morscher, 2021[10]															
Pasqualini, 2021[8]															
Manji, 2022[7]															
Harris, 2016[5]															
Cash, 2021[16]															
Bautista, 2021[9]															
Harttrampf, 2017[6]															
van Tilburg, 2021[13]															
Conference Abstract															
Slotkin, 2022[20]															
DeNardo, 2022[45]															
Conference Abstract and Clinical Trial Registry															
Cole, 2021 (NCT02095132) [44,47]															
Akshintala, 2021 (NCT02867592) [22,46]															
Akshintala, 2022 (NCT03041701) [21,32]															
Clinical Trial Registry															
CTR: NCT03441360[26]															
CTR: NCT03245450[27]															

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. Are subjects lost to follow-up described? 10. Are the p-values reported? 13. Were the facilities where subjects were treated representative? 16. Have unplanned analyses been clearly indicated? 18. Were statistical tests appropriate? 19. Compliance with the intervention reliable? 20. Main outcome measures reliable? 27. Were methods of determining sample sizes reported?

Boxes highlighted in red: No; boxes highlighted in green: Yes, boxes highlighted in grey: Not Applicable; boxes highlighted in orange: Unable to Determine. CTR = Clinical Trial Record.

Table 2.1 Demographic characteristics of new studies

Author, date (Reference)	Countries performed (language if not English)	Study design		Patient enrolment dates	Inclusion/exclusion criteria			Intervention(s)	Number of R+R RMS patients (total)	Age (median (range), ^mean)	Median prior lines of therapy (range)	Comment
		Phase	Single /multi centre		Disease	Age	Other					
Standard systemic therapies - multiple agent												
Metts, 2022[11]	USA	I	Multi	Oct 2012 - June 2019	Relapsed; refractory; all solid tumours	1-18 years	No effective therapy known. Measurable disease. Patients could not have previously received irinotecan and temozolomide in combination	Metformin, vincristine, irinotecan, temozolomide *Cycle 1: Vincristine: 1.5mg/m² IV on days 1 and 8; Irinotecan: 50mg/m² IV on days 1–5; Temozolomide: 100mg/m² orally on days 1–5 in a 21-day cycle.* *Cycle 2: Metformin and VIT (as in cycle 1). Metformin 666-2000mg/m²/day po bd on days 1-21 of 21 day cycle. (Max 12 cycles)* *Patients could only receive metformin if they had adequate haematologic recovery. If not, second cycle of VIT given with temozolomide dose reduced to 50mg/m². At end of cycle 2, those who didn't achieve haematological recovery were removed from study.* *Trial amended in 2015 to include metformin from cycle 1 and temozolomide starting dose reduced to 50mg/m²/day*	2 <18 years (26)	RMS: 12 years (9-15 years)	RMS: 3.5 (2-5)	Both alveolar RMS.
Novel agents - single agents												
Akshintala, 2021 (Supplemented by CTR)[22,46]	USA	II	Multi	May 2017 - Oct 2020	Relapsed; refractory	2-30 years	Six strata: OS, ESFT, RMS, NRSTS, WT and rare tumours. Includes newly diagnosed patients with no known curative therapy. Measurable disease. Excluded previously treated with cabozantinib or another MET/HGF inhibitor	Cabozantinib *40mg/m²/day po on days 1-28 of 28 day cycle*	14 included, 1 ineligible (109)	RMS: 19.3 years (5.7-26.8 years), 6 <18 years	NR	
Takagi, 2022[14]	Japan	I	Multi	Oct 2017 - Dec 2020	Refractory; all solid tumours	3-18 years	Measurable disease, Resistant to more than two types of chemotherapy regimens. Excluded patients who previously received olaparib or other PARP inhibitors, or allogeneic HSCT.	Olaparib *62.5-187.5mg/m² po bd for 28 day cycles (Cycle 0 lasted 3 days - patients given one dose of olaparib for pharmacokinetic analysis)*	2 (15)	DL3 group only: 8 years (5-16 years)	RMS: >2	Both alveolar RMS.
Cash, 2021[16]	USA	I	Multi	NR	Relapsed; refractory; solid or CNS tumour	1-21 years	Measurable disease. No effective therapy known.	Prexasertib (LY2606368) *80-150mg/m² IV on days 1 and 15 of 28 day cycle (max 13 cycles)*	4 (30)	WP: 9.5 years (2-20 years)	WP: 2 (1-8)	
DeNardo, 2022[45]	USA	I/II	NR	NR	Relapsed; refractory; all solid tumours	<22 years	Measurable disease.	Elraglusib (9-ING-41) *9.3-15mg/kg IV twice weekly, as single agent or in combination with irinotecan, cyclophosphamide +topotecan, or temozolomide+irinotecan, in 21-*	2 (23)	WP: 14.2 years	WP: 2 (0-14)	Supplemented with info from CTR. 2 alveolar RMS.

