Living REFoRMS update 6 (REFoRMS LSR-6) report

Updates to methods from LSR-5 (PROSPERO CRD42022380185)

Searches

For LSR-6, the same standard database searches and OpenAlex searches were conducted as per the LSR-5 report.[1] We applied a date limit of 2024 to current for the database searches. Database searches and OpenAlex searches were run on 28th April 2025.

Screening, data extraction and quality assessment

The eligibility criteria for the studies, data extraction and quality assessment processes were unchanged. Additional data were extracted for each study, reflecting increased interest in drug targets and tumour mutations.

Results of LSR-6

Study selection

From 2,062 records identified from the searches, 78 were eligible after title and abstract screening (see Figure 1).

Following full-text screening and tracking of previously included conference abstracts (CAs) and clinical trial records (CTRs), six full text papers reporting seven studies were included.[2-7] Of these, one paper was identified from tracking a previous CA,[3] two from tracking previous CTRs.[6,7] Two papers were originally identified in LSR-5 but further information was provided from the corresponding author for LSR-6.[4,5] Two of the full-texts identified in LSR-6 related to three previously extracted studies (two previous studies reported in one paper), meaning further data were now available.[2,6] These publications are classed as new full-text papers, but not new studies. Therefore, six new publications (of seven studies) including four new studies were included in the synthesis.

Two authors were contacted for further information to determine eligibility for inclusion in LSR-6. One author confirmed that no participants with rhabdomyosarcoma were included in the study and thus this was excluded. No response has been received from the other author at the point of writing this report. Any responses received following the publication of this report will be included in the next update (LSR-7).

