Living REFoRMS update 2 (REFoRMS LSR-2) report

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

Searches

The second 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). Additional details can be found on the PROSPERO record.

The standard searches were conducted in line with the original review on 18th and 19th April 2023.

Screening

The eligibility criteria for the studies as part of Living-REFoRMS 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 LSR-1 methods.

Data extraction and quality assessment

Data extraction and quality assessment was performed in line with baseline review methods. Minor changes to the data fields were made in this update to reflect changes to the evidence identified and to improve ease of reporting (e.g., for ease of creating evidence summary tables used in dissemination, and identification of different study designs and intervention types).

A modified Downs and Black Checklist was used, as described in LSR-1.[3]

Study selection

From 5,540 studies identified from the database searches, 111 were eligible at title and abstract screening. A detailed flow sheet of the LSR-2 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, six studies providing results were included,[4-9] including two conference abstracts [CAs][7,9] (one[7] of which were extracted alongside associated clinical trial registry record[10] [CTR]) and four full-text papers[6,8] (including one that was identified during CTR tracking[5], and one identified from CA tracking[4]). One of the identified full-text studies (Akshintala 2023) was also included in LSR-1 as a CA and CTR: this study is reported separately.[8]

Eight authors were contacted for further information, but we received no responses.

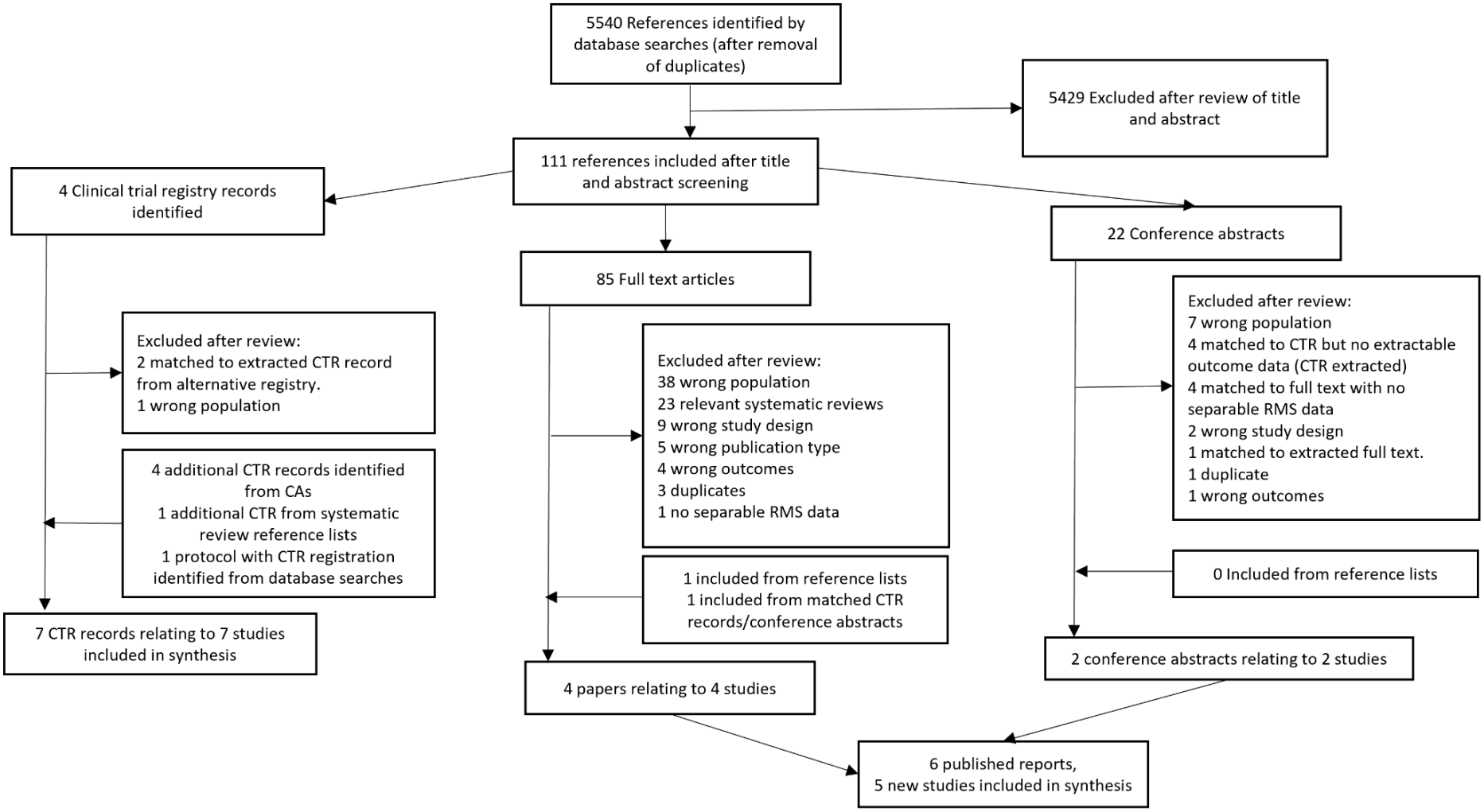

Figure 1: LSR-2 flowsheet

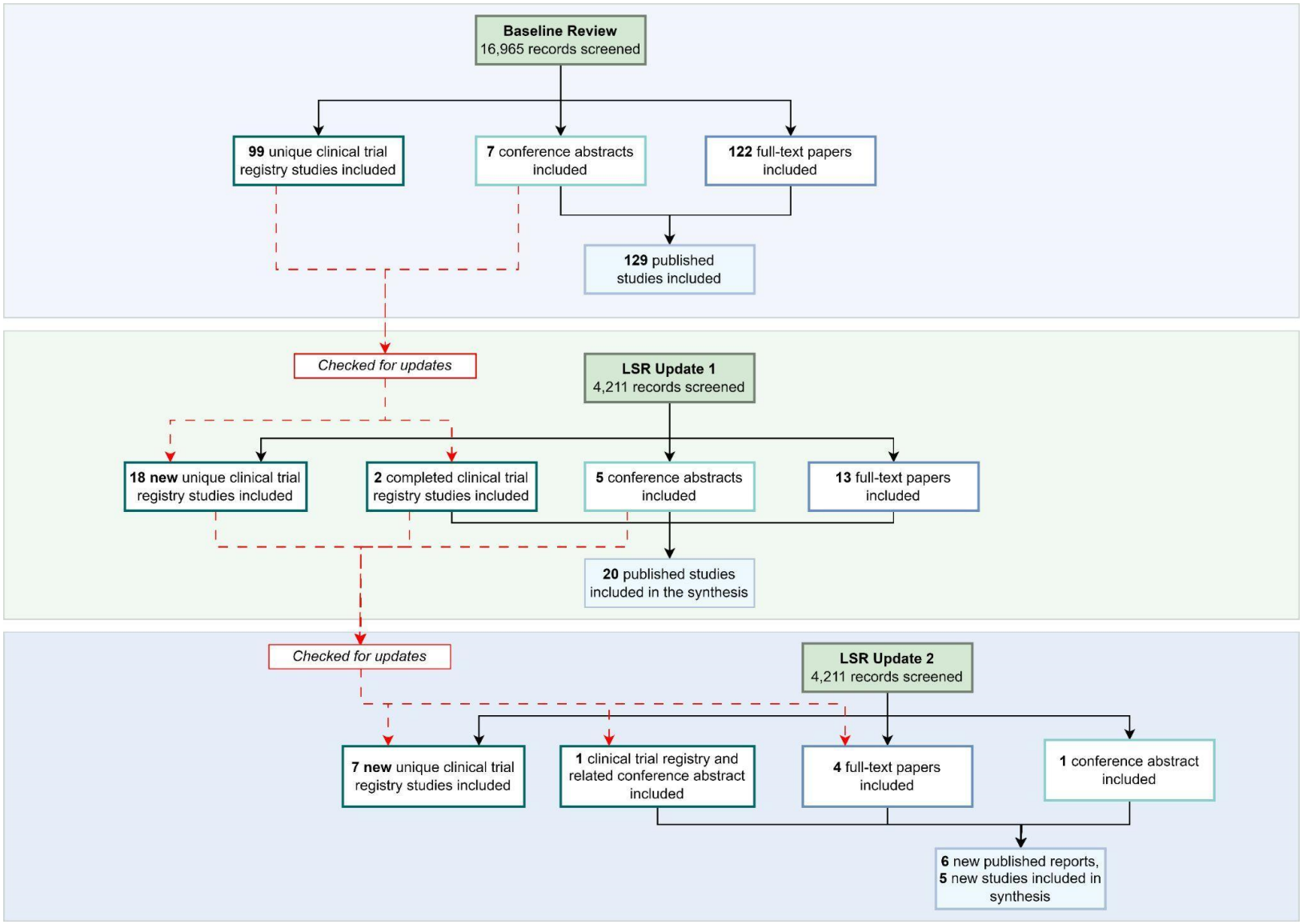

Figure 2: Flowsheet of included studies in REFoRMS

Updates of previously identified CTRs

Of the 99 unique CTRs identified in the baseline review, four had newly identified conference abstracts[7,11-13] (one of which contributed relevant data to LSR-2[7]), one had newly identified conference abstract and had also posted extractable data on the trial registry website[12] (which was not eligible for inclusion). Three CTRs had newly identified full-text publications, one of which contributed relevant data to LSR-2[5]. The other full-text papers did not include RMS patients nor provided separable data for RMS patients so were not eligible for inclusion. [14,15]

