Supplemental Tables

Supplemental Table S1 Search strategies

Source	Query		Retrieval	Search date
1 MEDLINE via PubMed using automated term mapping; no limits used	#1	((oral OR low dose) AND maintenance) AND chemotherapy		
	#2	metronomic AND chemotherapy		
	#3	#1 OR #2		
	#4	random AND child AND cancer		
	#5	#3 AND #4	105 references	16 Jun 2023
	Update search			
	#6	#5 AND 2023/06/16:2023/09/08[edat]	106 references	08 Sep 2023
2 Cochrane Library via Wiley using combinations of MeSH terms and text (searched in title, abstract, and keywords); no limits used	#01	MeSH descriptor: [Administration, Oral]		
	#02	(oral):ti,ab,kw		
	#03	#1 or #2		
	#04	MeSH descriptor: [Maintenance Chemotherapy]		
	#05	(maintenance AND chemotherapy):ti,ab,kw		
	#06	#4 or #5		
	#07	#3 and #6		
	#08	MeSH descriptor: [Administration, Metronomic]		
	#09	(metronomic AND chemotherapy):ti,ab,kw		
	#10	#08 or #9		
	#11	#7 or #10		
	#12	MeSH descriptor: [Random Allocation]		
	#13	MeSH descriptor: [Randomized Controlled Trial]		
	#14	MeSH descriptor: [Randomized Controlled Trials as Topic]		
	#15	random*		
	#16	#12 or #13 or #14 or #15		
	#17	MeSH descriptor: [Adolescent]		
	#18	MeSH descriptor: [Child]		
	#19	MeSH descriptor: [Infant]		
	#20	pediatric* or paediatric* or child* or adolescent* juvenile* or toddler* or infant* or neonate*		
	#21	#17 or #18 or #19 or #20		
	#22	MeSH descriptor: [Neoplasm]		
	#23	cancer* or malignanc* or neoplasm* or tumor* or tumour* or carcinoma* or sarcoma* or neuroblastoma* or rhabdomyosarcoma* or RMS or osteosarcoma* or Ewing sarcoma* OR primitive neuroectodermal or PNET or esthesioneuroblastoma* or non-rhabdomyosarcoma soft-tissue sarcoma*		
	#24	#22 or #23		
	#25	#11 and #16 and #21 and #24	142 trials	16 Jun 2023
	Update search			
	#26	#25 with Cochrane Library publication date from Jun 2023 to Sep 2023, in Trials	143 trials	08 Sep 2023
3 ClinicalTrials.gov; limits used as indicated	Condition or disease: Neoplasm; Intervention/Treatment: Metronomic; Age: Child (birth to 17 years); Study phase: Phase 2 or Phase 3; Study type: Interventional		0 additional references	18 Aug 2023
4 ISRCTN registry; limits used as indicated	Neoplasm Metronomic (Phase 2 or Phase 3)		0 additional references	18 Aug 2023
Reference lists	–		36 references	–

Supplemental Table S2 Risk of bias assessment decision criteria

Item	Criteria for judging an unclear, low, or high risk of bias
Random sequence generation (selection bias)	Low: If adequately described Unclear: If not reported High: If not adequately described
Allocation concealment (selection bias)	Low: If adequately described Unclear: If not reported High: If not adequately described
Blinding of participants and personnel (performance bias)	Low: If blinding was addressed though not necessarily performed Unclear: If not reported High: If negated
Blinding of outcome assessment (detection bias)	Low: If adequately described Unclear: If not reported High: Not applicable because blinding of outcome assessment was regarded not appropriate
Incomplete outcome data (attrition bias)	Low: If the authors explained the excluded data and the attrition (lost other than death) was less than 10% in a single arm Unclear: If the attrition (lost other than death) was 10% or more but less than 20% in a single arm High: If the attrition (lost other than death) was 20% or more in a single arm
Selective reporting (reporting bias)	Low: If patient flow and primary/secondary outcomes were provided and treatment groups were evenly balanced for baseline characteristics and an intention-to-treat analysis was applied, and if there were no significant differences between the two treatment groups with respect to condition, treatment, or outcome measurement. Unclear: If there were no pertinent reporting. High: If patient flow and primary/secondary outcomes were not provided, or treatment groups were not evenly balanced for baseline characteristics, or if the authors based their conclusions on invalid biomarkers. Unclear: If there were no reports that favor either low or high risk. High: If patient flow and primary/secondary outcomes were not provided, or treatment groups were not evenly balanced for baseline characteristics, or if the authors based their conclusions on invalid biomarkers.
Other bias	Low: If funding was not industry based Unclear: If funding and conflicts of interest were not reported High: If the sponsor provided industry-based funding and if authors were employees or consultants of the sponsor, or if the early discontinuation of the study was not predefined

Supplemental Table S3 Included studies (n=3)