Author, date (Reference)	Countries performed (language if not English)	Study design		Patient enrolment dates	Inclusion/exclusion criteria			Intervention(s)	Number of R+R RMS patients (total)	Age (median (range), ^mean)	Median prior lines of therapy (range)	Comment
		Phase	Single /multi centre		Disease	Age	Other					
								day cycles				
CTR: NCT03441360[26]	USA	II	Multi	April 2018 - Jan 2022	Relapsed; refractory	1-18 years	RMS, NRSTS and EWS. Excluded patients who previously received eribulin mesylate.	Eribulin *1.4mg/m² IV on days 1 and 8 of 21 day cycle*	8 (23)	RMS: ^10.4 years (SD: 4.53 years)	NR	
CTR: NCT03245450[27]	UK, France, Italy, Germany, Greece, Poland, Spain, Switzerland	I/II	Multi	March 2018 - May 2021	Relapsed; refractory; All solid tumours (excluding CNS tumours)	6 months to 25 years	Measurable disease. Phase II only open to recruit patients with RMS, NRSTS & EWS. No prior exposure to eribulin mesilate within 6 months of study for phase I, and no prior use of eribulin mesilate or irinotecan hydrochloride for phase II	Eribulin *1.4mg/m² IV on days 1 and 8 of 21 day cycle* Irinotecan hydrochloride *20mg/m² or 40mg/m² IV on days 1-5 of 21 day cycle in schedule A.* *100mg/m² or 125mg/m² IV on days 1 and 8 of 21 day cycle in schedule B*	9 (40)	RMS: ^11.05 years (SD: 3.845 years)	NR	
Novel agents - multiple agents												
Slotkin, 2022[20]	USA	I/II	NR	NR	Relapsed; refractory	≥12 months	RMS and DSRCT. Can have received any number of prior therapies including irinotecan	Prexasertib *80-150mg/m² on days 1-10 of 21 day cycle* Irinotecan *20mg/m² on days 1-10 (DL1) or days 1-5 (DL2A) of 21 day cycle*	2 (21)	NR	NR	Supplemented with info from CTR. 16/21 previously received irinotecan.
Cole, 2021 (Supplemented by CTR) [44,47]	USA, Canada	II	Multi	NR	Relapsed; refractory	<21 years	All solid and CNS tumours for phase I. Phase II: NBL, MB/CNS embryonal tumours, RMS. Measurable disease.	Adavosertib *85mg/m²/dose po on days 1-5 of 21 day cycle* Irinotecan *90mg/m²/dose po on days 1-5 of 21 day cycle*	10 (39)	RMS: 11 years (4-16 years)	NR	
Pasqualini, 2021[8]	NR	II	Multi	Aug 2016 - July 2017	Relapsed; refractory; all solid tumours	<18 years	Measurable disease. Programmed cell death 1 ligand 1 (PD-L1) expression and high tumour mutation burden were 'enrichment criteria'.	Nivolumab *3mg/kg/dose IV on days 1 and 15 of 28 day cycle* Cyclophosphamide *25mg/m² po bd on days 1-7 and 15-21 of 28 day cycle* + irradiation *whenever appropriate, started at least 2 weeks after first nivolumab. (Max 2 years)*	2 (13)	RMS: 13.05 years (11.8-14.3 years)	WP: 3.5 (1-5)	2 alveolar RMS. 2 metastatic at relapse. Both RMS patients received irradiation (one to extremity, one to whole lung). Individual participant mutations described in manuscript
Akshintala, 2022 (Supplemented by CTR) [21,32]	USA	I/II	NR	NR	Relapsed; refractory; RMS only	2+ years	Measurable disease.	Ganitumab *18mg/kg IV every 2 weeks.* Dasatinib *60mg/m²/dose (max 100mg) po od (DL1) or 60mg/m²/dose (max 70mg) por bd (DL2) on continuous schedule.* *Cycle 1 is day -7 to 27, all other cycles 28 days*	14 (14 - 13 in phase I, 1 in phase II)	RMS: Phase I: 18 years (8-29 years). All patients: ^15.86 years (SD: 7.62 years)	RMS: Phase I 3 (1-6)	7 alveolar RMS, 6 embryonal RMS, 1 NR. 7 patients under 18 years (4 in Phase I DL1, 2 in Phase I DL2, and 1 in Phase II)

Author, date (Reference)	Countries performed (language if not English)	Study design		Patient enrolment dates	Inclusion/exclusion criteria			Intervention(s)	Number of R+R RMS patients (total)	Age (median (range), ^mean)	Median prior lines of therapy (range)	Comment
		Phase	Single /multi centre		Disease	Age	Other					
Biomarker driven studies												
Eckstein, 2022[15]	USA	II	Multi	Dec 2017 - Aug 2019	Relapsed; refractory; all solid tumours	1-21 years	Includes lymphomas and histiocytic disorders. Required one of following actionable alterations: ARAF, BRAF, NRAS, KRAS, HRAS, MAP2K1, GNA11, GNAQ, NF1, and BRAF. Excluded LGG and concomitant use of CYP3A4/ CYP2C19 -inducing or-inhibiting agents. Patients with actional BRAF V600 mutation preferentially assigned to separate subprotocol.	Selumetinib *25mg/m² (max dose 75mg) po bd for 28 day cycles (max 2 years)*	5 <18 years (20)	RMS: 10 years (5-16 years)	NR	3 embryonal RMS, 1 spindle cell RMS, 1 RMS NOS. Individual participant mutations described in manuscript
Morscher, 2021[10]	NR	I/II	NR	Nov 2016 - June 2018	Relapsed; refractory; all solid tumours	<18 years	No effective therapy known. Measurable disease. Had advanced molecular profiling. RMS patients in Arm F only.	Vistusertib (AZD2014) *30mg/m² po bd for 3 consecutive days on, 4 days off* Topotecan *0.5mg/m²/day on days 1-5 of 28 day cycle* Temozolomide *100mg/m²/day po od on days 1-5 of 28 day cycle In absence of toxicity, TOTEM escalated to 100% paediatric combination RP2D and vistusertib to 36mg/m². Vistusertib reduced to 20mg/m² in case of toxicity.*	3 (10)	Arm F: 8.5 years (2.2-17.8 years) at diagnosis	Arm F: 3.5 (2-7)	2 alveolar RMS, 1 embryonal RMS. 2 PAX-FOXO1 fusion positive, 1 PAX-FOXO1 fusion negative. Arm F: 7 relapsed, 3 refractory.
Geoerger, 2017[4]	NR	I	Multi	May 2013 - June 2014	Relapsed; refractory	1-21 years	NBL, MRT, or other tumours with documented evidence of cyclin D-CDK4/6-INK4-Rb pathway abnormalities. Measurable disease. Exclude patients with prior exposure to CDK4/6 inhibitors or any prior allogeneic HSCT	Ribociclib (LEE011) *350mg/m² po od on days 1-21 of 28 day cycle*	1 (15)	Subgroup (including RMS patient): 6 years (2-20 years)	Subgroup (including RMS patient): ≥4* (0-≥4)	
Bautista, 2021[9]	NR	I/II	Multi	Oct 2016 - June 2019	Relapsed; refractory	<18 years	Advanced molecular tumour profiling at treatment failure. Patients where TOTEM was considered an appropriate treatment choice whose tumours had D-CDK4/6 pathway–activating alterations: CDK4/6amplification, CDKN2A and/or CDKN2Bdeletion, or other D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities with wild-type Rb gene. Measurable disease.	Ribociclib *175-350mg/m² po od on days 6-21 of 28 day cycle* Topotecan *0.5-0.75mg/m² IV on days 1-5 of 28 day cycle* Temozolomide *100-150mg/m² po od on days 1-5 of 28 day cycle* **(Arm A)**	2 (14)	WP: 14.2 years (0.8-19.1 years) at study entry	WP: 2 (1-5)	1 alveolar RMS, 1 embryonal RMS. Individual participant mutations described in manuscript
							Advanced molecular tumour profiling at treatment failure. Patients with alterations in cell cycle (as arm A) and/or the PI3K/AKT/mTOR pathway: PI3K (including PIK3CA, PIK3CB, PIK3R1, or others),	Ribociclib *90-260mg/m² po od on days 1-21 of 28 day cycle* Everolimus *2.5-3.5mg/m² po od on days 1-28 of 28 day cycle*	2 (18)	WP: 13.1 years (5.6-19.6 years) at study	WP: 3 (1-5)	1 alveolar RMS, 2 embryonal RMS. Individual participant mutations described in

