Living REFoRMS update 4 (REFoRMS LSR-4) report

Updates to methods from LSR-3 (PROSPERO CRD42022380185)[1]

Searches

The approach to searching for update 4 has not changed since LSR-3. We applied limits of 2023 to current for these searches. Database searches were run on 3rd May 2024 and OpenAlex searches on 8th May 2024.

Screening

The eligibility criteria for the studies were the same as those set out in the original review, as listed on PROSPERO.[1] Study selection was conducted using EPPI reviewer software. Screening was performed in line with LSR-3 methods.

Data extraction and quality assessment

Data extraction was performed in line with baseline review methods.

Following the completion of LSR-3, it was decided that future updates would only use the MINORS tool[2] for quality assessment. As previously explained[3], one question in the MINORS tool (regarding the consecutive recruitment of patients) was not deemed appropriate to the assessment of quality in early phase trials in childhood cancer, and therefore was not included in this update.

Results of LSR-4

Study selection

From 4,053 records identified from the searches, 104 were eligible after title and abstract screening. A detailed flowsheet of the LSR-4 process can be found in Figure 1. A simplified flowsheet of studies included in the REFoRMS project (baseline review and all updates) can be found in Figure 2.

Following full-text screening, four full text papers[4-7] and one conference abstract (CA)[8] (identified from tracking previous CAs) were included.

Six authors were contacted for further information to determine eligibility for inclusion in this review. We have not received any replies at the time of preparing this report. Any responses received following the publication of this report will be included in the next update (LSR-5).