In LSR-1, 18 new CTRs were identified, of which three had newly published conference abstracts that were identified in LSR-2, although these were not eligible for inclusion in LSR-2 as they did not provide separable data for RMS patients. These conference abstracts will continue to be tracked for full-text publications.[16-18]

Of the 55 CTRs identified to be currently open at the time of LSR-1, 52 (95%) continue to be reported as open. Since the last update, three CTRs are reported to have commenced recruitment, six CTRs have finished recruitment (and are currently 'active not recruiting'), one study is now reported to be completed (but no outputs have been reported), and two studies have terminated. Of the 20 CTRs identified as completed but not yet reported at the time of the LSR-1, two (10%) have newly identified information available, one of which was also identified during LSR-2 searches.

Newly identified CTRs

Seven new CTRs were identified and extracted for LSR-2. Two were identified in the update search (including one CTR record and one protocol), four were included after being identified from new conference abstracts, and one was identified during citation searching.

Published studies

Demographics of new studies

Five studies contributed seven new cohorts to REFoRMS LSR-2.[4-7,9] The reported countries of recruitment were: USA (four studies),[4,5,7,9] Puerto Rico (1 study)[7] and one international multicentre study that did not report its locations[6]. Where reported, most studies were completed in one country (60%).[4,5,9]

Two studies contributing four cohorts included in REFoRMS LSR-2 were molecular registry studies which evaluated biomarker driven monotherapies.[5,6] Outside of the molecular registry studies, one study looked at a biomarker-driven monotherapy,[7] one evaluated multi-agent novel therapies,[4] and one evaluated surgery and HIPEC[9].

Of the five new studies identified by the update, most were published in 2022 (n=2)[5,7] or 2023 (n = 2)[6,9] as expected. One was identified prior to this (in 2020), which was identified when CAs were being checked for updates.[4]

Demographics of participants in new studies

Sixteen 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 (80%),[4,6,7,9] and one also included newly diagnosed patients[5]. Only one study recruited patients >30 years old.[5] Children less than 1 year old were excluded from 2 of the 5 new studies.[4,7]

Four studies reported the sex of included patients (one for rhabdomyosarcoma patients only,[6] and three for the whole study population[4,5,7]), no studies reported gender, one did not specify whether they had reported sex or gender (and were presumed to report sex)[9]. 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, 1 (14%) participant was male and 6 (86%) were female.