Author, date (Reference)	Countries performed (language if not English)	Study design		Patient enrolment dates	Inclusion/exclusion criteria			Intervention(s)	Number of R+R RMS patients (total)	Age (median (range), ^mean)	Median prior lines of therapy (range)	Comment
		Phase	Single /multi centre		Disease	Age	Other					
							AKT,TSC, or mTOR FRB domain (excluding kinase domain) mutations, TORC1- or TORC2-activating mutations, or gain and loss of PTEN. Measurable disease.	**(Arm B)**		entry		manuscript
Immunotherapy												
Loeb, 2022[12]	NR	I	Multi	NR, data cut-off July 2021	All solid tumours	<18 years	No effective therapy known. Includes lymphoma. Progressed with standard therapy	Avelumab *10-20mg/kg IV every 2 weeks*	5 (21)	RMS: 9 years (8-14 years)	WP: 3* (1-4+)	At relapse: 1 stage 3, 4 stage 4.
Metronomic Chemotherapy												
Manji, 2022[7]	Canada	I	Multi	March 2015 - April 2019	Relapsed; refractory; all solid tumours	2-21 years	Excluded known CNS metastasis, or concurrent use of CYP3A4/PgP substrates, QTc prolonging medications, or other anticancer agents	Metronomic pazopanib *125-160mg/m^2 po od for 28 day cycles (not given on cycle 1 day 1)* + topotecan *0.12-0.4mg/m^2 po od for 28 day cycles*	4 (30)	WP: 12 years (3-20 years)	WP: 1.5 (0-10) systemic therapies	All had received at least one prior therapy including chemotherapy, radiotherapy or both
Molecular Registry Studies												
Harris, 2016[5]	USA	PM	Multi	Sept 2012 - Nov 2013	Relapsed; refractory	≤30 years	High risk extracranial solid tumour (high risk defined as overall survival for a patient group with the same diagnosis, grade, and stage estimated to be no more than 25%)	BKM120 *Dose, method of administration and frequency NR*	1 (3)	"child"	NR	1 embryonal RMS. Individual participant mutations described in manuscript
Harttrampf, 2017[6]	France	PM	Single	NR	Relapsed; refractory; all solid tumours	6 months +	Includes CNS tumours. Have to have received at least one prior treatment line	Lenvatinib **(Matched treatment)** *Dose, method of administration and frequency NR*	1 (14)	RMS: 12.9 years	RMS: 1	1 embryonal RMS. 1 metastatic at diagnosis and relapse. Individual participant mutations described in manuscript
								Temsirolimus, vincristine, irinotecan, temozolomide **(Matched treatment)** *Dose, method of administration and frequency NR*	1 (14)	RMS: 4.7 years	RMS: 1	1 alveolar RMS. 1 PAX-FOXO1 fusion positive. 1 metastatic at diagnosis. Individual participant mutations described in manuscript
Van Tilburg, 2021[13]	Germany, Austria, Finland, Poland, Greece, Switzerland, Sweden, the	PM	Multi	Jan 2015 - Sept 2019	Relapsed; refractory	<40 years	Malignant disease. Measurable disease. Mo effective therapy known. Primary paediatric diagnosis had to be before 21 years.	Nivolumab **(Matched treatment)** *Dose, method of administration and frequency NR*	1 (147)	RMS: 15 years	NR	Individual participant mutations described in manuscript
								Trametinib **(Matched treatment)** *Dose, method of administration and frequency NR*	4 (147)	RMS: 4 years (3-4 years)	NR	Individual participant mutations described in manuscript
								Palbociclib	1 (147)	RMS: 11	NR	Individual participant

Author, date (Reference)	Countries performed (language if not English)	Study design		Patient enrolment dates	Inclusion/exclusion criteria			Intervention(s)	Number of R+R RMS patients (total)	Age (median (range), ^mean)	Median prior lines of therapy (range)	Comment
		Phase	Single /multi centre		Disease	Age	Other					
	Netherlands							**(Matched treatment)** *Dose, method of administration and frequency NR*		years		mutations described in manuscript
								Ponatinib **(Matched treatment)** *Dose, method of administration and frequency NR*	1 (147)	RMS: 15 years	NR	Individual participant mutations described in manuscript
								Ponatinib + Ruxolitinib **(Matched treatment)** *Dose, method of administration and frequency NR*	1 (147)	RMS: 13 years	NR	Individual participant mutations described in manuscript
								Ribociclib **(Matched treatment)** *Dose, method of administration and frequency NR*	2 (147)	RMS: 14 years (12-16 years)	NR	Individual participant mutations described in manuscript

* Data has been calculated for RMS patients specifically. ^ mean

bd = twice daily; CNS = central nervous system; CTR = clinical trial record; DL = dose level; DSRCT = desmoplastic small round cell tumours; ESFT = Ewing's sarcoma family of tumours; EW = Ewing's sarcoma; HSCT = haematopoietic stem cell transplant; IV = intravenous; MB = medulloblastoma; MRT = malignant rhabdoid tumour; NBL = neuroblastoma; NOS = not otherwise specified; NR = not reported; NRSTS = non-rhabdomyosarcoma soft tissue sarcoma; OS = osteosarcoma; PM = precision medicine; po = orally; R+R = relapsed and refractory; RMS = rhabdomyosarcoma; SD = standard deviation; TOTEM = topotecan & temozolomide; UK = United Kingdom; USA = United States of America; VIT = vincristine, irinotecan & temozolomide; WP = whole population; WT = Wilm's tumour

Table 3.1 Outcome data for new studies

Regimen	Author, date (Reference)	Total number of relevant CYP$	Responses (number of CYP)				Response rate % (95% CI) CR+PR	Median Survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Standard systemic therapy - multiple agents										
Metformin, vincristine, irinotecan, temozolomide	Metts, 2022[11]	1 R+R RMS	0	1	0	0	100%*	NR	NR	
Novel agents - single agent										
Cabozantinib	Akshintala, 2021 (Supplemented by CTR) [22,46]	13 R+R RMS	0	0			0% (0-24.71%)	PFS at 1 yr: 0%	OS at 1yr: 25% (6.01-50.48%)	Note: OS includes all 13 RMS patients (only 6 within eligible age range for REFoRMS)
Olaparib	Takagi, 2022[14]	1 Refractory RMS	0	0		0	0%*	NR	NR	1 evaluable RMS patient had non-complete remission/progressive disease for between 17-18 months
Prexasertib (LY2606368)	Cash, 2021[16]	3 R+R RMS	0	0	0	3	0%*	NR	NR	
Elraglusib (9-ING-41)	DeNardo, 2022[45]	*2# R+R RMS*	0	0	1		0%*	NR	NR	
Eribulin	CTR: NCT03441360[26]	8 R+R RMS	0	0			0%	1.74 (95% CI 1.12-2.86)	5.08 (95% CI 1.74-6.47)	
Eribulin	CTR: NCT03245450[27]	9 R+R RMS					11.1%	2.69 (90% CI 1.28-8.87)	NR	1 patient with an objective response but exact response not reported. CBR was 55.6%.
Novel agents - multiple agents										
Prexasertib + Irinotecan	Slotkin, 2022[20]	2 R+R RMS	0	0	2	0	0%*	NR	NR	
Adavosertib + Irinotecan	Cole, 2021[44,47] (Supplemented by CTR)	10 R+R RMS	0	0	2	8	0%*	NR	NR	Patients with SD for duration of 8 and 10 cycles.
Nivolumab, cyclophosphamide + irradiation	Pasqualini, 2021[8]	2 R+R RMS	0	0	0	2	0%*	1.7 (1.7-1.7)	3.1 (2.7-3.5)	
Ganitumab + dasatinib	Akshintala, 2022 (Supplemented by CTR) [21,32]	10 R+R RMS (9 in phase 1, 1 in phase 2)		1	1		Inconsistent between conference abstract and CTR	DL1: 1.93 (1.7-5.83) Phase 2: 0.88	NR	PR inconsistent between conference abstract and CTR. PFS at 4 months: DL1: 20%, with at least 1 being under 18 years Phase 2: 0% PR at DL2 sustained for 5 cycles and SD at DL1 was for 6 cycles (inconsistent between conference abstract and CTR)