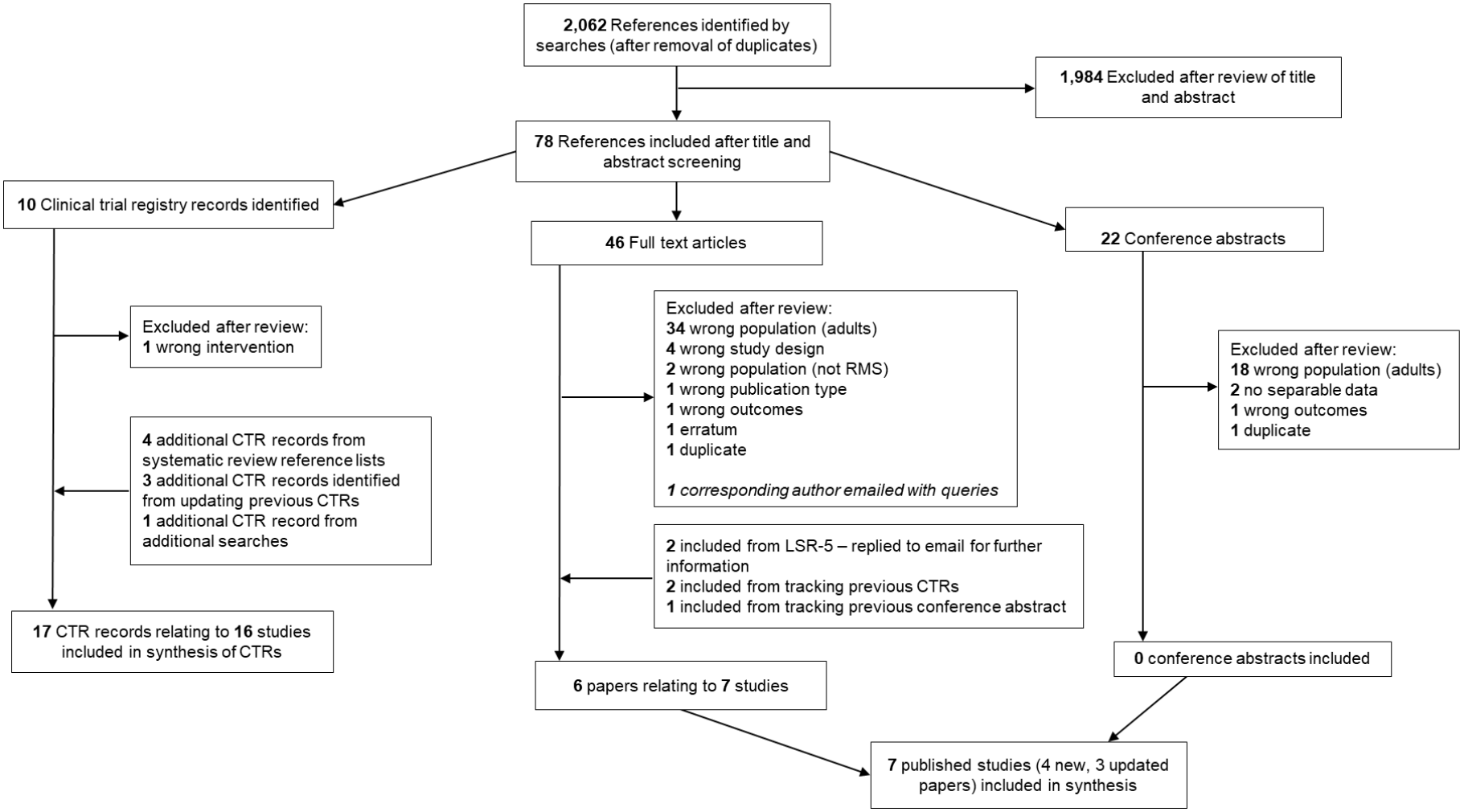

Figure 1. LSR-6 flowsheet

Updates of previously identified CTRs

One hundred and forty-five CTRs were checked for updates. Seven CTRs had newly identified CAs, three had posted data on the trial registry website, and seven CTRs had newly identified full-text publications. Of the newly identified outputs, only three provided data that was relevant to LSR-6 (all full-text publications reporting on four trials).[2,6,7]

Of the 65 CTRs identified to be currently open (i.e. recruiting) at the time of the last update, 53 continue to be reported as currently open. Three continue to be not yet recruiting. Since LSR-5, one CTR has opened recruitment, seven have finished recruitment (currently 'active not recruiting'), five are reported as completed, four terminated, three unknown, and one withdrawn. Of the 24 CTRs identified as completed but not yet reported at the time of the last update, five (20.8%) have new information available. Two do not have data separable for participants with rhabdomyosarcoma. Three have extractable data suitable in the LSR-6 synthesis.[2,6]

Newly identified CTRs

Seventeen new CTRs relating to 16 studies were included in LSR-6.[8-24] Nine were identified in the update search,[8-16] three from other CTRs,[17-19] four during citation searching of systematic reviews,[20-23] and one from additional searches[24].

Published studies

Demographics of included studies

Seven studies (reported across six full text manuscripts) contributed seven cohorts to LSR-6.[2-7] Of these, three studies had already been identified and thus LSR-6 provided updated data for these studies rather than entirely new studies.[2,6] Five studies were performed in the USA[2,4-7] (one also recruited in Canada[6]), one in China,[3] and the other across Europe[2].

Two studies evaluated novel single-agent therapies,[2,3] four studies evaluated novel multi-agent therapies,[2,4-6] and one study evaluated CAR-T cells[7].

Almost all studies identified by the update were published in 2025 (n=5, 71%).[2,3,6,7] Two studies were published in 2024 and had been identified in LSR-5 but could not be included until now due to a lack of information.[4,5]

Demographics of participants in included studies

At least 43 children and young people (CYP) with relapsed and refractory rhabdomyosarcoma were included in the studies. Four cohorts included fewer than five CYP with relapsed/refractory rhabdomyosarcoma.[3-5,7] Three studies recruited CYP with sarcomas only,[2,3] whilst the remainder recruited a variety of tumour types[4-7]. Two studies included infants younger than one years old.[2,4]

All of the studies reported the sex (n=2)[3,6] or gender (n=5)[2,4,5,7] of included CYP (four for CYP with rhabdomyosarcoma specifically[2,6,7]). Sex or gender was reported as a binary characteristic in all studies. Where reported for CYP with rhabdomyosarcoma specifically, the male to female ratio was 23:15 (60% male).

Only three studies (37 CYP) reported both the ethnicity and race of the CYP with rhabdomyosarcoma.[2,6] In these studies, 26 participants were white (70%), three black or African American (8%), and eight not reported (22%). Five of these 37 CYP were Hispanic or Latino (14%), 32 non-Hispanic/non-Latino (86%). Two studies provided race and ethnicity data for the whole population or relevant subgroup of the whole population,[4,5] while two provided no race/ethnicity data[3,7].

Histopathology of the rhabdomyosarcoma was infrequently reported (14% of CYP). Where given, four CYP had embryonal disease,[3,6,7] and two had alveolar[3,5]. One study reported the molecular characteristics of some of the CYP with RMS.[6] In this study, one evaluable CYP with rhabdomyosarcoma was reported to have a PAX:FOXO1 fusion positive tumour, and one was reported to have a PAX:FOXO1 fusion negative tumour (from a total of 20 CYP with rhabdomyosarcoma).[6]

Quality assessment of included studies

Studies reported adequate information in relation to most MINORS tool assessment criteria[25], with two studies[3,4] providing adequate information on all domains (see Table 1). All studies provided a clearly stated aim, prospectively collected data, used appropriate study endpoints (outcomes measures), and used an appropriate follow-up period (frequently to death of the participant). In contrast, many studies did not use unbiased assessments of study outcomes as response rates were not independently evaluated, or did not report who assessed response.

Outcomes of included studies

Outcome data were available for at least 37 CYP with relapsed/refractory rhabdomyosarcoma.

Survival

Three cohorts (involving 16 CYP with rhabdomyosarcoma) reported Progression Free Survival (PFS).[2,7] Median PFS ranged from 1.7 to 4 months.

Two cohorts reported Overall Survival (OS).[2,7] Both cohorts reported median OS - one cohort reported 5.1 months for six patients[2], and 4.4 months for one patient in the other cohort[7].