Three studies reported both the ethnicity and race of included patients, but this was not rhabdomyosarcoma-specific.[4,5,7] Two studies reported neither race or ethnicity for any of the included patients.[6,9]

Quality assessment of new studies

Quality assessment of new studies was similar to that within the baseline review and LSR-1 (Figure 3). Similar challenges with using the Downs and Black criteria for molecular registry studies were observed.

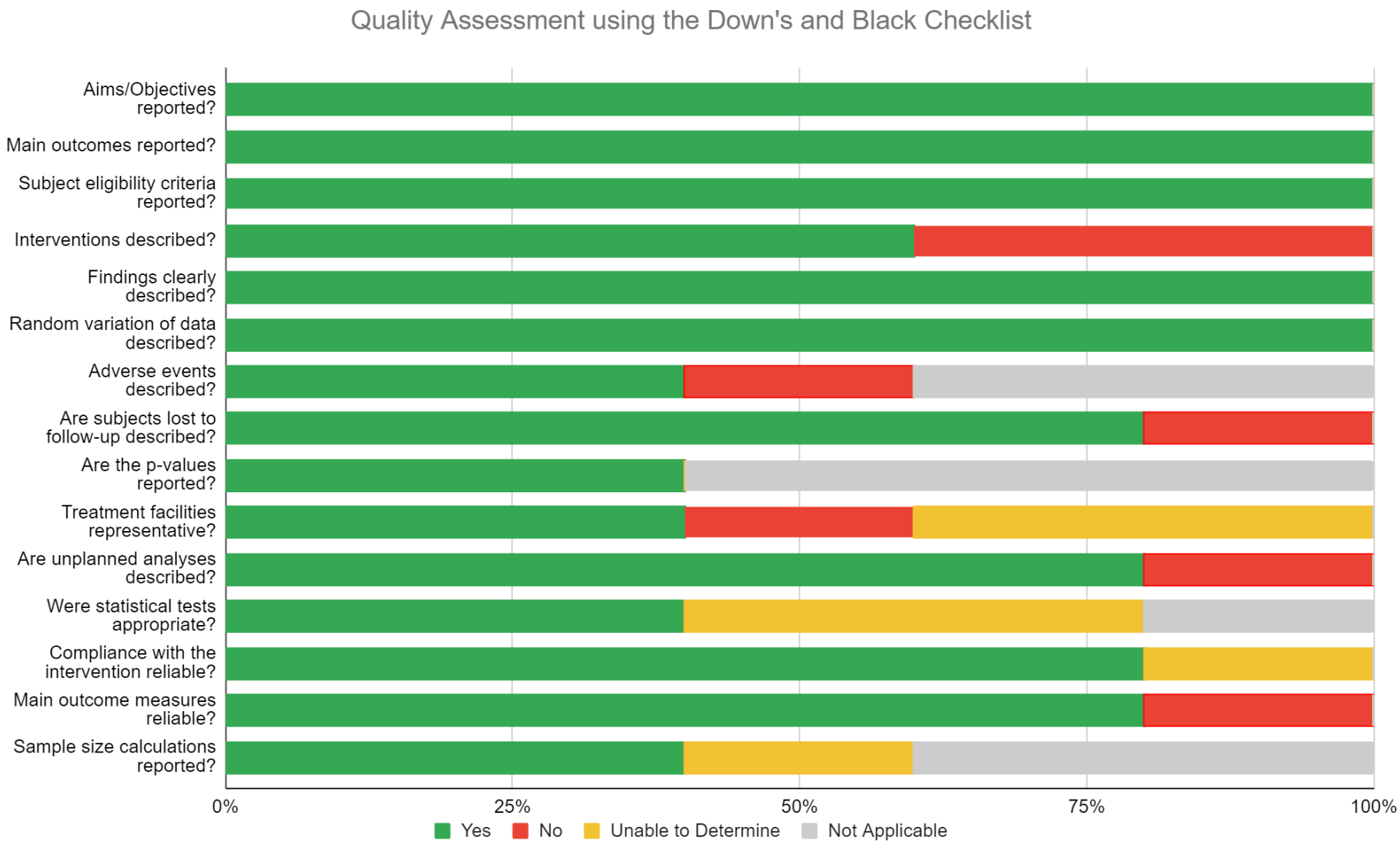

Figure 3: Graphical representation of the quality assessment of newly identified studies

Outcomes of new studies

Five new studies reporting seven cohorts contributed data to the outcome synthesis.[4-7,9] The number of evaluable rhabdomyosarcoma patients was clear for most studies (the number of rhabdomyosarcoma participants in one study was unclear, but it was at least one[4]). The majority of cohorts (85%) reported outcome data for five or fewer patients with relapsed and refractory rhabdomyosarcoma.[4-7]

Survival

No study reported Progression Free Survival (PFS) or Time to Progression (TTP). One study of surgery and HIPEC reported Overall Survival - which was 20.4 months (standard deviation: 6.6 months) for six participants.[9] Notably this study only included patients with resectable intra-abdominal disease and excluded those with metastases outside the abdomen. Given this selective sample of patients, caution should be taken when interpreting these results, as the duration of survival in this study may not be generalisable to populations with more extensive disease.

Response rate

No CRs or PRs were reported within the new studies in 16 children and young people with relapsed and refractory rhabdomyosarcoma where the RECIST response was known.

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

Quality of Life

No new study reported quality of life data.

Adverse Events (AEs)

Adverse events were variably reported. Two molecular registry studies (with four cohorts) did not report any AE data.[5,6]. Three studies contributed new AE data. Within these studies, 53 participants were evaluable for toxicities.[4,7,9] Specific AEs varied by study treatment.