Biomarker driven studies										
Selumetinib	Eckstein, 2022[15]	5 R+R RMS	0	0	0	5	0%*	<2 months *	Approx 4 months*	
Vistusertib (AZD2014), topotecan, temozolomide	Morscher, 2021[10]	3 R+R RMS	0	0	0	3	0%*	NR	NR	
Ribociclib (LEE011)	Geoerger, 2017[4]	1 R+R RMS	0	0	0	1	0%*	NR	NR	RMS patient progressed at 5-6 weeks.
Ribociclib, Topotecan, Temozolomide **(Arm A)**	Bautista, 2021[9]	2 R+R RMS	0	0	0	2	0%*	NR	NR	
Ribociclib + Everolimus **(Arm B)**	Bautista, 2021[9]	2 R+R RMS	0	0	0	2	0%*	NR	NR	
Immunotherapy										
Avelumab	Loeb, 2022[12]	3 R+R RMS	0	0	0	3	0%*	NR	NR	
Metronomic chemotherapy										
Metronomic pazopanib + topotecan	Manji, 2022[7]	4 R+R RMS	0	0	0	4	0%*	NR	NR	
Molecular Registry Studies										
BKM120	Harris, 2016[5]	1 R+R RMS	0	0			0%*	NR	NR	
Lenvatinib **(Matched treatment)**	Harttrampf, 2017[6]	1 R+R RMS	0	0	0	1	0%*	NR	NR	
Temsirolimus, vincristine, irinotecan, temozolomide **(Matched treatment)**	Harttrampf, 2017[6]	1 R+R RMS	0	1	0	0	100%*	NR	NR	Temsirolimus added to ongoing VIT. PR (-57%) after SD (-7.5%) to VIT alone. PR after 4 cycles then underwent subsequent surgical complete resection.
Nivolumab **(Matched treatment)**	Van Tilburg, 2021[13]	1 R+R RMS					NR	8.9	26.3	
Trametinib **(Matched treatment)**	Van Tilburg, 2021[13]	1 1st relapse, 3 other R+R RMS					NR	4.1 (3.5-4.9)	5.6 (4.4-17.3)	
Palbociclib **(Matched treatment)**	Van Tilburg, 2021[13]	1 R+R RMS					NR	1.3	8.6	
Ponatinib **(Matched treatment)**	Van Tilburg, 2021[13]	1 R+R RMS					NR	25.3	41.6	
Ponatinib + Ruxolitinib **(Matched treatment)**	Van Tilburg, 2021[13]	1 R+R RMS					NR	22.5	23.5	Patient reported to have received treatment for 724 days but overall survival for 715 days.
Ribociclib **(Matched treatment)**	Van Tilburg, 2021[13]	2 R+R RMS					NR	2.0 (1.6-2.5)	7.0 (6.8-7.1)	

$ = evaluable, RMS patients; *calculated from provided information

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

CBR = clinical benefit rate; CI = confidence intervals; CR = complete response; CTR = clinical trial record; CYP = children and young people; DL = dose level; NR = not reported; OS = overall survival; PR = partial response; PD = progressive disease; PFS = progression free survival; R+R = relapsed & refractory; RMS = rhabdomyosarcoma; SD = stable disease; TTP = time to progression; VIT = vincristine, irinotecan & temozolomide

Table 4.1 Adverse Event data

Intervention	Author, year (reference)	Number evaluable for toxicity (RMS)	Total number AEs			AE details provided by manuscript
			DLT	G3	G4	
Standard systemic therapies - multiple agent						
Metformin, vincristine, irinotecan, temozolomide	Metts, 2022[11]	22 (18 for DLT) (2 RMS)	2	115E	25E	2 DLTs occurred at 2000mg/m2/day dose: 2 G3 **diarrhoea** requiring hospitalisation and 48h of IV hydration. AEs associated with cycles including metformin: Anemia (15E G3), **Febrile Neutropenia** (2E G3), Hearing Impaired (1E G3), Abdominal Pain (2E G3), **Diarrhoea** (5E G3, 1E G4), Nausea (2E G3), **Vomiting** (2E G3), Gait Disturbance (1E G3), Pain (1E G3), Allergic Reaction (1E G3), Alanine Aminotransferase (7E G3), Aspartate aminotransferase (2E G3), lymphocyte count decrease (1E G3, 1E G4), **Neutrophil count decrease** (17E G3, 11E G3), **platelet count decrease** (4E G3, 5E G4), **Weight loss** (2E G3), White blood cell decrease (9E G3, 1E G4), Anorexia (2E G3), Dehydration (5E G3, 1E G4), Hypokalemia (3E G3), Hypomagnesemia (2E G3), Hypophosphateaemia (1E G3), Backpain (1E G3), Generalised muscle weakness (1E G3), Pain in extremity (1E G3), Aphonia (1E G3), Depressed levels of consiousness (2E G3), Dysarthria (1E G3), Headache (2E G3), Hydrocephalus (1E G3), Nervous System Disorders [other] (1E G3), Peripheral Motor Neuropathy (1E G3), Seizure (1E G4), Confusion (1E G3), Hallucinations (1E G3), Hypoxia (1E G3). AEs associated with cycles not including Metformin: anaemia (1E G3), **febrile neutropenia** (1E G3), ear pain (1E G3), **Nausea** (1E G3), Fatigue (1E G3), Fever (1E G3), Enterocolitis infectious (1E G3), **Neutrophil count decreas**e (1E G4), **Platelet count decrease** (1E G3, 2E G4), Dehydration (1E G3), Hyponatraemia (1E G3), haematuria (2E G3), hypoxia (1E G3), hypotension (1E G4).
Novel agents - single agents						
Cabozantinib	Akshintala, 2021 (Supplemented by CTR) [22,46]	104 (13 RMS)	20P in C1, 39P in later Cs			38.46% (95% CI: 13.86 to 68.42) of RMS patients experienced AEs. 78P all-cause **mortality** (10 RMS). SAEs (specific grade not reported): 36P experienced at least 1 SAE (2 RMS) 2P anaemia; 1P heart failure; 2P pericardial effusion; 1P pericardial tamponade; 1P left ventricular systolic dysfunction; 2P abdominal pain; 1P colitis; 2P **constipation**; 1P esophageal stenosis; 1P other gastrointestinal disorders; 1P ileus; 1P **nausea**; 1P oral pain; 3P **vomiting**; 1P edema face; 1P fatigue; 2P fever; 1P localised edema (RMS); 2P non-cardiac chest pain; 1P eye infection; 2P other infections (not specified); 1P sepsis; 1P skin infection; 3P lung infection; 1P wound dehiscence; 2P alanine aminotransferase increase; 1P alkaline phosphatase increase; 3P aspartate aminotransferase increase; 3P blood bilirubin increase; 2P **weight loss**; 1P ejection fraction decrease; 1P anorexia; 3P dehydration; 2P hyponatremia; 1P hypophosphatemia; 1P other metabolism/nutrition disorder (not specified); 1P chest wall pain; 2P flank pain; 1P muscle weakness lower limb; 2P tumour pain; 1P leukaemia secondary to chemotherapy; 1P dysarthria (RMS); 1P headache; 1P intracranial haemorrhage; 1P other nervous system disorder (not specified); 1P paresthesia; 1P seizure; 1P stroke (RMS); 1P dysesthesia; 3P dyspnea (1 RMS); 3P hypoxia; 3P pleural effusion; 1P pleuritic pain; 4P pneumothorax; 1P productive cough; 1P respiratory failure; 1P rhinorrhea; 1P sore throat; 2P hypotension; 2P thromboembolic event (1 RMS) Other non serious AEs reported but not extracted.
Olaparib	Takagi, 2022[14]	11				TEAEs Grade >/= 3: 6P any TEAE, 1P pneumonia, 3P lymphocytopenia, 3P **neutropenia,** 2P decrease number of white blood cells. One patient developed AML 3 months after cessation of olaparib