Response rate

Most cohorts (n=4, 57%) showed no objective responses.[2-5] In three cohorts, responses were seen.[2,6,7] One reported an ORR of 100% but this was a partial response in a single patient lasting only a few months, so should be interpreted with caution.[7] The remaining two cohorts reported partial responses in approximately 10% of the cohorts.[2,6]

Disease control rate (which considers stable disease as well as complete and partial response, DCR) was reported across six (86%) of the cohorts.[2,3,5-7] This was mainly in the 40-60% range, when looking at the larger cohorts. Two cohorts reported duration of response, which was on average only 2-3 months.[2,6]

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

Quality of Life

No new study reported quality of life data.

Adverse Events (AEs)

All seven studies contributed new AE data.[2-7] Within the studies that reported Grade 3/4 AEs, 209 participants (including at least 43 with rhabdomyosarcoma) were evaluable for toxicities. Most AEs were haematological. Additional specific AEs varied by study treatment (see Table 4). Two studies explicitly reported deaths during follow-up, but none were felt to be treatment related.[2]

New CTRs

Seventeen new CTR records of 16 new CTR studies were identified.[8-24] Reported start dates ranged between 2010 and 2025. Twelve studies were reported as having an academic sponsor,[10,13,14,16-24] three studies with a pharmaceutical company as sponsor[8,9,11,12] and one study with personal sponsorship[15]. We identified nine currently open studies,[8-12,14,17-19,24] three studies pending recruitment,[13,15,16] three studies had closed recruitment,[20-22] and one completed with no identified published results[23].

Four studies included all solid tumours in their eligibility criteria,[11,21-23] two studies included limited sarcoma subgroups,[14,16] two studies restricted to sarcoma only,[12,20] and three studies restricted to rhabdomyosarcoma only[10,13,15]. A further five studies included a wider range of malignancies (including solid, central nervous system and haematological cancers).[8,9,17-19,24] Eligible ages varied: upper age limits ranged from 18 to 49 years, with 18 and 21 years being the most common cut-offs. Five studies had no upper age limit,[15,17-20] including two studies recruiting patients of any age[17,18]. Fourteen studies were open to recruiting infants (5 included <1 year old) and/or young children[8-11,13-18,20-24], while two studies were restricted to patients ≥12 years[12,19].

Fifteen studies were single-arm and evaluated a range of therapies including: two novel single agent therapy studies,[17,18] five novel multi-agent therapy studies,[8-12,19] six cellular therapy studies,[13,16,20-23] one immunotherapy study[14] and one vaccine study[15]. Nine of these studies restricted their eligibility criteria to CYP with specific genetic mutations/alterations (see Table 5 for details).[14,16-23] One study was a multi-arm molecular registry study.[24]

Fifteen studies provided a single recruitment country including: USA (six studies),[11-13,20,21,23] UK (five studies),[16-19,24] China[10], Italy[22] and Russian Federation[14] (one study for each country). One study provided multiple recruitment countries,[8,9] whilst another study did not provide recruitment location information[15].

Summary of new studies

The REFoRMS LSR-6 update identified data from seven cohorts reported across six published papers of at least 43 CYP with relapsed and refractory rhabdomyosarcoma. Three cohorts provided updated data relating to previously identified studies. Therefore **overall**, the REFoRMS systematic review has identified **179** published early phase studies of interventions to date, including **over >1350** CYP with relapsed/refractory rhabdomyosarcoma.

Survival outcomes were provided by three of the seven studies, whilst all studies provided response rates. Four cohorts were small (≤5 CYP with rhabdomyosarcoma) and thus, caution should be taken when interpreting the effectiveness of these interventions as generalisability to other CYP with rhabdomyosarcoma is likely to be limited.

Overall, 62 clinical trials are reported to be open for recruitment. The number of newly identified clinical trials evaluating targeted therapies in individuals with particular genetic alterations is still increasing (from 50% to 56% since the last update). Many of the newly identified CTRs in this update related to cellular therapies - identified through reference checking of an identified systematic review.

Tables

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

Author, Year	MINORS assessment criteria						
	Clearly stated aim	**Prospective collection of data**	**Appropriate endpoints**	**Unbiased assessment of endpoint**	**Appropriate follow-up**	**Loss to follow-up <5%**	**Prospective sample size calculation**
Casanova, 2025[2]	Reported and adequate	Reported and adequate	Reported and adequate	Reported but inadequate	Reported and adequate	Reported and adequate	Reported but inadequate
Lu, 2025[3]	Reported and adequate	Reported and adequate	Reported and adequate	Reported and adequate	Reported and adequate	Reported and adequate	Reported and adequate
Foster, 2024[4]	Reported and adequate	Reported and adequate	Reported and adequate	Reported and adequate	Reported and adequate	Reported and adequate	Reported and adequate
Cramer, 2024[5]	Reported and adequate	Reported and adequate	Reported and adequate	Reported but inadequate	Reported and adequate	Reported but inadequate	Reported and adequate
Dela Cruz, 2025[6]	Reported and adequate	Reported and adequate	Reported and adequate	Reported but inadequate	Reported and adequate	Reported and adequate	Reported and adequate
Steffin, 2025[7]	Reported and adequate	Reported and adequate	Reported and adequate	Reported but inadequate	Reported and adequate	Reported but inadequate	Reported and adequate