All-cause mortality was reported in one study, with the cause of death not being clearly reported.[7] No study explicitly reported treatment related or potentially treatment related deaths.

New CTRs

Seven new CTR studies (and one associated published protocol) were identified.[19-26] Reported start dates of the studies ranged between 2015 and 2023 (early start dates for some CTRs is associated with the reference list/cross checking that takes place during each LSR update).

Two studies were reported as having an academic sponsor[21,25] and five a pharmaceutical sponsor[19,22-24,26].

We identified four currently open studies,[19,21,23,24] one study was active not recruiting[25] and two studies were reported as completed with no identified published results (completed in December 2020 and April 2023)[22,26].

The seven CTRs contributed eleven cohorts evaluating a range of therapies, including novel single agent therapies (one cohort),[25] novel multi-agent therapies (one cohort),[22] biomarker driven therapies alone (three cohorts)[19,24,26] or in combination with other systemic therapies (two cohorts),[21,26] standard single-agent systemic therapies (two cohorts)[25] and immunotherapy alone (one cohort)[23] or in combination with systemic therapies (one cohort)[23].

Two studies restricted eligibility to participants with sarcoma,[23,25] and five included a wider range of malignancies[19,21,22,24,26]. The majority (n=6) included relapsed and refractory patients,[19,21,22,24-26] with one study also including newly diagnosed patients [23]. Eligible ages varied. Two studies had a lower age limit of 12 years old,[19,23] and one had a lower age limit of 16 years old,[25] so children were only eligible for four studies. Upper age limits were varied and ranged from 17 years to 25 years. Three studies had no upper age limit.[19,23,25] Young infants were excluded in three studies: two excluded 6 to 12 month olds,[21,24] and one excluded those less than one month old[26].

Most studies were located in multiple countries, almost all were open in North America (n = 6),[19,21-24,26] others were located in Europe (n = 3)[22,24,26] and in Asia (n = 3)[23-25].

Summary of new data

The REFoRMS LSR-2 identified five new published studies of 16 children and young adults with relapsed and refractory rhabdomyosarcoma. This means that **overall**, the REFoRMS systematic review has identified **154** published early phase studies of interventions, including **over 1200** children and young people with relapsed/refractory rhabdomyosarcoma.

As there was only a six-month period in between LSR-1 and 2, this update yielded far fewer studies compared to LSR-1 (which had a period of sixteen months in between the two searches), and the database searches only contributed four published studies included in this analysis. Additional studies were also identified via citation searching, and checking conference abstracts and CTR records for updates; this highlights the importance of using multiple methods to identify new relevant literature.

In LSR-2, we identified a new published full-text article of a study that has already contributed data to REFoRMS in a previous update. In LSR-1, a CA and CTR record with result was identified and extracted, however the results from this Phase I/II study included patients who were over the age of 18.[27,28] In LSR-2, the full-text version of the Phase I trial was published with IPD that enabled results for the under 18s to be extracted separately.[8] This posed new challenges for the REFoRMS team, about how to synthesise updated data and new reports to previously reported outputs. The outputs from the CTR and CA and the full-text were mostly consistent, however the full-text failed to report a grade 4 adverse event. This may not have been reported as the full text only reported adverse events that had happened in >10% of people.

In previous updates and in the baseline review, survival outcomes were reported relatively frequently (LSR-1: 35% reported PFS, and 25% reported OS; baseline review: 21% reported PFS and 20% reported OS). However, in this update, only one study including a selective group of patients reported survival outcomes. Of the studies that reported RECIST response criteria in this review, no children or young people with relapsed or refractory rhabdomyosarcoma achieved a partial or complete response to treatment. While it's important to note that the number of rhabdomyosarcoma patients in these studies were very small (all included 5 participants or fewer), so the results may not be generalizable, the findings are disappointing and highlight the difficulty of finding effective treatments for children and young people with relapsed or refractory rhabdomyosarcoma.

The number of currently open studies identified from CTRs is still high with 56 studies currently recruiting highlighting the options available but bringing challenges in terms of decision making.

Suggestions for new adaptations/changes for next update

For LSR-3, standard searches will be changed, and database searching will be restricted to CENTRAL, Embase ('conference abstracts' only), Cochrane CDSR, DARE and the International HTA database. PROSPERO and clinical trial registries will continue to be searched. Medline and Web of Science searches will be discontinued (as they have not identified any unique records in the past two updates). Snowball citation searching will continue. A binary ML classifier of 5 will be implemented to score records from OpenAlex and the remaining database searches: retain and screen records with a score >6 (and discard records with a score ≤6. OpenAlex searches will not change.

Following advice from the Clinical Advisory Group (CAG), searches will be limited to only look at studies published up to 10 years prior to each update search. Furthermore, CAs and CTRs previously included REFoRMS will only be checked for updates if they have been published within 10 years of each update search.

For LSR-3, we will update the data-extraction form for CTRs, to facilitate the reporting of the types of treatments being studied, as well as extracting additional data on mutation status from newly identified studies, and when checking for updates to clinical trials or newly completed studies. This was deemed important by our CAG to reflect the increase in research into biomarker driven therapies and molecular registry studies.