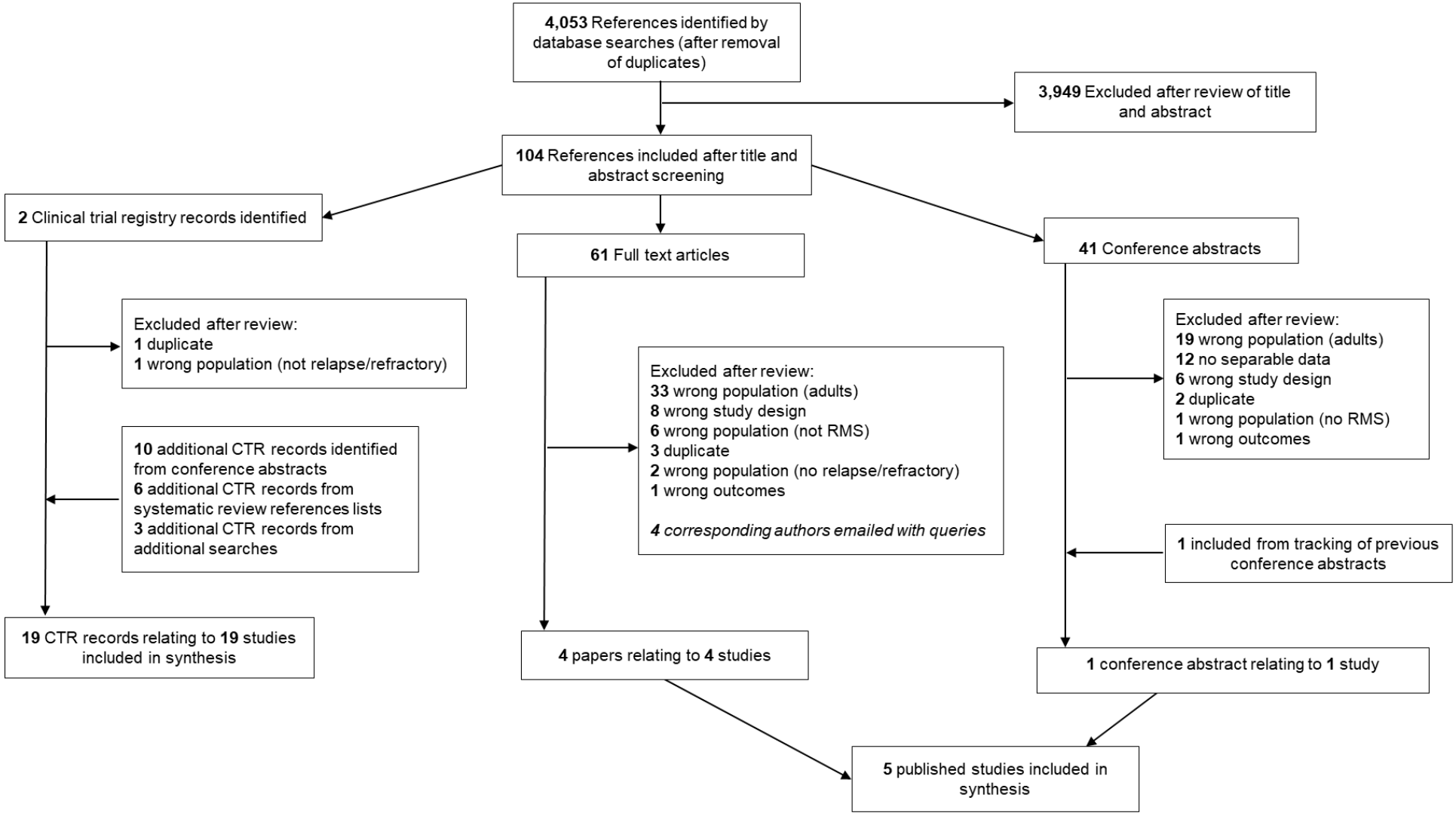

Figure 1. LSR-4 flowsheet

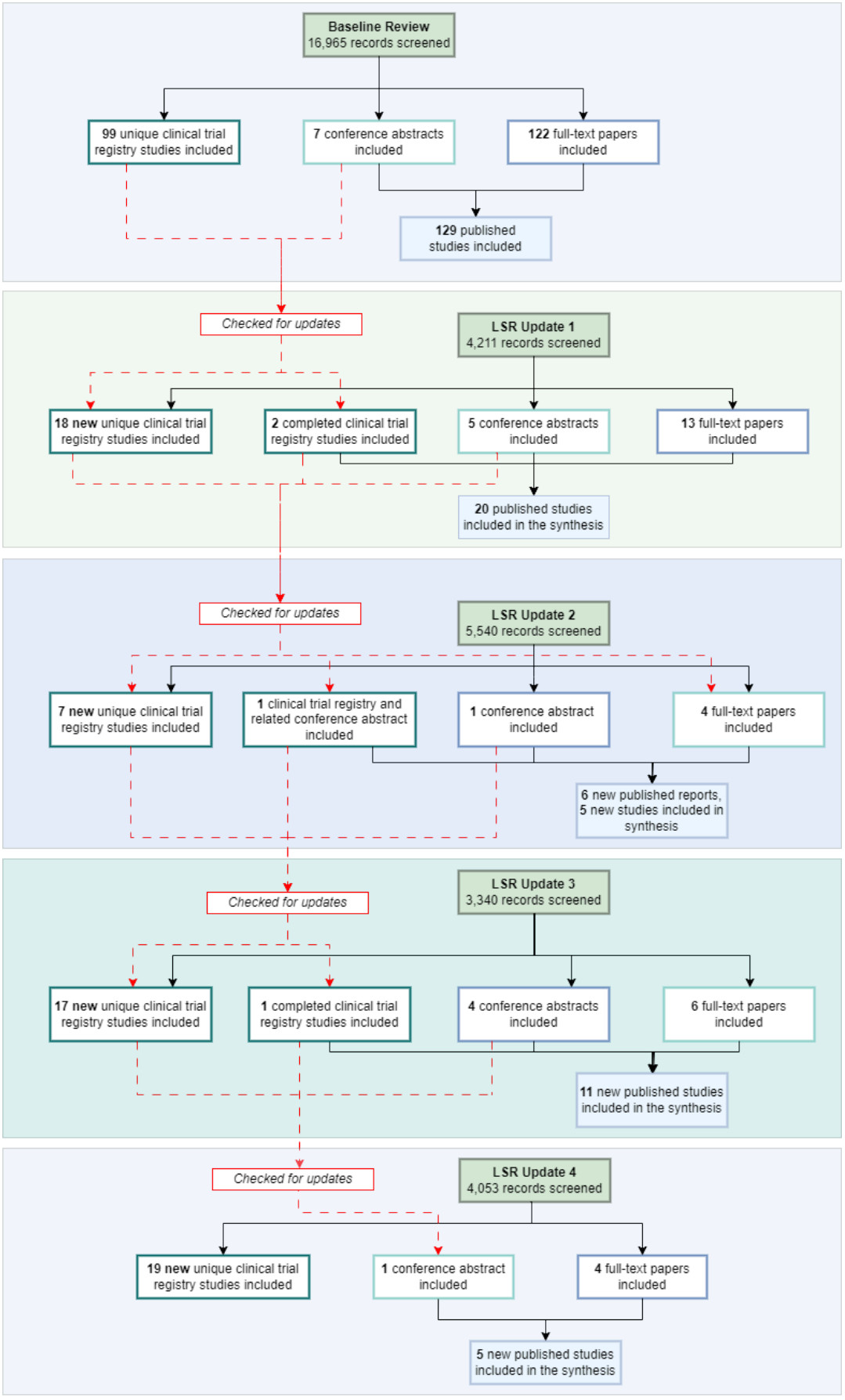

Figure 2. Flowsheet of included studies in REFoRMS

Updates of previously identified CTRs

One hundred and eighteen clinical trial registry records (CTRs) were checked for updates. Thirteen CTRs had at least one newly identified CA, five had posted data on the trial registry website, and seven CTRs had newly identified full-text publications. Three of the newly identified outputs provided data that was relevant to LSR-4.[5,6,8] Six CTR records were no longer tracked.

Of the 51 CTRs identified to be currently open at the time of the last update, 41 continue to be reported as currently open. Three continue to be not yet recruiting. Since LSR-3, eight CTRs have finished recruitment (currently 'active not recruiting'), five are now reported as completed, one has been terminated, one is unknown and one has re-opened recruitment. Of the nineteen CTRs identified as completed but not yet reported at the time of the last update, five (26.3%) have new information available, including one CA[8] and one full-text publication[6] (also identified from LSR-4 database searches) included in the LSR-4 synthesis.

Newly identified CTRs

Nineteen new CTRs were identified and extracted for LSR-4. Ten were identified from new CAs[9-18], six during citation searching of relevant systematic reviews identified in LSR-4[19-24], and three from additional searches[25-27]. No new eligible CTRs were identified from the LSR-4 database searches.

Published studies

Demographics of new studies

Five studies contributed 19 new cohorts to LSR-4.[4-8] More than half (n=13; 68%) of these cohorts were from one molecular registry study which included 13 children and young people (CYP) with rhabdomyosarcoma receiving individual treatments tailored to their tumour biology.[5] The studies reported countries of recruitment including: USA (3 studies)[5,6,8], France (2 studies)[4,7], as well as Belgium[7], Lebanon[5], and the United Kingdom[4] (1 study each). Three studies (60%) were completed in multiple countries.[4,5,7]

Two studies evaluated multi-agent novel therapies[4,8], two studies were molecular registry studies where CYP received individualised treatment matched to the mutations within their tumour[5,6], and one study investigated metronomic chemotherapy[7].

Four studies (80%) identified by the update were published in 2024[4-7], while one study was published in 2020[8]. The study published in 2020 had not been identified from previous searches, and was retrieved from additional tracking in LSR-4.

Demographics of participants in new studies

At least 27 children and young people with relapsed and refractory rhabdomyosarcoma were included in the newly identified studies. Four studies of 18 cohorts included fewer than five CYP with relapsed/refractory rhabdomyosarcoma[4-7]. In one study, at least one CYP with relapsed/refractory rhabdomyosarcoma was included, but the exact cohort size is unknown.[8] All of the studies recruited CYP with a variety of tumour types.[4-8] Three studies included infants younger than one years old.[4,6,7]

Two studies reported the sex of included CYP (one for CYP with rhabdomyosarcoma specifically[6]), two studies reported gender (one for CYP with rhabdomyosarcoma specifically[7]), while one study did not report sex or gender (one CA)[8]. Sex/gender was reported as a binary characteristic in all studies included in the review. Where sex/gender was reported for CYP with rhabdomyosarcoma specifically, the male to female ratio was equal (1:1).

One study reported both the ethnicity and race of the CYP with rhabdomyosarcoma[6]. In this study, all three CYP were white; and the ethnicity was hispanic for all three CYP. Four studies reported neither race or ethnicity for any of the included CYP with rhabdomyosarcoma.[4,5,7,8]

Four studies reported the molecular characteristics of rhabdomyosarcoma tumours.[4-7] Of these studies, three reported the fusion status of CYP with rhabdomyosarcoma (n=20) whereby 11 CYP (55%) were PAX:FOX fusion positive and nine (45%) were PAX:FOX fusion negative.[4-6] A range of other mutations and genetic alterations were identified, as described in Table 2.