Table 2. Demographic characteristics of new studies

Author, Year	Countries performed	Study design		Patient enrolment dates	Inclusion/exclusion criteria			Intervention(s)	No. of R+R RMS patients (total)	Median age (range)	Median prior lines of therapy (range)	Comments
		Phase	Single / multi centre		Disease	Age	Other					
Novel agent - single agents												
Casanova *, 2025[2]	USA	Phase 2	Multi	17 April 2018 to 22 February 2021	Relapsed, refractory. RMS, NRSTS and EWS only. Measurable disease	≥12 months to <18 years		Eribulin *1.4mg/m^2 IV on days 1 & 8 of 21-day cycle*	8 (21)	RMS: 9.5 (4-17) years	RMS: 2 (1 to ≥4)	Data relates to NCT03441360 trial
Lu, 2025[3]	China	Phase 1	Single	29 December 2020 to 7 September 2022	Relapsed, refractory, all sarcomas. Measurable disease. Includes high risk disease in frontline	5-18 years	Excluded patients with symptomatic brain metastases, prior reactions to TKIs	Anlotinib *8,10 or 12mg od, po on days 1-14 of each 21-day cycle*	3 (21)	SG: 12.5 (5-18) years	SG: 3 (1-6)	At least 1 alveolar RMS and 1 embryonal RMS. Additional maintenance group including 5 RMS patients, not included in synthesis as unable to identify if relapsed/refractory
Novel agent - multiple agents												
Casanova *, 2025[2]	France, Germany, Italy, Poland, Spain, UK (Switzerland and Greece reported on CTR)	Phase 2	Multi	5 November 2019 to 9 July 2021	Relapsed, refractory. RMS, NRSTS and EWS only. Measurable disease	>6 months to ≤25 years	Excluded if prior progression on irinotecan	Eribulin *1.4mg/m^2 IV on days 1 & 8* Irinotecan *40mg/m^2, IV on day 15 of 21-day cycle*	9 (27)	RMS: 11.6 (4-17) years	RMS: 3 (1 to ≥4)	Data relates to NCT03245450 trial 6 of the RMS cohort previously received irinotecan
Foster, 2024[4]	USA	Phase 1	Mutli	November 2017 to December 2020	Relapsed, refractory, all solid tumours + brain	>6 months to ≤21 years		Pevonedistat *15-35mg/m^2, IV on days 1,8,10,12 of 28-day cycle (days*	1-4 (30)	WP: 13 (1-21) years	WP: 2 (1-13)	

Author, Year	Countries performed	Study design		Patient enrolment dates	Inclusion/exclusion criteria			Intervention(s)	No. of R+R RMS patients (total)	Median age (range)	Median prior lines of therapy (range)	Comments
		Phase	Single / multi centre		Disease	Age	Other					
					tumours. Measurable/ evaluable disease			*1, 3 & 5 for cycles 2+)* Irinotecan *50mg/m^2, IV, days 8-12 (days 1-5 for cycles 2+)* Temozolomide *100mg/m^2, po, days 8-12 (days 1-5 for cycles 2+)*				
Cramer, 2024[5]	USA	Phase 1	Multi	July 2017 to June 2021	Relapsed, refractory, all solid tumours + brain tumours	≥12 months to ≤21 years	Excluded bone marrow metastases, and those who have progressed or experienced severe toxicity on prior irinotecan & temozolomide combined (or combined with another mTOR inhibitor)	Nab-sirolimus *15-35mg/m^2, IV on days 1 & 8 of 28-day cycle* Irinotecan *90mg/m^2, po, days 1-5 (cycle 2 onwards)* Temozolomide *125mg/m^2, po, days 1-5 (cycle 2 onwards)* *Max 35 cycles*	1 (21)	SG: 12 (2-20) years	SG: 2 (1-6)	Patient had alveolar RMS
Dela Cruz, 2025[6]	Canada, USA	Phase 1/2	Multi	16 November 2017 to 30 September 2022	Relapsed, refractory, all solid tumours + brain tumours. Measurable/ evaluable disease	Phase 1: ≥2 years to ≤18 years. Phase 2: ≥2 years to ≤21 years	Phase 2 limited to RMS, EWS, HGG, and excluded patients with ≥3 prior VEGF/VEGFR-targeted therapies (including combined with mTOR inhibitors). Excluded hepatoblastoma, lymphomas and untreated CNS	Lenvatinib *8 or 11mg/m^2, od, po* Everolimus *3mg/m^2, od, po. 28-day cycles, max 7 cycles*	20 (64)	RMS: 15 (2-21)	RMS: 2.5 (1 to ≥3)	At least 2 patients with embryonal RMS, 1 *PAX-FOXO1* positive, 1 *PAX-FOXO1* negative. 3 first relapse, 7 second relapse, 10 ≥3 relapses. Some information supplemented by NCT03245151 trial. Data relates to phase 2 of trial.