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**
Vo, 2022[7]															
Ecker, 2023[6]															
Guillen, 2023 [9]															
Cole, 2020[4]															
Church, 2022[5]															

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 2.2 Demographic characteristics of new studies

Author, date (Reference)	Countries performed	Study design		Patient enrolment dates	Inclusion/exclusion criteria			Intervention(s)	Number of R+R RMS patients (total)	Age (median (range))	Median prior lines of therapy (range)	Comment
		Phase	Single/ multi centre		Disease	Age	Other					
Novel agents - multiple agents												
Cole, 2020[4]	USA	I	Multi	Mar 2014-Oct 2016	Relapsed; refractory; all solid tumours	1-21 years	Measurable disease, must be able to swallow tablets	Adavosertib *50-110mg/m² po od on days 1-5 of 21 day cycle, given 1 hour after irinotecan* Irinotecan *70-90mg/m2 po od on days 1-5 of 21 day cycle*	*1#* (37)	WP: 13.2 years (2-20)	WP (n=35): 3 (1-11)	
Biomarker driven studies												
Vo, 2022[7]	USA, Puerto Rico	II	Multi	Nov 2018-Mar 2021	Relapsed; refractory; all solid tumours	1-21 years	Tumours harbouring *MAPK* active alterations, measurable disease, and body surface area >0.54	Ulixertinib *260 or 350 mg/m² po bd on continuous schedule on 28-day cycles for up to two years.*	20 (5)	WP: 12 (5-20)	NR	4/5 RMS patients had NRAS mutation
Molecular Registry Studies												
Ecker, 2023[6]	Germany (and 25 countries)	PM	Multi	Feb 2017-Feb 2019	Relapsed; refractory;all solid tumours	≤ 21 years at primary diagnosis	Includes CNS-tumours	Regorafenib **(Matched treatment)** *Dose, method of administration and frequency NR*	12 RMS patients (1 received targeted therapy)	RMS: 5 years	NR	Participant had *FGFR-4* expression
Church, 2022[5]	USA	PM	Multi	Nov 2015-Dec 2018	Relapsed; refractory; 'high risk' tumours, All solid tumours	≤ 30 years	Newly diagnosed high risk (expected 2-year progression-free survival of ≤50%) tumours included, excludes CNS-tumours *345 participants included in the molecular registry study, including 45 RMS patients. 3 RMS patients received matched treatments.*	Palbociclib **(Matched treatment)** *Dose, method of administration and frequency NR*	1 (345)	RMS: 13 years	5	Participant had alveolar RMS with *CDK4* amplification
								MDM2 inhibitor **(Matched treatment)** *Dose, method of administration and frequency NR*	1 (345)	RMS: 6 years	12	Participant had alveolar RMS with *MDM2* amplification
								Trametinib **(Matched treatment)** *Dose, method of administration and frequency NR*	1 (345)	RMS: 10 years	1	Participant had alveolar RMS with *PTPN11* mutation
Other												
Guillen, 2023[9]	USA	I	NR	June 2019-June 2022	Relapsed; refractory, RMS only	Paediatric	'Resectable primary refractory or recurrent intra-abdominal'. Patients with metastasis not limited to peritoneum are excluded. No prior HIPEC experience	Surgery and HiPEC *Cisplatin doses varies between 54mg to 143mg* *Doxorubicin doses varied between 8.1mg to 21mg*	6 (6)	NR	NR	5 embryonal RMS, 1 RMS NOS. All had surgical resection prior to HIPEC

Author, date (Reference)	Countries performed	Study design		Patient enrolment dates	Inclusion/exclusion criteria			Intervention(s)	Number of R+R RMS patients (total)	Age (median (range))	Median prior lines of therapy (range)	Comment
		Phase	Single/ multi centre		Disease	Age	Other					
Updated data with additional study output												
Akshintala, 2023[8]	*USA*	*I*	*Multi*	*July 2017-Sept 2020*	*Relapsed; refractory; RMS only*	*No age limit*	*Measurable disease, must be able to swallow tablets, alveolar and embryonal RMS only, no known brain metastases*	*Ganitumab 18mg/kg IV every 2 weeks. Dasatinib 60mg/m²/dose (max 100mg) po od (DL1) or 60mg/m²/dose (max 70mg) po bd (DL2) on continuous schedule. Cycle 1 is day -7 to 27, all other cycles 28 days*	*6 <18s (13)*	*SG (<18s): 9.5 years (8-13)*	*SG (<18s): 4 (2-4)*	7 alveolar RMS, 6 embryonal RMS. 2 RMS patients were fusion positive, 4 fusion negative.

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

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

Table 3.2 Outcome data for new studies

Regimen	Author, date (Reference)	Total no. of relevant CYP$	Responses (number of CYP)				Response rate % (95% CI) CR+PR	Median Survival (months), range		Comments
			CR	PR	SD	PD		PFS/TTP	OS	
Novel agents - multiple agents										
Adavosertib and Irinotecan	Cole, 2020[4]	*1#*	0	0			0%*	NR	NR	No response or prolonged SD
Biomarker driven studies										
Ulixertinib	Vo, 2022[7]	5	0	0			0%*	NR	NR	
Molecular Registry Studies										
Regorafenib	Ecker, 2023[6]	1	0	0	0	1	0%*	NR	NR	Participant died within six months of receiving treatment
Palbociclib	Church, 2022[5]	1	0	0	0	1	0%*	NR	NR	
MDM2 Inhibitor	Church, 2022[5]	1	0	0	0	1	0%*	NR	NR	
Trametinib	Church, 2022[5]	1	0	0	0	1	0%*	NR	NR	
Other										
Surgery plus HIPEC (Cisplatin and Doxorubicin)	Guillen, 2023[9]	6	NR				NR	See comment	20.4 (Standard Deviation, 6.6)	Of the non-deceased patients, median survival of 36 +/- 7.5 months, and mean RFS (relapse free survival): 14 months
Updated data with additional study output										
Ganitumab and Dasatinib	Akshintala, 2023[8]	4	0	0	1	3	0%*	NR	NR	Participant had SD for six cycles