Quality assessment of new studies

The majority of studies reported adequate information in relation to most MINORS tool assessment criteria, but all studies had at least one domain inadequately reported (see Table 1). All studies prospectively collected data and reported these methods apriori. In contrast, most studies did not include adequately assessed endpoints, whereby response rates were not evaluated by an independent panel. The study by Vo (2020)[8] is of lower quality overall, however this is expected given this was a conference abstract where word counts limit the amount of information available to report.

The MINORS question relating to whether loss to follow-up was less than 5% was sometimes difficult to answer. While most studies clearly reported the number of CYP involved at all time points, in many cases the loss of CYP to follow-up was greater than 5%. Drop out from clinical trials in this relapsed/refractory population is relatively common - as CYP progress or do not tolerate the drug prior to response being evaluated (usually after two cycles). For this question, we considered studies to be adequately reported if loss to follow-up was less than 5%, or the characteristics and patient flow of the enrolled population were described.

Outcomes of new studies

Overall, data on outcomes were available for 22 CYP with relapsed/refractory rhabdomyosarcoma.

Survival

Fifteen cohorts reported Progression Free Survival (PFS), each including only one CYP with rhabdomyosarcoma.[5,6] PFS for any individual across these cohorts ranged from 25 to 295 days. Four CYP, all treated with different interventions, experienced PFS of six months or more.[5,6] In one study, two (of three) cohorts reported a higher PFS for CYP receiving the treatment under investigation compared to their most previous intervention.[6] This ratio, comparing PFS from the last treatment to the current treatment, is an outcome becoming more widely reported in early phase trials. No cohort reported overall survival (OS).

Response rate

Most cohorts (n=12, 63.2%) showed no objective responses.[4-7] In five cohorts, each including one CYP with rhabdomyosarcoma, responses were seen.[5,6] For one study, the total number of CYP with rhabdomyosarcoma was unclear so the objective response rate could not be determined.[8] In another study, one CYP with no evidence of disease prior to commencement of targeted therapy remained disease-free.[5]

All cohorts reported combined results for CYP with relapsed and refractory rhabdomyosarcoma and thus it was not possible to examine outcomes for separate groups (refractory, first relapse, subsequent relapse).

Quality of Life

No new study reported quality of life data.

Adverse Events (AEs)

Adverse events were variably reported. Two studies (both molecular registry studies) did not report any AE data.[5,6] Three studies contributed new AE data[4,7,8], although one did not provide details of the severity/grade of adverse events[8]. Within the studies that reported Grade 3/4 AEs, 25 participants were evaluable for toxicities.[4,7] Most AEs were haematological. Additional specific AEs varied by study treatment (see Table 4). No study explicitly reported treatment-related or potentially treatment-related deaths.

New CTRs

Nineteen new CTR studies were identified.[9-27] Reported start dates of the studies ranged between 2013 and 2024. Ten studies were reported as having an academic sponsor[10,11,14,19-21,24-27], and nine a pharmaceutical sponsor[9,12,13,15-18,22,23].

We identified 12 currently open studies[9-13,15-18,20,21,24], four studies had closed recruitment[22,25-27], and one was reported as completed with no identified published results[14]. Two studies had an unknown trial status.[19,23]

Seventeen studies were single-arm and evaluated a range of therapies, including: eleven studies of novel single agent therapies[9-12,15-17,20,22-24] (7 of which were targeted therapies[9,10,12,15,16,20,24]), novel multi-agent therapies (2 studies)[26,27], molecular registry studies (1 study)[21], cellular therapies (2 studies)[14,25], and cellular and vaccine therapy combined (1 study)[19]. Two studies were non-comparative and multi-arm, evaluating a novel agent alone or in combination with other therapies.[13,18]

Seventeen studies included all solid tumours in their eligibility criteria[9-18,20,22-27], whilst one study restricted eligibility to sarcoma only[19], and one study included a wider range of malignancies[21]. Three studies included newly diagnosed CYP.[9,19,23] Eligible ages varied: upper age limits ranged from 18 years to 80 years. Ten studies had no upper age limit.[9,10,12,13,15-18,23,24] Seven studies were open to infants and young children[11,14,19,22,25-27] while seven studies were limited to those aged 12 years and older[9,12,13,15-18]. Two studies did not provide details of the included age range.[20,21]

Nine CTR studies restricted their eligibility criteria to CYP with specific genetic mutations/alterations. These included: *GD2* positive cancers (1 study)[25], *TP53 Y220C*

mutations (1 study)[13], *RET* gene alteration (1 study)[16], *ALK* rearrangement/activating *ALK* mutation (1 study)[12], *ROS1* gene fusions (1 study)[20], *NTRK 1-3* gene fusion (2 studies[23,24], including 1 restricted in phase 2 only[23]), and *ROS1* gene fusion or *NTRK 1-3* gene fusions (2 studies[9,22], including 1 restricted in phase 2 only[22]).

Countries where studies were open for recruitment included the USA (n=13)[9,12-18,22,24-27], UK (9)[9,10,12,13,16,17,20-22], Spain (6)[9,12,13,16,17,22], Canada[9,12,16,18,22], France[9,12,13,16,22], Italy[9,12,13,16,22], and Republic of Korea[9,12,13,16,22] (5 in each), Australia[9,12,13,16], China[9,19,22,23], Germany[9,13,16,22], Singapore[9,12,13,16], and Taiwan[9,12,16,22] (4 in each), Denmark[9,16,18], Hong Kong[9,16,22], and Japan[9,11,16] (3 in each), Netherlands[9,12] (2), as well as Belgium[9], Hungary[9], Israel[16], Poland[9] and Switzerland[16] (1 in each).

Summary of new studies

The REFoRMS LSR-4 update identified five new published studies (19 cohorts) of at least 27 children and young people with relapsed and refractory rhabdomyosarcoma. This means that **overall**, the REFoRMS systematic review has identified **166** published early phase studies of interventions, including **over 1,300** children and young people with relapsed/refractory rhabdomyosarcoma.

Similar to LSR-3, we identified many new CTRs during this update, all of which were obtained through checking CAs and reviews. Some studies used the term “advanced sarcoma” in their title rather than the terms “relapsed/refractory” which may be why they have not been captured in the database searches. This term primarily relates to adult approaches to cancer care, but eligibility criteria mean that CYP could potentially be included. The identification of additional studies through citation searching, and checking CAs and CTR records for updates, highlights the importance of using multiple methods to identify new relevant literature.

Survival outcomes were provided by two out of five studies, whilst all studies provided response rates. Cohorts were all small 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, **54** 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.

Although not eligible for inclusion in this review, we acknowledge the recent publication by Metts et al. (2024)[28] which provides a pooled analysis of survival outcomes for children and young people with relapsed and refractory rhabdomyosarcoma in a selected group of studies. Each trial reviewed in this paper has previously been included in the REFoRMS review (throughout various stages of updates).