Author, Year	Countries performed	Study design		Patient enrolment dates	Inclusion/exclusion criteria			Intervention(s)	No. of R+R RMS patients (total)	Median age (range)	Median prior lines of therapy (range)	Comments
		Phase	Single / multi centre		Disease	Age	Other					
							metastases. Minimum BSA 0.6m^2					
Cellular therapies												
Steffin, 2025[7]	USA	Phase 1	Single	NR	Relapsed, refractory, all solid tumours	1-18 years	At least one prior salvage treatment. Have to have GPC3-positive solid tumours	15.GPC3 CAR T cells *1-3 x10^7, IV after lymphodepletion with cyclophosphamide + fludarabine*	1 (12)	RMS: 11 years	At least 2	1 patient with metastatic embryonal RMS

* Casanova 2025 reports two independent trials in one published paper

BSA = body surface area; CAR-T = chimeric antigen receptor-T cells; CNS = central nervous system; CTR = clinical trial record; EWS = Ewing's sarcoma; HGG = high grade glioma; IV = intravenous; mTOR = mammalian target of rapamycin; NR = not reported; NRSTS = non-rhabdomyosarcoma soft tissue sarcoma; od = once daily; po = orally; RMS = rhabdomyosarcoma; R+R = relapsed and refractory; SG = subgroup; TKI = tyrosine kinase inhibitor; UK = United Kingdom; USA = United States of America; VEGF/VEGFR = vascular endothelial growth factor (VEGF) and its receptors; WP = whole population

Table 3. Outcome data for new studies

Regimen	Author, Year	Total no. of relevant CYP$	Responses (number of CYP)				Response rate		Median survival (range)		Comments
			CR	PR	SD	PD	ORR % (95% CI)	DCR % (95% CI)	PFS/TTP	OS	
Novel agent - single agents											
Eribulin	Casanova *, 2025[2]	6 R+R RMS	0	0	3	3	0% (0-36.9)	50%	1.7 (95% CI 1.1-2.9) months	5.1 (95% CI 1.7-6.5) months	
Anlotinib	Lu, 2025[3]	3 R+R RMS	0	0	2	1	0%	67%	NR	NR	
Novel agent - multiple agents											
Eribulin, Irinotecan	Casanova *, 2025[2]	9 R+R RMS	0	1	4	4	11.10% (90% CI 0.6-42.9)	55.6%	2.7 (95% CI 1.3-8.9) months	NR	DOR for RMS patients - 2.9 months. Of the 6 who had previously had irinotecan, 1 PR, 3 SD, 2 PD.
Pevonedistat, Irinotecan, Temozolomide	Foster, 2024[4]	1-4 R+R RMS	0	0			0%	NR	NR	NR	Information provided via email communications with author: 'No patients with RMS had a disease response following therapy'
Nab-sirolimus, Irinotecan, Temozolomide	Cramer, 2024[5]	1 R+R RMS	0	0	0	1	0%	0%	NR	NR	
Lenvatinib, Everolimus	Dela Cruz, 2025[6]	16 R+R RMS	0	2	6	8	10% (1.2-31.7%)	40% (19.1 - 63.9%)	NR	NR	4 not assessable. ORR/DCR as reported by study which includes 4 non-evaluable patients. DOR - median 2.4 months, range 2.1-2.76. Additional 2 RMS patients in phase 1 with no objective response
Cellular therapies											
15.GPC3 CAR-T cells	Steffin, 2025[7]	1 R+R RMS	0	1	0	0	100%	100%	4 months	4.4 months	

$ = evaluable CYP with RMS. * Casanova 2025 reports two independent trials in one published paper

CAR-T = chimeric antigen receptor-T cells; CI = confidence interval; CR = complete response; CYP = children and young people; DCR = disease control rate; DOR = duration of response; NR = not reported; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; R+R = relapsed and refractory; RMS = rhabdomyosarcoma; SD = stable disease; TTP = time to progression