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

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

Table 4.2 Adverse Event data

Intervention	Author, year (reference)	Number evaluable for toxicity (RMS)	Total number AEs			AE details provided by manuscript
			DLT	G3	G4	
Novel agents - multiple agents						
Adavosertib and Irinotecan	Cole, 2020[4]	27 (>1 RMS)	2p			DLTs: 2P Dehydration; 1P **Diarrhoea**; 1P Hypotension at DL5 25 AEs G3 or higher in Cycle 1 Grade 3+ AEs in Cycle 1 (All dose levels): 3P **diarrhoea**; 1P **vomiting**; 1P **nausea**; 6P **lymphocyte count decrease**, 1P anaemia, 3P WBC decrease, 6P **neutrophil count decrease**, 1P hypotension, 1P hypophosphatemia, 2P hypokalemia.
Biomarker-driven studies						
Ulixertinib	Vo, 2022[7]	20 (5)	8			DLTs: 3 DLTs in C1; 8P experienced DLTs in all cycles. DLTs included **fatigue, anorexia,** rash, **nausea**, **vomiting, diarrhoea,** dehydration, increased creatinine, hypoalbuminemia, hypernatremia and hip fracture. *Serious AEs:* 1P **febrile neutropenia**; 1P abdominal pain; 1P ascites; 1P colitis;, 4P **nausea**; 1P **vomiting**; 1P cholecystitis; 1P infections/infestations NOS; 1P sepsis; 1P wound infection; 1P hip fracture; 1P creatinine increase; 1P anorexia; 3P dehydration; 1P hypernatremia; 2P hypoalbuminemia; 2P depressed level of consciousness; 1P headache; 1P urinary retention; 1P pleural effusion; 1P rash acneiform; 1P stevens johnson syndrome; 2P disease progression; 1P fatigue Death: 1P **death NOS;** 4P **all cause mortality**
Molecular Registry Studies						
Regorafenib	Ecker, 2023[6]					No AE data reported
Palbociclib	Church, 2022[5]					No AE data reported
MDM2 Inhibitor	Church, 2022[5]					No AE data reported
Trametinib	Church, 2022[5]					No AE data reported
Other						
Surgery plus HIPEC (Cisplatin and Doxorubicin)	Guillen, 2023[9]	6		3P		3P experienced G3 AEs within 15 days of treatment: 1E respiratory infection; 1E infections; 1E pancytopenia; 1E abdominal pain; 1E urinary leakage; 1E hydronephrosis; 1E acute kidney injury; 1E hypocalcemia; 1E hyponatremia; 1E hypokalaemia; 1E anaemia; 1e of 'AM' - unable to determine what this is.
Updated data with additional study output						
Ganitumab and Dasatinib	Akshintala, 2023[8]	11 (3)	3	11		DLTs: 1P G3 **Diarrhoea** at DL1; 1P G3 pneumonitis and hypoxia, and 1P G3 haematuria at DL2 *Attributable to dasatinib*: 1P **diarrhoea** (DL1); 2P hypokalemia (DL1/DL2); 1P hypophosphatemia (DL1) *Attributable to dasatinib or ganitumab:* 1P dyspnea (DL2), 1P **vomiting** (DL2); 1P anaemia (DL2); 2P **lymphocyte count decrease** (DL2); 1P **neutrophil count decrease** (DL1); 1P **platelet count decrease** (DL2)

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

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

Table 5.2 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: Recruiting								
NCT04796012	VITAS: Atezolizumab in Combination With Chemotherapy for Pediatric Relapsed/Refractory Solid Tumors[29]	USA; Academic	23 (E)	18/04/2023-01/01/2025*	Atezolizumab with Vincristine, Irinotecan and Temozolomide	Response rates, Adverse events, Overall Survival, Progression Free Survival, Dose Limiting Toxicities, Duration of Response	Relapsed, Refractory, All solid tumours, Children, Young adults, Measurable disease. Subjects must not have previously progressed while receiving regimens that include irinotecan or temozolomide. For RMS efficacy cohort - at least 8/17 patients must have a PD-L1(+) tumour.	≥ 6 months to ≤ 18 years. Discrepancy in CTR record
NCT05103358	Phase 2 Basket Trial of Nab-sirolimus in Patients With Malignant Solid Tumors With Pathogenic Alterations in TSC1/TSC2 Genes (PRECISION 1)[19]	USA, Puerto Rico; Pharmaceutical	120 (E)	15/02/2022 - 31/12/2025	Nab-sirolimus (IV infusion)	Response rates, Adverse events, Overall Survival, Progression Free Survival, DOR, patient-reported outcomes, disease control rate, time to response	Solid tumours, must have received all standard therapies appropriate for their tumour type, or be unlikely to tolerate or derive clinically meaningful benefit, no satisfactory treatment options. Must have pathogenic inactivating TSC2 or TSC1 alteration. Measurable disease on CT or MRI	12 years and older
NCT04775485	A Study to Evaluate DAY101 in Pediatric and Young Adult Patients With Relapsed or Progressive Low-Grade Glioma and Advance Solid Tumors (FIREFLY-1)[24]	UK, USA, Germany, Canada, Australia, Denmark, Germany, Israel, Republic of Korea, Netherlands, Singapore, Switzerland; Pharmaceutical	140 (E)	22/04/2021-28/02/2024	DAY101 (pan-RAF inhibitor) - 420 mg/m2 (max 600 mg) orally once weekly for each 28-day treatment cycle for 26 cycles	Response rates, Adverse events, Progression Free Survival, Duration of response, quality of life, PKs, clinical benefit rate, time to response	All solid tumours, Evidence of radiographic progression after at least one line of systemic therapy, known or expected RAF fusion (for solid tumour arm), Measurable disease. Excluded if additional previously-known activating molecular alterations, Excluded if know or suspected NF1.	6 months to 25 years
NCT03425279	Phase 2 CAB-AXL-ADC Safety and Efficacy Study in Adult and Adolescent Patients With Sarcoma[23]	USA, Hong Kong, Taiwan; Pharmaceutical	120 (E)	15/02/2018-01/12/2024	BA3011 alone (Phase 1) or in combination with a PD-1 inhibitor (Phase 2)	Response rates, Adverse events, Overall Survival, Progression Free Survival, PKs, DOR, TTR, Disease control rate	Sarcoma, Measurable disease	12 years and older (Phase 2)
Recruitment status: Active, not recruiting								
jRCTs031190152	JCOG1802: A randomized phase II trial of 2nd line treatment for advanced soft tissue sarcoma comparing trabectedin, eribulin and pazopanib (2ND-STEP)[25]	Japan; Academic	120 (E)	06/01/2020-04/06/2026	ARM A: Trabectedin 1.2 mg/m2 IV on day 1 for 24 hours every 3 weeks ARM B: Eribulin 1.4 mg/m2 IV on day 1 and 8 for 2-5 minutes every 3 weeks. ARM C: Pazopanib 800 mg/day orally more than 1 hour before meals or more than 2 hours after meals every day	Response rates, Adverse events, Overall Survival, Progression Free Survival, Disease Control Rate	Soft-tissue sarcomas only, Young adults, Disease progression, measurable or non-measurable disease, Relapsed, Refractory	16 years or older
Recruitment status: Completed								