We also acknowledge an erroneous extraction in LSR-3. We extracted a CTR as if it was a new trial. We have since realised that it had been extracted before and should have been removed in a previous update for not recruiting any CYP with rhabdomyosarcoma. We have updated the flowsheet accordingly (Figure 2).

Suggestions for new adaptations/changes for next update

In this update, the utility of searching the PROSPERO database was assessed. All included PROSPERO records were checked for published systematic reviews, and these included reviews were then checked for eligible studies, and nothing new or useful was identified. Systematic reviews are not eligible for inclusion in the review, but are used to identify potentially relevant early phase studies. Given the extensive search methods we perform, it was felt that the likelihood of missing relevant systematic reviews was minimal if PROSPERO searching was stopped. We will not search the PROSPERO database in future updates.

Regarding CTRs, we have made the decision to no longer track trials with a 'withdrawn', 'suspended', 'terminated' or 'unknown' recruitment status where the number of participants is confirmed to be zero. Given that no CYP have been recruited on these trials, no results will be published, and thus, there is no benefit to tracking these trials.

Further adaptations to the CTR data extraction sheet will be made prior to the next update to facilitate the extraction process. For example, a separate question about whether the treatments being investigated are targeted or not. In the next update, data extraction will be conducted using Google Sheets, rather than Qualtrics. These adaptations will improve data extraction and the synthesis of results.

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
Gatz, 2024[4]	Reported and adequate	Reported and adequate	Reported and adequate	Reported but inadequate	Reported and adequate	Reported and adequate	Reported and adequate
*Vo, 2020[8]	Reported but inadequate	Reported and adequate	Reported but inadequate	Not reported	Not reported	Reported but inadequate	Not reported
Saulnier Sholler, 2024[5]	Reported and adequate	Reported and adequate	Reported and adequate	Reported and adequate	Reported and adequate	Reported but inadequate	Not reported
Acanda De La Rocha, 2024[6]	Reported and adequate	Reported and adequate	Reported and adequate	Reported but inadequate	Reported and adequate	Reported and adequate	Reported and adequate
Andre, 2024[7]	Reported and adequate	Reported and adequate	Reported and adequate	Reported but inadequate	Reported and adequate	Reported and adequate	Reported and adequate

* This is conference abstract, so it is anticipated that the level of reporting would be reduced, owing to limited word counts

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 agents - multiple agents												
Gatz, 2024[4]	UK, France	Phase 1/2	Multi	November 2016 to March 2020	Relapsed, refractory, all solid tumours, measurable disease	<18 years	Included haematological malignancies Advance tumour molecular profiling at relapse	Adavosertib *25 or 100mg/m^2 po capsules, bd on days 1-3 (additional dose levels: 75 and 125mg/m^2)* Carboplatin *AUC 5, de-escalating to AUC 4, IV infusion on day 1 of a 21-day cycle*	4 (20)	WP: 11.2 (1.4- 18.5) years at diagnosis and 14 (3.4- 23.5) years at study entry	WP: 3 (2-8)	4 ARMS. 1 RMS *PAX3:FOXO1*; 1 RMS *PAX3:FOXO1*, *TP53* alt, LOH in *FANCA;* 1 RMS *PAX7:FOXO1*, *CDK4* focal amp, *FRS2* focal amp; *MDM2* amp + LOH, LOH of *PTEN* and *FANCF* alt; 1 RMS *PAX3:FOXO1*, *ASXL* alt, *TP53* alt +LOH
Vo, 2020[8]	USA	Phase 1	Multi	NR	Relapsed, refractory, advanced sarcoma	6-30 years		**Plan A - PAZIT** Pazopanib *225-450mg/m^2 po on days 1-21 of 21-day cycle* Irinotecan *50mg/m^2 IV or 90mg/m^2 po on days 1-5* Temozolomide *100mg/m^2 po on days 1-5* **Plan B - PAZIT (amended due to DLTs)** Pazopanib *225mg/m^2 po on days 1-21 of 21-day cycle* Irinotecan *25-37.5mg/m^2 IV or 45-67.5mg/m^2 po on days 1-5* Temozolomide *100mg/m^2 po on days 1-5*	At least 1 (16)	WP: 16 (7-21) years	NR	
Molecular Registry Studies												
Saulnier Sholler, 2024[5]	USA, Lebanon (based on	Feasibility study	Multi	8 July 2014 to 10 June 2018	Relapsed, refractory, measurable	≤21 years at diagnosis	Neuroblastoma and CNS tumours or rare	Everolimus, Tamoxifen, Trametinib, Vorinostat *Dose, method of administration and*	1 (144 received matched	RMS: ≥10 years	NR	*CDKN2A* del, *HRAS* mut, *PIK3CA* mut, Chr 1q gain

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					
	CTR record)				disease	and >12 months at enrolment	solid tumours were eligible. Includes tumours with no effective therapy known and new diagnoses. At least one tumour lesion available for biopsy	*frequency NR for all cohorts in this study*	therapy)			
								Bortezomib, Sorafenib, Vorinostat, Myrrh	1 (144)	RMS: ≥10 years	NR	*PAX3:FOXO1* mut, *CDK4* gain, *TERT* gain, Chr 5p gain
								Pemetrexed, Carboplatin, Vorinostat, Vinblastine	1 (144)	RMS: <10 years	NR	*FBXW7* del, *RB1* del, Chr 11q del
								Pemetrexed, Dasatinib, Sirolimus, Vorinostat	1 (144)	RMS: <10 years	NR	*MDM2* gain, *MCYN* gain, *NRAS* gain
								Crizotinib, Nelarabine, Pemetrexed, Myrrh	1 (144)	RMS: ≥10 years	NR	*PAX3:FOXO1* mut, *MYCN* gain
								Crizotinib, Dacarbazine, Irinotecan, Pemetrexed	1 (144)	RMS: ≥10 years	NR	*PAX3:FOXO1*, *CDK6* gain, *MDM4* gain, *PIK3CA* alt, Chr 10p and 10q del
								Crizotinib, Dacarbazine, Pemetrexed, Temozolomide	1 (144)	RMS: <10 years	NR	*PAX3:FOXO1*, *CDK4* gain, Chr 17q gain
								Temsirolimus, Trametinib, Vemurafenib, Vorinostat	1 (144)	RMS: <10 years	NR	*BRAF* mut, *CDKN2A* del & structural variant breakpoint, *FBXW7* mut, *KRAS* mut, Chr 8q & Chr 7q gain
								Palbociclib, Pazopanib, Vinorelbine, Curcumin	1 (144)	RMS: ≥10 years	NR	*CDK4* gain, *MYCN* gain
								Temozolomide, Crizotinib, Palbociclib	1 (144)	RMS: ≥10 years	NR	*PAX3:FOXO1*, *CDK4* gain
								Decitabine, Olaparib, Pemetrexed, Temozolomide	1 (144)	RMS: <10 years	NR	*ARID1A* alt, *NF1* structural variant breakpoint, Chr Yp del
								Crizotinib, Decitabine, Temozolomide, Trametinib	1 (144)	RMS: <10 years	NR	*BCOR* del, *CDKN2A* mut, *NRAS* mut,