Intervention	Author, year (reference)	Number evaluable for toxicity (RMS)	Total number AEs			AE details provided by manuscript
			DLT	G3	G4	
Prexasertib (LY2606368)	Cash, 2021[16]	25 (3 RMS)	0			Grade >/= 3 AEs: 25P **neutrophil count decrease** (6P at 80mg/m2, 5P at 100mg/m2, 4P at 125mg/m2, 10P at 150mg/m2) - 22 were Grade 4, 17P white blood cell decrease (4P at 80mg/m2, 3P at 100mg/m2, 3P at 125mg/m2, 7P at 150mg/m2), 6P **platelet count decrease** (1P at 80mg/m2, 2P at 100mg/m2, 2P at 125mg/m2, 1P at 150mg/m2), 3P anaemia (1P at 100mg/m2, 1P at 125mg/m2, 1P at 150mg/m2), 6P lymphocyte count decrease (2P at 80mg/m2, 2P at 125mg/m2, 2P at 150mg/m2), 1P alanine aminotransferase increase (100mg/m2)
Elraglusib (9-ING-41)	DeNardo, 2022[45]	At least 21			1	1 G4 hypotension/infusion reaction (of 15P) in combination arm with irinotecan or cyclophosphamide/topotecan. No elraglusib-attributable SAEs experienced in 6P in single agent elraglusib arm. No other G3/4 AEs reported.
Eribulin	CTR: NCT03441360[26]	21 (8 RMS)				All 21P with at least one TEAE (8 RMS), and 11P with SAEs (6 RMS). 20P with all-cause **mortality** (8 RMS). SAEs (exact grade not reported): 1P **neutropenia**; 1P anaemia (RMS); 1P cardiac tamponade (RMS); 1P left ventricular dysfunction (RMS); 1P pericardial effusion (RMS); 1P sinus bradycardia; 1P mouth haemorrhage (RMS); 3P pyrexia (1 RMS); 1P pneumonia; 1P bone pain; 1P costochondritis; 1P muscle weakness (RMS); 2P malignant neoplasm progression (1 RMS); 2P malignant pleural effusion (1 RMS); 1P neuralgia; 1P headache (RMS); 1P seizure (RMS); 1P dyspnoea (RMS); 1P epistaxis (RMS); 1P pleural effusion; 1P pneumothorax; 1P pulmonary oedema; 1P respiratory failure. Non-serious AEs also reported but not extracted
Eribulin	CTR: NCT03245450[27]	40 (9 RMS)				40P at least one TEAE (9 RMS). 17P with SAE (5 RMS). 15P with all-cause **mortality** (4 RMS). Serious AEs (exact grade not reported): 2P **febrile neutropenia**, 1P abdominal pain (RMS), 4P pyrexia (1 RMS), 1P bacteraemia, 1P device related infection (RMS), 1P sepsis, 1P upper respiratory tract infection (RMS), 1P malnutrition, 1P pain in jaw, 5P malignant neoplasm progression (1 RMS), 2P malignant pleural effusion (1 RMS), 1P dyspnoea (RMS). Non-serious AEs also reported but not extracted
Novel agents - multiple agents						
Prexasertib + Irinotecan	Slotkin, 2022[20]	NR				48% **neutropenia** (grade NR) 48% **nausea** (grade NR) 52% fatigue (grade NR) Cytopenias were managed with the aid of growth factor support in all patients once the RP2D was established
Adavosertib + Irinotecan	Cole, 2021 (Supplemented by CTR) [44,47]	Phase 2 potion of study: 30 during C1 (7 RMS), 39 overall (10 RMS)	2 (1 RMS)			3/39 P had all-cause **mortality** (including 1 RMS) SAEs (exact grade not reported): 27/39 reported at least one SAE (including 7/10 RMS patients) 6P anaemia (2 RMS); 7P hearing impairment; 1P optic nerve disorder; 2P **diarrhoea** (1 RMS); 3P **nausea** (1 RMS); 3P **vomiting** (2 RMS); 1P non-cardiac chest pain (RMS); 1P retropharyngeal infection (RMS); 1P lung infection; 2P wound infection (both RMS); 1P activated partial thromboplastin time prolonged; 8P lymphocyte count decrease (1 RMS); 15P neutrophil count decrease (3 RMS); 6P **platelet count decrease**; 2P urine output decrease (1 RMS); 6P white blood cell decrease; 3P anorexia (1 RMS); 1P dehydration (RMS); 1P hyperglycemia (RMS); 2P hypokalemia (1 RMS); 3P hyponatremia (2 RMS); 1P hypophosphatemia; 1P obesity; 3P tumour pain (1 RMS); 1P ataxia; 1P cognitive disturbance; 1P depressed level of consciousness; 1P headache; 2P hydrocephalus; 1P seizure; 1P acute kidney injury (RMS); 1P urinary tract obstruction (RMS); 1P dyspnea (RMS); 2P hypoxia (1 RMS); 1P bradypnea; 1P stridor;