Table 4. Adverse Event data

Intervention	Author, Year	Number evaluable for toxicity (RMS)	Total number AEs			AE details provided by manuscript
			DLT	G3	G4	
Novel agent - single agents						
Eribulin	Casanova*, 2025[2]	21 (8)				21P with ≥TEAE - 20P experienced any grade treatment-related TEAE (7 RMS). 13P with ≥G3 TR-TEAE (3 RMS). G5 TEAEs: 2 malignant neoplasm progression (1 RMS), 1 respiratory failure - none were treatment-related. ≥G3 TEAEs: 9 **neutrophil count decrease** (2 RMS), 6 anaemia (4 RMS), 8 white blood cell count decrease (1 RMS), 2 aspartate aminotransferase increase (2 RMS), 3 lymphocyte count decrease (1 RMS), 3 alanine aminotransferase increase (2 RMS), 1 pyrexia (RMS), 1 decreased appetite, 2 pain in extremity (1 RMS), 1 hypokalemia (RMS), 1 hypophosphatemia (RMS), 1 hypotension (RMS) *Some discrepancies to the data on CTR*
Anlotinib	Lu, 2025[3]	34 (8, only 3 R+R)	2P	10E	0	DLTs: 1P with G3 hematuria (DL 8mg, <35kg), 1P with G3 hand-foot syndrome (DL 8mg, <35kg) G3 AEs: 2P **neutropenia**, 1P abdominal pain, 2P hand-foot syndrome, 1P hematuria, 1P hypertension, 1P appendicitis, 1P intestinal obstruction, 1P total bilirubin elevation
Novel agent - multiple agents						
Eribulin, Irinotecan	Casanova*, 2025[2]	27 (9)				27P with ≥1 TEAE - 26P experienced any grade treatment-related TEAE (8 RMS). 24P with ≥G3 TR-TEAE (8 RMS). G5 TEAEs: 1 abdominal pain (RMS), 3 malignant neoplasm progression (1 RMS), 1 malignant pleural effusion (RMS) - none were treatment-related. ≥G3 TEAEs: 3 **diarrhoe**a, 14 **neutrophil count decrease** (6 RMS), 4 anaemia (1 RMS), 1 **nausea**, 9 **neutropenia** (3 RMS), 1 fatigue (RMS) *Some discrepancies to the data on CTR*
Pevonedistat, Irinotecan, Temozolomide	Foster, 2024[4]	30 (1-4)	2			DLTs: **platelet count decrease** and ≥G3 flu-like symptoms (both in cycle 1 at 35mg/m^2 dose). Cycle 1 ≥G3 AEs: lymphocyte count decrease (17%), white blood cell decrease (13%), **neutrophil count decrease** (7%). RP2D was determined to be 35mg/m^2 G3+ AEs across all cycles, all dose levels: 8P white blood cell decreased, 2 anaemia, 4 ALA increase, 1 **diarrhoea**, 1 AST increase, 10 lymphocyte count decrease, 6 **neutrophil count decrease**, 2 **platelet count decrease**, 1 **vomiting**, 1 hypokalaemia, 1 flu-like symptoms

Intervention	Author, Year	Number evaluable for toxicity (RMS)	Total number AEs			AE details provided by manuscript
			DLT	G3	G4	
Nab-sirolimus, Irinotecan, Temozolomide	Cramer, 2024[5]	21 (1)	6	41		Cycle 1 DLTs: 4 **thrombocytopenia** (1 at DL1, 2 at DL1-1, 1 at DL-2), 1 **mucositis** (DL-2 PK cohort). Cycle 2 DLTs: 1 t**hrombocytopenia** (DL1). MTD for Nab-sirolimus was 15mg/m^2/dose. ≥G3 non-DLTs: 5 white blood cell decrease (2 at DL1, 1 at DL-1, 2 at DL-2), 5 anemia (2 at DL1, 3 at DL-1), 7 lymphocyte count decrease (1 at DL1, 6 at DL-2), 3 **platelet count decrease** (1 at DL-1, 2 at DL-2), 10 **neutrophil count decrease** (3 at DL1, 1 at DL-1, 6 at DL-2), 3 Alanine aminotransferase increased (2 at DL1, 1 at DL-2), 1 hypokalemia (DL-1), 2 hypophosphataemia (DL1), 1 aspartate aminotransferase increased (DL1), 1 hyperphosphataemia (DL-2), 1 fever (DL-2), 1 gum infection (DL1), 1 skin infection (DL-2)
Lenvatinib, Everolimus	Dela Cruz, 2025[6]	64 (20) in phase 2	3E in 2P			DLTs: 1P with G3 proteinuria. 1P with G3 hypertriglyceridemia and G4 hypercholesterolemia. Phase 1 treatment-related TEAEs: 13P with at least 1 ≥G3 TR-TEAE. All reported in DL1: 1P hypertension, 3P hypertriglyceridemia, 1P **diarrhoea**, 3P proteinuria, 1P blood cholesterol increase, 1P lymphocyte count decrease, 2P headache, 2P **platelet count decrease**, 1P ALT increase, 1P anemia Phase 2 treatment-related TEAEs: 24P with at least 1 ≥G3 TR-TEAE. 1P hypertension (RMS), 7P hypertriglyceridemia (2 RMS), 1P abdominal pain (RMS), 3P **diarrhoea**, 3P proteinuria (2 RMS), 3P stomatitis (all RMS), 1P blood cholesterol increased, 2P decreased appetite (both RMS), 7P lymphocyte count decrease (3 RMS), 1P **nausea** (RMS), 1P **neutrophil count decrease**, 2P **platelet count decrease** (1 RMS), 1P WBC count decrease, 1P ALT increased (RMS), 3P anemia (1 RMS). 3P discontinued treatment due to TR-TEAEs (1 RMS)
Cellular therapies						
15.GPC3 CAR-T cells	Steffin, 2025[7]	12 (1)				Cytokine release syndrome more common in 15.GPC3 CAR-T than in GPC3 CAR-T (Relative Risk 3.3). The inducible caspase 9 (iC9) safety switch was deployed in three patients treated with 15.CAR T cells, all of whom responded well. AE data for combined cohort of adults and children provided in supplementary data of paper