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
NCT03236857	A Study of the Safety and Pharmacokinetics of Venetoclax in Pediatric and Young Adult Patients With Relapsed or Refractory Malignancies[22]	UK, USA, France, Germany, Canada, Australia, Netherlands, Switzerland; Pharmaceutical	143 (A)	08/11/2017-19/04/2023	Venetoclax with or without chemotherapy (Dexamethasone and/or vincristine and/or pegasparaginase OR cytarabine and/or etoposide and/or pegasparaginase; tyrosine kinase inhibitor; cytarabine OR azacitidine OR decitabine; rituximab and/or dexamethasone and/or vincristine; cyclophosphamide and/or topotecan) - orally OD	Response rates, Adverse events, PKs, Dose limiting Toxicities, RP2D	Relapsed, Refractory, All solid tumours, Children, Young adults	0-25 years
NCT02124772	Study to Investigate Safety, Pharmacokinetic (PK), Pharmacodynamic (PD) and Clinical Activity of Trametinib in Subjects With Cancer or Plexiform Neurofibromas and Trametinib in Combination With Dabrafenib in Subjects With Cancers Harboring V600 Mutations[26]	USA, France, Canada, Australia, UK; Pharmaceutical	139 (A)	15/01/2015-29/12/2020*	Part A/B: Trametinib (orally, once daily)- 0.0125 to 0.04mg/kg/day Part C: Trametinib (orally once daily): 0.0125 or 0.032mg/kg/day with Dabrafenib (orally, twice daily) (2.63 or 5.25 mg/kg/day)	Response rates, Adverse events, PKs, Palatability of medications	Relapsed, Refractory, All solid tumours, Children, Young adults, Measurable/evaluable disease, Part B and C BRAF V600 mutation	1 month to 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; CT = computerised tomography; CTR = clinical trial registry; DOR = duration of response; E = estimated enrolment; HRQoL = health-related quality of life; MRI = magnetic resonance imaging; NR = not reported; PKs = pharmacokinetics; RMS = rhabdomyosarcoma; RP2D = recommended phase two dose; STS = soft tissue sarcoma; TTR = time to response; UK = United Kingdom; USA = United States of America

References

1 Morgan, J. *et al. A living systematic review of early phase studies for children and young people with relapsed and refractory rhabdomyosarcoma (Living-REFoRMS). PROSPERO 2022 CRD42022380185* <https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022380185> (2022).

2 Morgan, J. *et al. A systematic review of early phase studies for children and young people with relapsed and refractory rhabdomyosarcoma. PROSPERO 2021 CRD42021266254* <https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021266254> (

3 Downs, S. H. & Black, N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* **52**, 377-384 (1998). https://doi.org:10.1136/jech.52.6.377

4 Cole, A. K. *et al.* Phase I Clinical Trial of the Wee1 Inhibitor Adavosertib (AZD1775) with Irinotecan in Children with Relapsed Solid Tumors: a COG Phase I Consortium Report (ADVL1312). *Clinical cancer research* **26**, 1213-1219 (2020). https://doi.org:doi:10.1158/1078-0432.Ccr-19-3470

5 Church, A. J. *et al.* Molecular profiling identifies targeted therapy opportunities in pediatric solid cancer. *Nature Medicine* **28**, 1581-1589 (2022). https://doi.org:doi:10.1038/s41591-022-01856-6

6 Jonas, E. *et al.* Molecular diagnostics enables detection of actionable targets: the Pediatric Targeted Therapy 2.0 registry. *European Journal Of Cancer* **180**, 71-84 (2022). https://doi.org:doi:https://doi.org/10.1016/j.ejca.2022.11.015

7 Vo, K. T. *et al.* Ulixertinib in patients with tumors with MAPK pathway alterations: Results from NCI-COG Pediatric MATCH trial Arm J (APEC1621J). *Journal of Clinical Oncology* **40**, 3009-3009 (2022). https://doi.org:doi:10.1200/JCO.2022.40.16_suppl.3009

8 Akshintala, S. *et al.* Phase I trial of Ganitumab plus Dasatinib to Cotarget the Insulin-Like Growth Factor 1 Receptor and Src Family Kinase YES in Rhabdomyosarcoma. *Clinical Cancer Research*, OF1-OF11 (2023). https://doi.org:doi:10.1158/1078-0432.Ccr-23-0709

9 Guillen, A., Krueger, A., Granberg, C. & Gargollo, P. A0196 - Toxicity of cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in pediatric patients with rhabdomyosarcoma: Early phase 1 trial experience and results. *Abstracts EAU23 - 38th Annual EAU Congress* **83**, S275-S276 (2023). https://doi.org:doi:https://doi.org/10.1016/S0302-2838(23)00246-4

10 Ulixertinib in Treating Patients With Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With MAPK Pathway Mutations (A Pediatric MATCH Treatment Trial). *https://classic.clinicaltrials.gov/ct2/show/NCT03698994* (2023).