Intervention	Author, year (reference)	Number evaluable for toxicity (RMS)	Total number AEs			AE details provided by manuscript
			DLT	G3	G4	
						1P tumour bleeding (RMS); 1P skin ulceration (RMS); 1P ventriculoperitoneal shunt; 2P hypertension (1 RMS); 1P hypotension Non-serious AEs also reported but not extracted
Nivolumab, cyclophosphamide + irradiation	Pasqualini, 2021[8]	13 (2 RMS)		17E	5E	Anaemia (4E G3), **Vomiting** (2E G3), lymphocyte count decrease (7E G3, 2E G4), **neutrophil count decrease** (3E G3, 1E G4), **Platelet count decrease** (1E G4), WBC decrease (1E G3, 1E G4).
Ganitumab + dasatinib	Akshintala, 2022 (Supplemented by CTR) [21,32]	11 for Phase 1 (all RMS), Not clear if phase 2 patient evaluable	3P (all G3)	4P related to ganitumab. 7P related to dasatinib	1P related to dasatinib	DLTs: 1P Grade 3 **diarrhoea** (DL1); 1P Grade 3 pneumonitis (DL2); 1P Grade 3 hematuria (DL2) All 14P had at least one non-serious or serious AE. 3P all-cause **mortality** (2P at DL1, 1P at DL2) Serious AEs (exact grade not reported): 1P pericardial effusion (DL2); 2P abdominal pain (1 at DL1, 1 at DL2); 1P ascites (DL2); 1P **nausea** (DL2); 1P oral haemorrhage (DL2); 2P **vomiting** (DL2); 1P fatigue (DL2); 2P fever (DL1); 1P Klebsiella pneumonia (DL1); 1P kidney infection (DL1); 1P urinary tract infection (DL1); 1P dehydration (DL2); 1P hypocalcemia (DL1); 1P hyponatremia (DL2); 2P back pain (1 at DL1, 1 at DL2); 1P tumour haemorrhage (Phase 2); 2P hematuria (1 at DL1, 1 at DL2); 1P bronchopulmonary haemorrhage (DL2); 2P hypoxia (1 at DL1, 1 at DL2); 1P pleuritic pain (DL1); 1P pneumonitis (DL2); 3P respiratory failure (2 at DL1, 1 at DL2) Other non-serious AEs reported but not extracted
Biomarker driven studies						
Selumetinib	Eckstein, 2022[15]	20				5 AEs G3 or higher CPK increase - 1P G4; lymphocyte count decrease - 1P G3; uveitis - 1 P G3; Thromboembolic event - 1P G3, **1P G5. 1P who died (G5) due to pulmonary embolus** 3 patients required dose modification, two of which discontinued selumetinib.
Vistusertib (AZD2014), topotecan, temozolomide	Morscher, 2021[10]	10 (9 for DLT; at least 2 RMS)	2	17E	4E	DLTs: 2P **thrombocytopenia** (1 G3, 1 G4 [prolonged]). Anaemia (2E G3), Leukopenia (2E G3), Lymphopenia (2E G3), **Neutropenia** (3E G3, 3E G4), **Thrombocytopenia** (7E G3, 1E G4), Lipase increased (1E G3).
Ribociclib (LEE011)	Geoerger, 2017[4]	32 (1 RMS)	3P during C1			25P had G3/4 AEs DLTS: 1 G3 fatigue at 280mg, 2 G4 **thrombocytopenia** at 470mg Grade 3/4 haematological AEs (expected to be study drug-related): **Neutropenia** - 20P (1 at 280mg, 11 at 350mg, 8 at 470mg), Leukopenia - 12P (7 at 350mg, 5 at 470mg), Anaemia - 1P (350mg), **Thrombocytopenia** - 9P (4 at 350mg, 5 at 470mg), Lymphopenia - 6P (2 at 350mg, 4 at 470mg) Grade 3/4 non-hematological AEs (expected to be study drug-related): Fatigue - 1P (280mg), Decreased appetite - 1P (280mg), AST increases - 1P (350mg)
Ribociclib, Topotecan, Temozolomide (Arm A)	Bautista, 2021[9]	14 (13 for DLT; 2 RMS)	3			48 G3/4 AEs (6 DL1, 42 DL2) AEs not clearly reported. DLTs: 1P G4 **thrombocytopenia** requiring transfusions > 7 days. 2P G4 **neutropenia** > 7 consecutive days (all at DL2) DL1: anaemia (1E G3/4 related to both treatments), leukopenia (2E G3/4 related to both treatments), **neutropenia** (1E G3/4 related to both treatments), lymphopenia (2E G3/4 related to both treatments). DL2: Anaemia (3E G3/4 related to both treatments), leukopenia (8E G3/4 related to both treatments), **neutropenia** (3E G3/4 related to Ribociclib, 5E G3/4 related to TOTEM, 17E G3/4 related to both), lymphopenia (3E G3/4 related to both treatments),

Intervention	Author, year (reference)	Number evaluable for toxicity (RMS)	Total number AEs			AE details provided by manuscript
			DLT	G3	G4	
						thrombocytopenia (2E G3/4 related to both treatments), ALT increase 1E G/4 related to Ribociclib.
Ribociclib + Everolimus (Arm B)	Bautista, 2021[9]	17 (14 for DLT; 2 RMS)	4			28 G3/4 AEs (2 DL1, 24 DL2, 2 DL3) AEs not clearly reported. DLTs: 1P G4 **thrombocytopenia** (DL2), 1P G1 arrhythmia leading to interruption (DL3), 1P G3 **mucositis,** 1P G3 **thrombocytopenia** (DL2 expansion) DL1: **Neutropenia** (1E G3/4 related to both treatments), Lipase increase (1E G3/4 related to both treatments). DL2: Leukopenia (5E G3/4 related to both treatments), **Neutropenia** (5E G3/4 related to both treatments), Lymphopenia (9E G3/4 related to both treatments), **Thrombocytopenia** (4E G3/4 related to both treatments), **Mucositis** (1E G3/4 related to both treatments). DL3: **Thrombocytopenia** (2E G3/4 related to both treatments)
Immunotherapy						
Avelumab	Loeb, 2022[12]	21 (18 for DLT)				16P G3+ AEs: 5P G3+ (Avelumab 10mg/kg); 11P G3+ (Avelumab 20mg/kg) All G3+ AEs: Anaemia (1P at 10mg/kg, 1P at 20mg/kg), Abdominal Pain (2P at 10mg/kg), Disease Progression (1P at 10mg/kg, 5P at 20mg/kg), Dyspnoea (1P at 10mg/kg, 1P at 20mg/kg), Hyponatraemia (1P at 10mg/kg, 2P at 20mg/kg), Back pain (1P at 20mg/kg), Arthralgia (1P at 20mg/kg), Fatigue (1P at 20mg/kg), **Nausea** (1P at 20mg/kg), Headache (1P at 20mg/kg), Hypophagia (2P at 20mg/kg), Hypertension (2P at 20mg/kg)
Metronomic chemotherapy						
Metronomic pazopanib + topotecan	Manji, 2022[7]	26 (DLT)	2			35 G3/4 Toxicities across all cycles DLTs: persistent G3 **thrombocytopenia** (1P) and persistent G3 ALT elevation (1P). **Thrombocytopenia** (4P G3/4, including 1 DLT), **Neutropenia** (9P G3/4), Lymphopenia (4P G3/4), Anaemia (5P G3/4), **Diarrhoea** (1P G3/4), ALT Elevation (2P G3/4, including 1 DLT), AST Elevation (3P G3/4), Hypoalbuminemia (1P G3/4), Lipase elevation (3P G3/4), Hypocalcemia (1P G3/4), Headache (1P G3/4), Pain (1P G3/4).
Non-comparative multi-arm studies						
BKM120	Harris, 2016[5]					No AE data reported
Lenvatinib (Matched treatment)	Harttrampf, 2017[6]					No AE data reported
Temsirolimus, vincristine, irinotecan, temozolomide (Matched treatment)	Harttrampf, 2017[6]					No AE data reported
Nivolumab (Matched treatment)	Van Tilburg, 2021[13]					No AE data reported
Trametinib (Matched treatment)	Van Tilburg, 2021[9]					No AE data reported
Palbociclib (Matched treatment)	Van Tilburg, 2021[9]					No AE data reported