AEs written in **bold** text represent the AEs most important to the parent group. * Casanova 2025 reports two independent trials in one published paper

AE(s) = adverse event(s); ALA = alpha-lipoic acid; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAR-T = chimeric antigen receptor-T cells; CTR = clinical trial record; DL = dose level; DLT = dose limiting toxicity; E = event(s); G = grade; MTD = maximum tolerated dose; P = patient(s); PK = pharmacokinetics; RP2D = recommended phase 2 dose; R+R = relapsed + refractory; RMS = rhabdomyosarcoma; TEAE(s) = treatment-emergent adverse event(s); WBC = white blood cells

Table 5. New clinical trial registry records

Clinical trial registry number	Planned locations; Sponsor	N	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
Recruitment status: Not yet recruiting							
NCT06865664	USA; Academic	50 (E)	29/05/25 - 01/04/29	**FGFR4-CAR T cells** (after lymphodepletion with fludarabine (30mg/m^2/day IV), cyclophosphamide (500mg/m^2/day IV) and cetuximab (250mg/m^2 IV weekly for 4 weeks))	Response rates, Adverse events, Progression Free Survival, Maximum Tolerated Dose, Dose Limiting Toxicities, Feasibility	Relapsed, Refractory, RMS only, ≥ 2 prior treatment regimens. Must be ≥15kg. No active CNS disease	3-39 years
NCT06932861	NR; Personal	5 (E)	01/05/25 - 01/05/28	**Personalised mRNA vaccines**	Adverse events	Refractory, RMS only	≥6 years
ISRCTN75533638	UK; Academic	12 (E)	03/10/24 - 31/12/33	Autologous **hBRCA84D CAR T cells** (IV)	Response rates, Adverse events, Overall Survival, Progression Free Survival, Feasibility, Time to progression	Relapsed, Refractory, RMS, Ewing's sarcoma, desmoplastic small round cell tumour. Measurable disease. Must have *expression of B7-H3*. Excluded if active CNS disease or prior gene/cell therapy products	1-24 years
Recruitment status: Recruiting							
NCT06521567 2024-511350-41-00	USA, Czechia, Denmark, Italy, Spain, Germany, France, Brazil; Pharmaceutical	95 (E)	06/03/25 - 02/01/32	**Cobolimab** + **Dostarlimab** (dose NR)	Response rates, Adverse events, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, PKs, Duration of response, RP2D	Relapsed, Refractory, RMS, melanoma, Hodgkin's lymphoma, glioma, osteosarcoma, hepatic tumours. Measurable disease. Excluded if uncontrolled CNS disease	≤21 years
NCT06816771	China; Academic	38 (E)	01/02/25* - 31/12/26	**Pazopanib** (po, od) with alternating **TGI/CIV** (nab-Paclitaxel + Gemcitabine + Ifosfamide/ cyclophosphamide + Irinotecan + Vinorelbine) (doses NR)	Response rates, Adverse events, Disease control rate	Relapsed, Refractory, RMS only, Measurable disease. Excluded if received anti-angiogenic drugs in last 3 months, CNS metastases, thrombosis within 3 months, or significant bleeding risk	2-18 years
NCT06721689	USA; Pharmaceutical	59 (E)	23/03/25 - 01/04/31*	**PEEL-224** +/- **vincristine** + **temozolomide** (doses NR)	Response rates, Adverse events, Progression Free Survival, Dose Limiting Toxicities, PKs	Relapsed, Refractory, All solid tumours, evaluable/measurable disease. Excluded if prior PEEL-224, CNS metastatic disease or prior allogeneic HSCT	1-18 years (RMS cohort)