11 Bacha, J. *et al.* Abstract CT135: A pilot clinical study of orotecan (oral irinotecan HCl, VAL-413) in patients with recurrent pediatric solid tumors. *Cancer Research* **83**, CT135-CT135 (2023). https://doi.org:10.1158/1538-7445.Am2023-ct135

12 Cruz, F. S. D. *et al.* A phase I/II study of lenvatinib (LEN) plus everolimus (EVE) in recurrent and refractory pediatric solid tumors, including CNS tumors. *Journal of Clinical Oncology* **38**, 10527-10527 (2020). https://doi.org:10.1200/JCO.2020.38.15_suppl.10527

13 Thakar, M. S. *et al.* Phase II trial using haploidentical hematopoietic cell transplantation (HCT) followed by donor natural killer (NK) cell infusion and sirolimus maintenance for patients with high-risk solid tumors. *Journal of Clinical Oncology* **38**, e23551-e23551 (2020). https://doi.org:10.1200/JCO.2020.38.15_suppl.e23551

14 Cascone, T. *et al.* Safety and activity of vandetanib in combination with everolimus in patients with advanced solid tumors: a phase I study. *ESMO Open* **6**, 100079 (2021). https://doi.org:10.1016/j.esmoop.2021.100079
15 Kramer, K. *et al.* Phase 1 study of intraventricular 131I-omburtamab targeting B7H3 (CD276)-expressing CNS malignancies. *Journal of Hematology & Oncology* **15**, 165 (2022). https://doi.org:10.1186/s13045-022-01383-4
16 de la Rocha, A. M. A. *et al.* Abstract LB358: Efficacy of a functional precision medicine approach in relapsed/refractory pediatric cancer patients: results from a prospective clinical study. *Cancer Research* **83**, LB358-LB358 (2023). https://doi.org:10.1158/1538-7445.Am2023-lb358
17 Drilon, A. E. *et al.* Long-term efficacy and safety of larotrectinib in a pooled analysis of patients with tropomyosin receptor kinase (TRK) fusion cancer. *Journal of Clinical Oncology* **40**, 3100-3100 (2022). https://doi.org:10.1200/JCO.2022.40.16_suppl.3100
18 Loriot, Y. *et al.* Tumor agnostic efficacy and safety of erdafitinib in patients (pts) with advanced solid tumors with prespecified fibroblast growth factor receptor alterations (FGFRalt) in RAGNAR: Interim analysis (IA) results. *Journal of Clinical Oncology* **40**, 3007-3007 (2022). https://doi.org:10.1200/JCO.2022.40.16_suppl.3007
19 Aadi Bioscience, I. Phase 2 Basket Trial of Nab-sirolimus in Patients With Malignant Solid Tumors With Pathogenic Alterations in TSC1/TSC2 Genes (PRECISION 1). *https://classic.clinicaltrials.gov/ct2/show/NCT05103358* (2023).
20 Makoto, E. *et al.* Protocol for the 2ND-STEP study, Japan Clinical Oncology Group study JCOG1802: a randomized phase II trial of second-line treatment for advanced soft tissue sarcoma comparing trabectedin, eribulin and pazopanib. *BMC Cancer* **23** (2023). https://doi.org:doi:https://doi.org/10.1186/s12885-023-10693-w
21 Medical, C. U. o. T. S. VITAS: Atezolizumab in Combination With Chemotherapy for Pediatric Relapsed/Refractory Solid Tumors. (2021). https://doi.org:doi:
22 AbbVie. *A Study of the Safety and Pharmacokinetics of Venetoclax in Pediatric and Young Adult Patients With Relapsed or Refractory Malignancies*, <https://classic.clinicaltrials.gov/ct2/show/NCT03236857> (2017).
23 Inc., B. *Phase 2 CAB-AXL-ADC Safety and Efficacy Study in Adult and Adolescent Patients With Sarcoma*, <https://clinicaltrials.gov/study/NCT03425279> (2023).
24 Inc., D. O. B. *A Study to Evaluate DAY101 in Pediatric and Young Adult Patients With Relapsed or Progressive Low-Grade Glioma and Advance Solid Tumors (FIREFLY-1)*, <https://clinicaltrials.gov/study/NCT04775485> (2023).
25 Kawano, M. *JCOG1802: A randomized phase II trial of 2nd line treatment for advanced soft tissue sarcoma comparing trabectedin, eribulin and pazopanib*, <https://rctportal.niph.go.jp/en/detail?trial_id=jRCTs031190152> (2019).
26 Pharmaceuticals, N. *Study to Investigate Safety, Pharmacokinetic (PK), Pharmacodynamic (PD) and Clinical Activity of Trametinib in Subjects With Cancer or Plexiform Neurofibromas and Trametinib in Combination With Dabrafenib in Subjects With Cancers Harboring V600 Mutations*, <https://classic.clinicaltrials.gov/ct2/show/NCT02124772> (2014).
27 Insulin-like Growth Factor 1 Receptor (IGF-1R) Antibody AMG479 (Ganitumab) in Combination With the Src Family Kinase (SFK) Inhibitor Dasatinib in People With Embryonal and Alveolar Rhabdomyosarcoma. *https://clinicaltrials.gov/ct2/show/NCT03041701* (2022).
28 Akshintala, S. *et al.* Results of a phase I trial of ganitumab plus dasatinib in patients with rhabdomyosarcoma (RMS). *Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO* **40** (2022). https://doi.org:doi:https://dx.doi.org/10.1200/JCO.2022.40.16_suppl.11561
29 Brandi, G. *et al.* The power of kindness: curative treatment with metronomic combination in advanced hepatocellular carcinoma. *Anti-Cancer Drugs* **33**, e781-e783 (2022). https://doi.org:https://dx.doi.org/10.1097/CAD.0000000000001202