Intervention	Author, year (reference)	Number evaluable for toxicity (RMS)	Total number AEs			AE details provided by manuscript
			DLT	G3	G4	
Ponatinib (Matched treatment)	Van Tilburg, 2021[9]					No AE data reported
Ponatinib + Ruxolitinib (Matched treatment)	Van Tilburg, 2021[9]					No AE data reported
Ribociclib (Matched treatment)	Van Tilburg, 2021[9]					No AE data reported

AEs written in bold text represent the AEs most important to the parent group.
AE = adverse event; AML = acute myeloid leukaemia; C = cycle(s); CI = confidence interval; CTR = clinical trial record; DL = dose level; DLT = dose limiting toxicity; E = event(s)/episode(s); G = grade; IV = intravenous; NR = not reported; P = patient(s); RMS = rhabdomyosarcoma; RP2D = recommended phase two dose; SAE = serious adverse event; TOTEM = topotecan & temozolomide; TEAE = treatment emergent adverse event

Table 5.1 New clinical trial registry records

Clinical trial registry number(s)	Title of registered clinical trial	Planned locations; Sponsor	Number of participants	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
Recruitment status: Not yet recruiting								
NCT05210374[34]	Disulfiram With Copper Gluconate and Liposomal Doxorubicin in Treatment-Refractory Sarcomas	USA; Academic	24 (E)	01/12/2022* - 01/11/2023*	Disulfiram, copper gluconate & liposomal doxorubicin	Response rates, Adverse events, Overall Survival, Dose Limiting Toxicities, RP2D, EFS, pharmacokinetics	Relapsed, Refractory, Children, Young adults, All sarcoma	≥1 year
NCT05457829[43]	Doxorubicin Hydrochloride Liposome Combined With Irinotecan Versus VIT Regimen in the Treatment of Pediatric Rhabdomyosarcoma	NR (but sponsor/contact in China); Academic & Pharmaceutical	88 (E)	30/07/2022 - 31/07/2026	Liposomal doxorubicin & irinotecan (Comparator: Vincristine, Irinotecan & Temozolomide, VIT)	Response rates, Adverse events, Overall Survival, Progression Free Survival, Disease control rate	Relapsed, Refractory, Rhabdomyosarcoma only, Children, Young adults, Patients who previously received any of these treatments excluded	6 months - 18 years (inclusive)
Recruitment status: Recruiting								
NCT05302921[35]	Neoadjuvant Dual Checkpoint Inhibition and Cryoablation in Relapsed/ Refractory Pediatric Solid Tumors	USA; Academic & Pharmaceutical	42 (E)	18/02/2022 - 01/07/2025	Nivolumab & ipilimumab (& cryoablation to one disease site)	Response rates, Adverse events, Biomarkers of checkpoint inhibition, health outcomes	Relapsed, Refractory, All solid tumours, Children, Young adults, Have to have at least two measurable/evaluable solid target lesions	1-39 years (inclusive)
CTRI/2022/04/042263[36]	Study Of Palbociclib Combined With Chemotherapy In Pediatric Patients With Solid Tumors	USA, Canada, Bulgaria, Hungary, India, Israel, Poland, Republic of Korea, Russian Federation, Slovakia, Sweden, Turkey, Ukraine; Pharmaceutical	75 (Target sample size)	15/05/2022 - NR	Palbociclib with temozolomide & irinotecan or with topotecan & cyclophosphamide	Response rates, Adverse events, Overall Survival, Progression Free Survival, EFS, Pharmacokinetics, Duration of response	Relapsed, Refractory, All solid tumours, Children, Young adults, Evaluable disease. RMS only eligible for phase 1	2-20 years (inclusive)
NCT05131386[37]	Multicohort Trial of Trabectedin and Low-dose Radiation Therapy in Advanced/Metastatic Sarcomas	Spain; Academic	85 (E)	28/05/2021 - 28/07/2024	Trabectedin & radiation therapy	Response rates, Adverse events, Overall Survival, Progression Free Survival, Time	Young adults, Metastatic and locally advanced disease. Different cohorts including STS, bone tumours and small round-cell sarcomas.	16-75 years (inclusive)