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					
												TP53 mut, Chr 8q gain, Chr Yp del
								Vinorelbine, Temsirolimus, Palbociclib, Vorinostat	1 (144)	RMS: ≥10 years	NR	Chr Yp del, Chr 10p del
Acanda De La Rocha, 2024[6]	USA	Feasibility study	Multi	21 February 2019 to 31 December 2022	Relapsed, refractory	≤21 years at enrolment	Recently had/scheduled for a biopsy/tumour excision or bone marrow aspiration, and were willing to have a blood draw or buccal swab done for genetic testing	Vincristine, Temozolomide, Irinotecan *Dose, method of administration and frequency NR for all cohorts in this study*	1 (25 enrolled for matched therapy)	RMS: 7 years	RMS: 3	Spindle cell RMS. *CDKN2A/2B* loss, *CBL* mut, *NRAS* mut, *GNAS* mut, MPL stop, *ROS1* mut
								Cyclophosphamide, Vinorelbine, Temsirolimus	1 (25)	RMS: 4 years	RMS: 3	Relapsed ARMS. *SMARCA4* mut, *BCOR* homozygous loss, *PAX3:FOXO1* mut, *PRDM1* mut
								Doxorubicin, Ifosfamide, Vincristine (inconsistent reporting in paper)	1 (25)	RMS: 8 years	RMS: 2	ARMS. *PAX3:FOXO1* mut
Metronomic chemotherapy												
Andre, 2024[7]	Belgium, France	Phase 1	Multi	March 2019 to September 2020	Relapsed, refractory, all solid tumours, measurable disease	<18 years at diagnosis	Had to be able to swallow oral medication. Excluded unstable CNS metastases and complete deficiency of DPD activity	Arm C: Nivolumab + Metronomic chemotherapy: Nivolumab *3mg/kg IV on day 1 and 15 of each cycle* Vinblastine *2mg/m^2 IV, weekly* Cyclophosphamide *30mg/m^2/day po, days 1-4 and days 15-18* Capecitabine *400-600mg/m^2 po, days 8-11 and days 22-25* *28-day cycles for a maximum of 2 yrs*	Arm C: 1 (7)	RMS: 9 years	WP: 3.5 (1-4)	1 ERMS with the following genetic alts: *PI3K3CA* mut, *MYOD1* mut, *GNAI2* mut, Chr 9p del (*CDKN2A/B*), TMB Mut 0.8Mb.

* data has been calculated for CYP with RMS specifically

alt = alteration; amp = amplification; ARMS = alveolar rhabdomyosarcoma; AUC - area under the curve; bd = twice daily; Chr = chromosome; CNS = central nervous system; CTR = clinical trial registration; CYP = children and young people; del = deletion; DLT = dose limiting toxicities; ERMS = embryonal rhabdomyosarcoma; IV = intravenous; LOH = loss of heterozygosity; mut = mutation; NR = not reported; po = orally; RMS = rhabdomyosarcoma; R+R = relapsed and refractory; SG = subgroup; TMB = tumour mutational burden; UK = United Kingdom; USA = United States of America; WP = whole population

Table 3. Outcome data for new studies

Regimen	Author, Year	Total no. of relevant CYP$	Responses (number of CYP)				Response rate % (95% CI) CR+PR	Median survival (range)		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Novel agents - multiple agents										
Adavosertib + Carboplatin	Gatz, 2024[4]	4 R+R RMS	0	0	0	4	0%*	NR	NR	2 RMS had clinical PD. 2 RMS received 2 cycles and 2 RMS received 1 cycle
Pazopanib, Irinotecan and Temozolomide (PAZIT)	Vo, 2020[8]	*1*# R+R RMS	0	0	1	0	UTD	NR	NR	CYP with RMS had prolonged SD for 9 cycles
Molecular Registry Studies										
Everolimus + Tamoxifen + Trametinib + Vorinostat	Saulnier Sholler, 2024[5]	1 R+R RMS	0	0	1	0	0%*	83 days	NR	
Bortezomib + sorafenib + vorinostat + myrrh	Saulnier Sholler, 2024[5]	1 R+R RMS	0	0	0	1	0%*	69 days	NR	
Pemetrexed + Carboplatin + vorinostat + vinblastine	Saulnier Sholler, 2024[5]	1 R+R RMS	0	0	1	0	0%*	81 days	NR	
Pemetrexed + dasatinib + sirolimus + vorinostat	Saulnier Sholler, 2024[5]	1 R+R RMS	0	0	1	0	0%*	86 days	NR	
Crizotinib + nelarabine + pemetrexed + myrrh	Saulnier Sholler, 2024[5]	1 R+R RMS	1	0	0	0	100%*	236 days	NR	
Crizotinib + dacarbazine + irinotecan + pemetrexed	Saulnier Sholler, 2024[5]	1 R+R RMS						295 days	NR	'No evidence of disease'. Patient course unclear, possible they had surgery with complete resection prior to receipt of matched therapy
Crizotinib + dacarbazine + pemetrexed + temozolomide	Saulnier Sholler, 2024[5]	1 R+R RMS	0	0			0%*	59 days	NR	Inconsistent reporting in supplementary material: Table S2 says SD but table S4 says PD
Temsirolimus + trametinib + vemurafenib + vorinostat	Saulnier Sholler, 2024[5]	1 R+R RMS	0	1	0	0	100%*	88 days	NR	PFS censored at 88 days
Palbociclib + pazopanib + vinorelbine + curcumin	Saulnier Sholler, 2024[5]	1 R+R RMS	0	1	0	0	100%*	112 days	NR	
Temozolomide + crizotinib + palbociclib	Saulnier Sholler, 2024[5]	1 R+R RMS	0	0	0	1	0%*	38 days	NR	
Decitabine + olaparib + pemetrexed	Saulnier	1 R+R RMS	0	0	0	1	0%*	53 days	NR	