Clinical trial registry number	Planned locations; Sponsor	N	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
NCT06709495	USA; Pharmaceutical	63 (E)	27/01/25 - 01/09/29	**PEEL-224** (200mg IV), **temozolomide** (5-250mg po) + **vincristine** (IV) (+ GCSF)	Response rates, Adverse events, Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Dose Limiting Toxicities, PKs, Duration of response, Median Duration of Stable Disease	Relapsed, Refractory, Sarcomas only. Evaluable or measurable disease. Must be ≥40kg. Excluded if prior PEEL-224 or allogeneic HSCT	12-49 years
NCT06669013	Russian Federation; Academic	40 (E)	20/05/21 - 01/09/25*	**Dinutuximab beta** + second line chemotherapy (combination of 2 of: carboplatin/ ifosfamide/ etoposide) (doses NR)	Response rates, Adverse events, Overall Survival, Progression Free Survival, Duration of response, Disease control rate	Relapsed, Refractory, RMS, Osteosarcoma, Ewing's sarcoma. Must have oligometastatic disease (1-5 metastases). Must have *GD2-positive* tumours	<18 years
NCT05770037	UK; Academic	30 (E)	18/12/23 - 01/10/29*	**Alectinib** 600mg po bd	Response rates, Adverse events, Overall Survival, Progression Free Survival, Duration of response, Durable clinical benefit, Best percentage change in sum of target lesion diameters, Time to treatment discontinuation, Growth modulation index (PFS2:PFS1 ratio), QoL	Relapsed, Refractory, Solid tumours + CNS + haematological, Must fulfil Determine master protocol, Must undergo fresh tissue biopsy. Must weigh ≥40kg and be able to swallow capsules. Must have *ALK-positive tumours*	All ages
NCT05770102	UK; Academic	30 (E)	25/10/23 - 01/10/29*	**Atezolizumab** 15 mg/kg (max 1200mg) IV every 21 days	Response rates, Adverse events, Overall Survival, Progression Free Survival, Duration of response, Durable clinical benefit, Best percentage change in sum of target lesion diameters, Time to treatment discontinuation, Growth modulation index, QoL	Relapsed, Refractory, Solid tumours + CNS + haematological, Must fulfil Determine master protocol, Must undergo fresh tissue biopsy. Must have *high TMB (≥10 mut/Mb), MSI-high or proven (previously diagnosed) CMMRD disposition.* Excluded if progressing/symptomatic CNS disease, or prior allogeneic HSCT	All ages
NCT05786716	UK; Academic	30 (E)	07/03/23 - 01/10/29*	**Trastuzumab** 8mg/kg loading then 6mg/kg IV every 21 days, and **pertuzumab** 14mg/kg (max 840mg) loading then 7mg/kg (max 420mg) IV every 21 days	Response rates, Adverse events, Overall Survival, Progression Free Survival, Duration of response, Durable clinical benefit, Best percentage change in sum of target lesion diameters, Time to treatment discontinuation, Growth	Relapsed, Refractory, Solid tumours + CNS + haematological, Must fulfil Determine master protocol, Must undergo a fresh tissue biopsy. Must have *HER2 amplification or activating mutations.* Excluded if requiring supplemental oxygen	≥12 years

Clinical trial registry number	Planned locations; Sponsor	N	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
					modulation index, QoL		
ISRCTN14503847	UK; Academic	400 (E)	23/03/23 - 01/10/32	**Molecular registry study** - multiple drugs dependent on mutations identified	Proportion of genetic events, Proportion of patients in whom treatment is altered, Proportion of patients who develop actional or novel treatment resistance, ctDNA levels, Feasibility.	Relapsed, Refractory, Solid tumours + CNS + haematological. Must have tissue from within 8 weeks of study entry	≤21 years
Recruitment status: Active, not recruiting							
NCT00902044	USA; Academic	36 (E)	11/02/10 - 01/07/32*	Autologous **HER2-specific T cells** (conditioned with fludarabine +/- cyclophosphamide)	Response rates, Adverse events, Dose Limiting Toxicities, in vivo expansion and persistence of infused T cells	Relapsed, Refractory, Sarcomas. Must have *HER2-positive* tumours	"Child, Adult, Older Adult"
NCT02932956	USA; Academic	10 (A)	17/12/18 - 01/02/37*	**GPC3-Car** (GAP T cells) (lymphodepletion with fludarabine + cyclophosphamide) (doses NR)	Response rates, Adverse events, Dose Limiting Toxicities, Median T cell persistence	Relapsed, Refractory, All solid tumours. Must have *GPC3-positive* tumours	1-21 years
NCT03373097	Italy; Academic	42 (E)	05/01/18 - 01/12/27*	**GD2-CART01** (with lymphodepletion)	Response rates, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, PKs	Relapsed, Refractory, All solid tumours, RMS only eligible for phase 2. Must have *GD2-positive* tumours. Excluded if untreated CNS disease	1-18 years
Recruitment status: Completed							
NCT02107963	USA; Academic	15 (A)	28/02/14 - 31/01/17	**Anti-GD2-CAR** engineered T cells (lymphodepletion with cyclophosphamide) (doses NR)	Response rates, Adverse events, PKs, feasibility	Relapsed, Refractory, All solid tumours, Weight ≥15kg. Must have *GD2-positive* tumours. Excluded if untreated CNS disease, or prior GD2-CAR T cells	1-35 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; bd = twice daily; CAR-T = chimeric antigen receptor-T cells; CMMRD = Constitutional Mismatch Repair Deficiency; CNS = central nervous system; ctDNA = circulating tumour DNA; E = estimated enrolment; G-CSF = Granulocyte Colony-Stimulating Factor; HSCT = haematopoietic stem cell transplant; IV = intravenous; MSI = microinstability; N = number of participants; NR = not reported; od = once daily; PFS = progression free survival; PKs = pharmacokinetics; po = orally; QoL = quality of life; RMS = rhabdomyosarcoma; RP2D = recommended phase 2 dose; TMB = tumour mutational burden; UK = United Kingdom; USA = United States of America

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