Clinical trial registry number(s)	Title of registered clinical trial	Planned locations; Sponsor	Number of participants	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
	(SYNERGIAS)					to progression, Pain, Quality of life	Received at least one previous systemic therapy and a maximum of three prior lines and no previous use of trabectedin. Not allowed previous radiotherapy.	
NCT05093322 (also Eudract no 2021-003602-41) [38]	A Study of Surufatinib in Combination With Gemcitabine in Pediatric, Adolescent, and Young Adult Patients With Recurrent or Refractory Solid Tumors	USA; Pharmaceutical	120 (E)	30/11/2021 - 30/06/2025	Surufatinib & gemcitabine	Response rates, Adverse events, Progression Free Survival, Dose Limiting Toxicities, Time to response, duration of response	Relapsed, Refractory, All solid tumours, Children, Young adults, Includes lymphoma. Measurable disease.	2-21 years (inclusive)
NCT05071209[40]	Elimusertib for the Treatment of Relapsed or Refractory Solid Tumors	USA, Canada; Academic	23 (E)	03/12/2021 - 30/06/2024	Elimusertib	Response rates, Adverse events, Dose Limiting Toxicities, Pharmacokinetics	Relapsed, Refractory, All solid tumours, Children, Young adults, Excludes CNS tumours. Includes alveolar RMS with PAX3-FOXO1 fusion, as well as cohorts of Ewing Sarcomas and other solid tumours with specific mutations	1-30 years (inclusive)
NCT05135975[41]	A Study of Cabozantinib as a Maintenance Agent to Prevent Progression or Recurrence in High-Risk Pediatric Solid Tumors	USA; Academic & Pharmaceutical	100 (E)	18/10/2021 - 01/12/2029*	Cabozantinib	Response rates, Adverse events, Overall Survival, Progression Free Survival, Duration of response	Relapsed, Refractory, Includes three cohorts: neuroblastoma, CNS tumours and sarcomas/other solid tumours. For RMS patients, specific focus on: BR1 with irradiated positive margins, BR2+, alveolar subtype or fusion-positive subtype, and BR2+, embryonal subtype, Group 4 at original diagnosis. Exclude patients with prior cabozantinib treatment	18 months to 40 years
NCT05429502[42]	Study of Efficacy and Safety of Ribociclib (LEE011) in Combination With Topotecan and Temozolomide (TOTEM) in Pediatric Patients With Relapsed or Refractory Neuroblastoma and Other Solid Tumors	Germany, Singapore, Spain; Academic & Pharmaceutical	231 (E)	27/12/2022 - 28/01/2028	Ribociclib, topotecan & temozolomide (TOTEM)	Response rates, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, Pharmacokinetics, Duration of response, Time to response	Relapsed, Refractory, Children, Young adults, Includes Neuroblastoma, Medulloblastoma, High-Grade Glioma, Malignant Rhabdoid tumour or RMS. RMS patients only eligible for Phase I, part B	1-21 years (inclusive)
NCT04239092[54]	9-ING-41 in Pediatric Patients With Refractory Malignancies. **This trial has a conference abstract with interim results that has also been extracted[45]**	USA; Pharmaceutical	68 (E)	05/06/2020 - 01/12/2024*	9-ING-41 alone or combined with: 1) irinotecan, 2) irinotecan and temozolomide, 3) cyclophosphamide and topotecan	Response rates, Adverse events	Relapsed, Refractory, Children, Young adults, Measurable/evaluable disease. All malignancies	<22 years
NCT02637687[48] (expanded access study NCT03025360)	A Study to Test the Safety and Efficacy of the Drug Larotrectinib for the Treatment of Tumors With NTRK-fusion in Children (SCOUT)	UK, USA, France, Germany, Canada, Australia, China, Czechia, Denmark, Ireland, Israel, Italy, Japan, Republic of Korea, Netherlands, Poland,	155 (E)	16/12/2015 - 22/09/2026	Larotrectinib	Response rates, Adverse events, Overall Survival, Progression Free Survival, Pharmacokinetics, Pain scores, HRQoL, Duration of response,	Relapsed, Refractory, All solid tumours, Children, Young adults, Includes CNS tumours. Must have a NTRK gene fusion	<21 years

Clinical trial registry number(s)	Title of registered clinical trial	Planned locations; Sponsor	Number of participants	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
		Russian Federation, Spain, Sweden, Switzerland, Turkey, Ukraine; Pharmaceutical				Clinical benefit rate		
NCT04083976[53]	A Study of Erdafitinib in Participants With Advanced Solid Tumors and Fibroblast Growth Factor Receptor (FGFR) Gene Alterations (RAGNAR)	UK, USA, France, Germany, Argentina, Australia, Belgium, Brazil, China, Denmark, Italy, Japan, Republic of Korea, Poland, Spain, Sweden, Taiwan; Pharmaceutical	336 (E)	20/11/2019 - 04/12/2028	Erdafitinib	Response rates, Adverse events, Overall Survival, Progression Free Survival, Duration of response, Disease control rate, Clinical benefit rate, HRQoL, Pharmacokinetics	Relapsed, Refractory, All solid tumours, Fibroblast growth factor receptor (FGFR) mutation or FGFR gene fusion. Measurable disease. Includes newly diagnosed patients with no acceptable standard therapies	6 years and older
Recruitment status: Available expanded access								
CTRI/2022/04/042263[39]	131I-omburtamab for the Treatment of Central Nervous System/Leptomeningeal Neoplasms in Children and Young Adults	USA; Academic & Pharmaceutical	NR - expanded access	NR-NR	50 mCi 131I-omburtamab	NR	All ages, Histological- confirmed disease of an embryonal malignancy (including RMS) or non-embryonal tumours will histological confirmation of B7-H3 activity. Must have CNS/leptomeningeal disease, treated with conventional therapies or for which no conventional therapy exists.	All ages
Recruitment status: Completed								
UMIN000026497[50]	Phase I trial of nivolumab in pediatric patients with malignant solid tumors or Hodgkin lymphoma	Japan; Academic	26 (Target sample size)	03/04/2017 - NR	Nivolumab	Response rates, Adverse events, Overall Survival, Progression Free Survival, Pharmacokinetics	Relapsed, Refractory, All solid tumours, Children, Young adults. Received at least two prior chemotherapy regimens	1-24 years (inclusive)
NCT03860376[52]	Ex Vivo Drug Sensitivity Testing and Mutation Profiling	USA; Academic	25 (A)	21/02/2019 - 31/12/2022	Personalised medicine	Response rates, Disease free survival	Relapsed, Refractory, Children, Young adults, All cancers	≤21 years
Recruitment status: Withdrawn								
NCT05116800[33]	Phase 2 Study of 9-ING-41 With Chemotherapy in Sarcoma	USA; Academic & Pharmaceutical	0 (A)	01/03/2022 - 01/08/2025	Gemcitabine & Docetaxel	Response rates, Progression Free Survival	Relapsed, Refractory, Children, Young adults, Soft tissue sarcoma and select bone sarcomas (osteosarcoma and Ewing sarcoma). No more than three prior lines of systemic therapy. No prior treatment with 9-ING-41, gemcitabine or docetaxel.	≥10 years
Recruitment status: Unknown								
NCT04213612[51]	DCV in the Treatment of Recurrence and Refractory Childhood Solid Tumors	NR (but sponsor/contact in China); Academic	21 (E)	30/12/2019 - 30/11/2020	Pegylated liposomal doxorubicin, cyclophosphamide & vincristine	Response rates, Adverse events, Maximum Tolerated Dose	Relapsed, Refractory, All solid tumours, Includes progressive disease. Measurable disease.	1-18 years
NCT02793466[49]	Durvalumab in Pediatric and Adolescent Patients	USA; Academic	36 (E)	01/07/2016* - 01/12/2020*	Durvalumab	Response rates, Adverse events, Maximum Tolerated Dose, Dose Limiting Toxicities, Pharmacokinetics, Duration of response	Relapsed, Refractory, All solid tumours, Children, Young adults, Includes lymphoma and CNS tumours. Measurable/evaluable disease	1-17 years

* 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; CNS = central nervous system; E = estimated enrolment; EFS = event free survival; FGFR = fibroblast growth factor receptor; HRQoL = health-related quality of life; NR = not reported; RMS = rhabdomyosarcoma; RP2D = recommended phase two dose; STS = soft tissue sarcoma; TOTEM = topotecan & temozolomide; UK = United Kingdom; USA = United States of America; VIT = vincristine, irinotecan & temozolomide

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