Regimen	Author, Year	Total no. of relevant CYP$	Responses (number of CYP)				Response rate % (95% CI) CR+PR	Median survival (range)		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
+ temozolomide	Sholler, 2024[5]									
Crizotinib + decitabine + temozolomide + trametinib	Saulnier Sholler, 2024[5]	1 R+R RMS	0	0	0	1	0%*	25 days	NR	
Vinorelbine + temsirolimus + palbociclib + vorinostat	Saulnier Sholler, 2024[5]	1 R+R RMS	0	0	0	1	0%*	51 days	NR	
Vincristine, Temozolomide + Irinotecan	Acanda De La Rocha, 2024[6]	1 R+R RMS	0	1	0	0	100%*	24 weeks	NR	PFS2/PFS1 ratio = 12
Cyclophosphamide + Vinorelbine + Temsirolimus	Acanda De La Rocha, 2024[6]	1 relapsed RMS	0	1	0	0	100%*	28 weeks	NR	PFS2/PFS1 ratio = 28
Doxorubicin + Ifosfamide + Vincristine (inconsistent reporting in paper)	Acanda De La Rocha, 2024[6]	1 R+R RMS	0	0	0	1	0%*	NR	NR	
Metronomic chemotherapy										
Nivolumab + metronomic chemo (vinblastine, cyclophosphamide and capecitabine)	Andre, 2024[7]	1 R+R RMS	0	0	0	1	0%*	NR	NR	Arm C only relevant cohort with CYP with RMS

$ = evaluable CYP with RMS; *calculated from provided information, # plus italicised indicates studies where exact number of evaluable CYP with RMS is unknown but is definitively >1

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

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 agents - multiple agents						
Adavosertib + Carboplatin	Gatz, 2024[4]	18 (4)	7P	73C incidences	29C incidences	DLTs (9 incidences in 7P out of 16 evaluable for DLTs): G3: 1P with **thrombocytopenia** (DL1) G4: 3P with **neutropenia** (DL1) G3-4: 5P **thrombocytopenia** (2P in DL1, 1P in DL-1; 2P in DL-2) Treatment-related AEs: G3: 18C with anaemia (5C in DL1, 10C in DL-1, 3C in DL-2), 18C with **neutropenia** (8 in DL1, 7 in DL-1, 3 in DL-2), 4C with leukopenia (3C in DL1, 1 in DL-1), 2C lymphopenia (1 DL-1, 1 in DL-2), 24C with **thrombocytopenia** (9 in DL1, 12 in DL-1, 3 in DL-2), 4C with **vomiting** (1C in DL1, 3C with DL-1), 1C with abdominal/gastrointestinal pain (in DL-1), 1C with **febrile neutropenia** (in DL1), 1C with hearing loss (in DL-2) G4: 9C with **neutropenia** (5C in DL1, 1C in DL-1, 3C in DL-2), 19C with **thrombocytopenia** (7 in DL1, 6 in DL-1, 6 in DL-2), 1C with general physical health deterioration (in DL-2)
Pazopanib, Irinotecan and Temozolomide (PAZIT)	Vo, 2020[8]	15	7 in 6P			First cycle DLTs reported **(grade NR): diarrhoea**, pancreatitis, colitis, **neutropenia**, hypertension, deep vein thrombosis and ALT increase (in 6P in total)
Molecular Registry Studies						
Multiple interventions, see Table 2	Saulnier Sholler, 2024[5]	No AE data reported				
Multiple interventions, see Table 2	Acanda De La Rocha, 2024[6]	No AE data reported				
Metronomic chemotherapy						
Nivolumab + metronomic chemo (vinblastine, cyclophosphamide and capecitabine)	Andre, 2024[7]	7 (1)		7 in 4P	0	>G3 AEs during whole treatment period for Arm C: 7 incidences in 4P experiencing AEs in arm C: Anaemia (1P), lymphopenia (2P), **thrombocytopenia** (1P), presyncope (1P), asthenia (1P), decreased appetite (1P)

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

AE = adverse event; ALT = alanine aminotransferase; C = cycle(s); DL = dose level; DLT = dose limiting toxicity; G = grade; P = patient(s); RMS = rhabdomyosarcoma

Table 5. New clinical trial registry records

Clinical trial registry number	Title of registered clinical trial	Planned locations; Sponsor	N	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
Recruitment status: Recruiting								
NCT05722886	DETERMINE (Determining Extended Therapeutic Indications for Existing Drugs in Rare Molecularly Defined Indications Using a National Evaluation Platform Trial) - Master Screening Protocol (DETERMINE)[21]	UK; Academic	825 (E)	01/03/23 - 01/10/29*	Molecular study. Arm 1: **Alectinib** (*ALK* positive); Arm 2: **atezolizumab** (high TMB, MSI high, or proven CMMRD); Arm 3: **entrectinib** (*ROS1* fusion positive); Arm 4: **trastuzumab** + **pertuzumab** (*HER2* amplification or activating mutations); Arm 5: **vemurafenib** + **cobimetinib** (*BRAF V600* mutation positive, adults only)	Response rates, Adverse events, Overall Survival, Progression Free Survival, Durable clinical benefit, DOR, Best percentage change in diameters, Time to treatment discontinuation, TTP, ratio TTP with trial treatment to TTP on most recent prior line, QoL, Feasibility data	Relapsed, Refractory, All solid tumours or haematological malignancies, mMust provide fresh biopsy, evaluable or measurable disease. Excluded if ongoing adverse events > grade 2. Excluded if progressing or symptomatic brain metastases	"Child, adult, older adult"
NCT05770544	DETERMINE Trial Treatment Arm 03: Entrectinib in Adult, Teenage/Young Adults and Paediatric Patients With *ROS1* Gene Fusion-positive Cancers. (DETERMINE)[20]	UK; Academic	30 (E)	01/06/24* - 01/10/29*	**Entrectinib**: for BSA ≥ 1.51m^2, a dose of 600mg oral daily. For BSA <1.5m^2, a dose of 100-400mg. 28-day cycles	Response rates, Adverse events, Overall Survival, Progression Free Survival, Durable clinical benefit, DOR, Best percentage change in diameters, Time to treatment discontinuation, TTP, ratio TTP with trial treatment to TTP on most recent prior line, QoL	Relapsed, Refractory. Must fulfil DETERMINE master protocol (NCT05722886), *ROS1* fusion positive, must undergo fresh biopsy, BSA ≥0.43m^2. Excluded if unable to swallow capsules or if progressing/ symptomatic brain metastases	"Child, adult, older adult"
NCT03093116	A Study of Repotrectinib (TPX-0005) in Patients With Advanced Solid Tumors Harboring *ALK*, *ROS1*, or *NTRK1-3* Rearrangements (TRIDENT-1)[9]	UK, USA, Canada, China, Denmark, France, Belgium, Germany, Italy, Australia, Hong Kong, Hungary, Japan, Republic of Korea, Poland, Netherlands, Singapore, Spain, Taiwan; Pharmaceutical company	500 (E)	07/03/17 - 29/02/28	**Repotrectinib**: oral capsules (dose NR)	Response rates, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, RP2D, PKs, DOR, Clinical benefit rate	Relapsed, Refractory, up front treatment also eligible. Must be able to swallow capsules, measurable disease. Must have *ROS1* or *NTRK1-3* gene rearrangement. Symptomatic brain metastases excluded	≥12 years (phase 2 only)
NCT04879121	Larotrectinib for the Treatment of *NTRK*	USA; Academic	13 (E)	30/04/21 - 11/11/25	**Larotrectinib**. Orally, bd on days 1-28, in 28 day cycles (dose NR)	Response rates, Adverse events, Overall Survival,	Relapsed, Refractory, All solid tumours, *NTRK1-3*	≥16 years

Clinical trial registry number	Title of registered clinical trial	Planned locations; Sponsor	N	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
	Amplification Positive, Locally Advanced or Metastatic Solid Tumors[24]					Progression Free Survival, DOR, ratio of TTP with intervention to TTP of most recent prior line, Clinical benefit rate	gene amplification, measurable disease. Exclude prior progression while receiving TKIs targeting *TRK*. Exclude if symptomatic or unstable brain metastases	
NCT05057013	HMBD-001 in Advanced *HER3* Positive Solid Tumours[10]	UK; Academic	135 (E)	10/11/21 - 01/09/26*	**HMBD-001**. IV infusion over a 21 or 28-day cycle dependent on dosing frequency (dose NR)	Response rates, Adverse events, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, RP2D, PKs	Relapsed, Refractory, All solid tumours, Symptomatic CNS metastases excluded	≥16 years
NCT05608148	Clinical Trial of GAIA-102 for Refractory/Relapse Neuroblastomas and Other Malignant Pediatric Solid Tumors[11]	Japan; Academic	56 (E)	26/10/22 - 25/08/27	**GAIA-102** (combination cohorts are for neuroblastoma patients only). IV. $5x10^6$ cells / dose at a fixed dose, 1-3 doses / week for 3 consecutive weeks	Response rates, Adverse events, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, Disease control rate	Relapsed, Refractory, All solid tumours, Excluded with CNS metastases. Excluded if had allogeneic HSCT	1 to 24 years
NCT05384626	A Study of NVL-655 in Patients With Advanced NSCLC and Other Solid Tumors Harboring ALK Rearrangement or Activating *ALK* Mutation (ALKOVE-1)[12]	UK, USA, France, Canada, Australia, Italy, Republic of Korea, Netherlands, Singapore, Spain, Taiwan; Pharmaceutical company	470 (E)	09/06/22 - 01/03/26*	**NVL-655**. Oral, od (dose NR)	Response rates, Adverse events, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, RP2D, PKs, DOR, Clinical benefit rate, TTR, QoL	Relapsed, Refractory, All solid tumours, Must weigh >40kg. Must have documented *ALK* rearrangement or activating *ALK* mutation, must have measurable disease. Excluded if known oncogenic driver alteration other than *ALK*	≥12 years (cohort 2f only)
NCT04585750	The Evaluation of PC14586 in Patients With Advanced Solid Tumors Harboring a *TP53 Y220C* Mutation (PYNNACLE)[13]	UK, USA, France, Germany, Australia, Italy, Republic of Korea, Singapore, Spain; Pharmaceutical company	230 (E)	29/10/20 - 14/07/26	**PC14586,** Oral, od in escalating doses +/- pembrolizumab 200mg IV every 3 weeks	Response rates, Adverse events, Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Dose Limiting Toxicities, RP2D, PKs/PDs, TTR, DOR, QoL, Disease control rate	Relapsed, Refractory, All solid tumours, *TP53 Y220C* mutation, measurable disease. Primary CNS tumour and brain metastases excluded. Known *KRAS* mutation excluded from Phase 2	≥12 years
NCT04905914	Study Of ATRN-119 In Patients With Advanced	USA; Pharmaceutical	45 (E)	09/01/23 - 01/06/25*	**ATRN-119**. Oral, od escalating doses (50, 100, 200, 350, 550 and	Adverse events	Advanced disease, All solid tumours, DNA damage	≥12 years

Clinical trial registry number	Title of registered clinical trial	Planned locations; Sponsor	N	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
	Solid Tumors (ABOYA-119)[15]	company			800mg)		response mutations, measurable disease. Excluded if CNS metastases	
NCT03157128	A Study of Selpercatinib (LOXO-292) in Participants With Advanced Solid Tumors, *RET* Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer (LIBRETTO-001) (LIBRETTO-001)[16]	UK, USA, Canada, France, Germany, Australia, Denmark, Hong Kong, Israel, Italy, Japan, Republic of Korea, Spain, Singapore, Switzerland, Taiwan; Pharmaceutical company	875 (E)	02/05/17 - 28/02/26	Oral **Selpercatinib** (dose and frequency NR)	Response rates, Adverse events, Overall Survival, Progression Free Survival, Maximum Tolerated Dose, Dose Limiting Toxicities, RP2D, Best change in Tumour size from baseline, DOR, time to any and best response, clinical benefit rate, PKs	Relapsed, Refractory, All solid tumours, *RET* gene alteration, measurable disease. Excluded if symptomatic CNS disease. Excluded if unresolved toxicities from prior therapy > grade 1	≥12 years
NCT04718675	A Dose Escalation and Cohort Expansion Study of KB-0742 in Participants With Relapsed or Refractory Solid Tumors or Non-Hodgkin Lymphoma[17]	UK, USA, Spain; Pharmaceutical company	280 (E)	08/02/21 - 01/12/25*	Escalating doses of oral **KB-0742**	Response rates, Adverse events, Progression Free Survival, Maximum Tolerated Dose, Dose Limiting Toxicities, RP2D, PKs, disease control rate, duration of disease control, DOR	Relapsed, Refractory, All solid tumours, body weight ≥40kg, evaluable/ measurable disease. Excluded if active CNS disease, or allogeneic HSCT within 6 months	≥12 years
NCT04855656	Study of RP-6306 Alone or in Combination With RP-3500 or Debio 0123 in Patients With Advanced Solid Tumors (MYTHIC)[18]	USA, Canada, Denmark; Pharmaceutical company	364 (E)	30/04/21 - 31/12/26	Oral **RP-6306**, alone or in combination with **RP-3500** or **Debio 0123**	Response rates, Adverse events, Progression Free survival, Maximum tolerated dose, RP2D, PKs, duration of response, clinical benefit rate	Relapsed, Refractory, All solid tumours, weight ≥40kg, eligible tumour biomarker: *CCNE1* amplification, *FBXW7* deleterious mutation, *PPP2R1A* deleterious mutation. Measurable disease. Excluded if uncontrolled symptomatic CNS metastases	≥12 years
Recruitment status: Active, not recruiting								
NCT03635632	C7R-GD2.CART Cells for Patients With Relapsed or	USA; Academic	94 (E)	23/04/19 - 01/12/39	**C7R-GD2.CAR-T cells** without lymphodepletion (dose level 2b:	Response rates, Maximum Tolerated Dose	Relapsed, Refractory, Confirmed expression of	1 to 74 years

Clinical trial registry number	Title of registered clinical trial	Planned locations; Sponsor	N	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
	Refractory Neuroblastoma and Other GD2 Positive Cancers (GAIL-N)[25]				$3x10^7$ on day 0 & day 7; dose level 3b: $1x10^8$ on day 0 & day 7)		GD2	
NCT02650401	Study Of Entrectinib (Rxdx-101) in Children and Adolescents With Locally Advanced Or Metastatic Solid Or Primary CNS Tumors And/Or Who Have No Satisfactory Treatment Options (STARTRK-NG)[22]	UK, USA, China, Canada, France, Germany, Hong Kong, Italy, Republic of Korea, Spain, Taiwan; Pharmaceutical company	69 (A)	03/05/16 - 15/06/25	Oral **entrectinib** (dose & frequency NR)	Response rates, Adverse events, Overall Survival, Progression Free Survival, Maximum Tolerated Dose, RP2D, PKs, Clinical Benefit Rate, TTR, DOR	Relapsed, Refractory, All solid tumours, Measurable/evaluable disease. For phase 2, must have *NTRK1/2/3* or *ROS1* gene fusions	0 to 18 years
NCT02975882	Nanoparticle Albumin-Bound Rapamycin, Temozolomide, and Irinotecan Hydrochloride in Treating Pediatric Patients With Recurrent or Refractory Solid Tumors[26]	USA; Academic	33 (A)	15/08/17 - 22/09/24	**Nanoparticle albumin-bound rapamycin** IV over 30 mins on days 1 and 8, **temozolomide** oral on days 1-5 beginning on cycle 2 and **irinotecan** oral on days 1-5 beginning on cycle 2. Every 21 days for up to 35 cycles	Response rates, Adverse events, Dose Limiting Toxicities, PKs	Relapsed, Refractory, All solid tumours, BSA≥0.2m^2, evaluable/measurable disease. Excluded if known bone marrow involvement, or deep vein thrombosis within past 6 months	1 to 21 years
NCT03323034	Pevonedistat, Irinotecan, and Temozolomide in Treating Patients With Recurrent or Refractory Solid Tumors or Lymphoma[27]	USA; Academic	30 (A)	11/01/18 - 22/09/24	**Pevonedistat** IV over 60 minutes on days 1/8/10 and 12, **temozolomide** oral od on days 8-12, and **irinotecan** IV over 90 minutes on days 8-12 of cycle 1. From cycle 2, patients receive **pevonedistat** IV over 60 minutes on days 1, 3, and 5, **temozolomide** oral od on days 1-5, & **irinotecan** IV over 90 minutes on days 1-5. Every 28 days for cycle 1 and 21 days for subsequent cycles, up to 17 cycles	Response rates, Adverse events, Maximum Tolerated Dose, Dose Limiting Toxicities, RP2D, PKs	Relapsed, Refractory, All solid tumours, Evaluable/measurable disease. Prior exposure to irinotecan or temozolomide eligible, prior exposure to pevonedistat not eligible	6 months to 21 years
Recruitment status: Completed								
NCT01875601	NK White Blood Cells and Interleukin in Children and Young Adults With Advanced Solid Tumors[14]	USA; Academic	16 (A)	11/06/13 - 08/09/15	**NK cell infusion** +/- escalating dose of **recombinant human interleukin-15**	Response rates, Adverse events, Feasibility	Relapsed, Refractory, All solid tumours, Evaluable/ measurable disease. Excluded if untreated metastatic CNS tumour	2 to 29 years

Clinical trial registry number	Title of registered clinical trial	Planned locations; Sponsor	N	Start date to end date	Intervention (+/- comparator)	Outcomes to be collected	Conditions being studied	Ages eligible
							involvement or if prior allogeneic HSCT	
Recruitment status: Unknown								
NCT04433221	Combination Immunotherapy Targeting Sarcomas[19]	China; Academic	20 (E)	01/07/20 - 31/12/23	Multiple sarcoma-specific **CAR-T cells** (1 IV infusion, CART $1x10^6$~$1x10^7$ cells/kg) and **sarcoma vaccines** (1-$5x10^6$ irradiated cells via subcutaneous injection)	Response rates, Adverse events, Overall Survival	Relapsed, Sarcoma only, stage III/IV first line treatment also eligible. Must have confirmed expression of CART target antigens. Excluded rapidly progressing disease and CNS disease. Previous treatment with any gene therapy excluded	6 months to 80 years
NCT04687423	Study of FCN-011 in Patients With Advanced Solid Tumor (Phase I) and *NTRK* Fusion Positive Advanced Solid Tumor (Phase II)[23]	China; Pharmaceutical company	82 (E)	13/04/21 - 31/03/24	**FCN-011**. Orally in ascending doses starting at 50mg bd or 100mg od	Response rates, Adverse events, Dose Limiting Toxicities, RP2D, death within 30 days of last dose, PKs	Relapsed, Refractory, All solid tumours, stage III/IV tumours, *NTRK* fusion positive, measurable disease. Excluded if uncontrolled/symptomatic brain metastases. Exclude patients previously receiving *TRK* gene TKIs (e.g. entrectinib) if treatment not discontinued within 28 days (phase 2 only)	≥16 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; BSA = body surface area; CMMRD = Constitutional Mismatch Repair Deficiency; CNS = central nervous system; DOR = duration of response; E = estimated enrolment; HSCT = haematopoietic stem cell transplant; IV = intravenous; MSI = Microsatellite instability; N = number of participants; NR = not reported; od = once daily; PKs = pharmacokinetics; QoL = quality of life; RP2D = recommended phase two dose; TKIs = tyrosine kinase inhibitors; TMB = tumour mutational burden; TTP = time to progression; TTR = time to response; UK = United Kingdom; USA = United States of America

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