Study ID	I vs C	Info	Reference	PM	Trials
Bisogno 2019	**MC vs Stop**	**Primary reference for the study**	**Bisogno G, De-Salvo GL, Bergeron C, Gallego-Melcon S, Merks JH, Kelsey A, et al. Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20(11):1566-1575.** [16]	**PM**	**Trials**
		NCT00339118; EudraCT 2005-000217-35	EpSSG (European Soft Tissue Sarcoma Study Group) protocol for non-metastatic rhabdomyosarcoma in children	–	Trials
		2018 ASCO Meeting	Bisogno G, De-Salvo GL, Bergeron C, Jenney M, Merks JHM, Minard-Colin V, et al. Maintenance low-dose chemotherapy in patients with high-risk (HR) rhabdomyosarcoma (RMS): A report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). J Clin Oncol. 2018;36(18_suppl).	–	Trials
		Review of various data of the RMS2005 study	Bisogno G, Minard-Colin V, Zanetti I, Ferrari A, Gallego S, Davila Fajardo R, et al. Nonmetastatic Rhabdomyosarcoma in Children and Adolescents: Overall Results of the European Pediatric Soft Tissue Sarcoma Study Group RMS2005 Study. J Clin Oncol. 2023;41(13):2342-2349.	PM	–
Pramanik 2017	**MC vs Placebo**	**Primary reference for the study**	**Pramanik R, Agarwala S, Gupta YK, Thulkar S, Vishnubhatla S, Batra A, et al. Metronomic chemotherapy vs best supportive care in progressive pediatric solid malignant tumors: A randomized clinical trial. JAMA Oncol. 2017;3(9):1222-1227.** [17]	**PM**	**Trials**
		Follow-up report on quality of life	Pramanik R, Agarwala S, Sreenivas V, Dhawan D, Bakhshi S. Quality of life in paediatric solid tumours: A randomised study of metronomic chemotherapy versus placebo. BMJ Support Palliat Care. 2023;13(2):234-237.	**PM**	**Trials**
		NCT01858571	Low-dose chemotherapy versus best supportive care in progressive pediatric malignancies	–	Trials
		CTRI/2013/06/003734	Low-dose chemotherapy versus best supportive care in progressive and/or refractory pediatric malignancies	–	Trials
		2016 ASCO Meeting	Pramanik R, Bakhshi S, Agarwala S, Gupta YK, Thulkar S, Vishnubhatla S, et al. Metronomic therapy versus best supportive care in progressive pediatric solid malignancies: A double-blind placebo controlled randomized study. J Clin Oncol. 2016;34(15_suppl).	–	Trials
		2017 SIOP Meeting	Pramanik R, Batra A, Bakhshi S, Thulkar S, Sreenivas V, Dhawan D, et al. Progressive paediatric solid tumours other than bone-sarcomas benefit from metronomic chemotherapy: A subgroup analysis from a double-blind placebo controlled randomized study. Pediatr Blood Cancer. 2016;63:S7-S8.	–	Trials
		Biomarker study	Pramanik R, Tyagi A, Agarwala S, Vishnubhatla S, Dhawan D, Bakhshi S. Evaluation of vascular endothelial growth factor (VEGF) and thrombospondin-1 as biomarkers of metronomic chemotherapy in progressive pediatric solid malignancies. Indian Pediatr. 2020;57(6):508-511.	PM	Trials
Senerchia 2017	**MAP–MC vs MAP**	**Primary reference for the study**	**Senerchia AA, Macedo CR, Ferman S, Scopinaro M, Cacciavillano W, Boldrini E, et al. Results of a randomized, prospective clinical trial evaluating metronomic chemotherapy in nonmetastatic patients with high-grade, operable osteosarcomas of the extremities: A report from the Latin American Group of Osteosarcoma Treatment. Cancer 2017;123(6):1003-1010.** [18]	**PM**	**Trials**
		2011 ASCO Meeting	Petrilli AS, Macedo CR, Toledo SRC, Pavoni-Ferreira PC, Grings M, Scopinaro M, et al. Preliminary safety and outcome report of the metronomic chemotherapy from the Latin American osteosarcoma treatment protocol 2006. J Clin Oncol. 2011;29(15_suppl):10032.	–	Trials

Abbreviation. ASCO: American Society of Clinical Oncology; CTRI: Clinical Trials Registry – India; I vs C: intervention versus comparator; MAP: methotrexate, adriamycin, and platinum; MC: Metronomic chemotherapy; NCT: ClinicalTrials.gov identifier (National Clinical Trial number); PM: retrieved from PubMed; SIOP: Societe Internationale d'Oncologie Pediatrique (International Paediatric Oncology Congress); Trials: retrieved from Trials, the Cochrane Central Register of Controlled Trials (CENTRAL)

Supplemental Table S4 Excluded references (n=40)

Registry/Meeting	Reference	Comment	Not of interest:	PM	Trials
NCT00567567	[No author]. Comparing two different myeloablation therapies in treating young patients who are undergoing a stem cell transplant for high-risk neuroblastoma	Comparing two different HDCT	Intervention	–	Trials
EudraCT: 2007-001478-10-PL	[No author]. CWS-2007-HR: A randomised phase-III trial of the Cooperative Weichteilsarkom Studiengruppe for localised high-risk rhabdomyosarcoma and localised rhabdomyosarcoma-like soft tissue sarcoma in children, adolescents, and young adults. CN-01841204	MC vs no therapy, parents refused randomization	Study type	–	Trials
NCT00339118	[No author]. EpSSG (European Soft Tissue Sarcoma Study Group) protocol for non-metastatic rhabdomyosarcoma in children	Related to Bisogno 2019 [16]	Registry	–	Trials
ACTRN12616001524482	[No author]. EWING 2008 Clinical trial for the treatment of Localized and Disseminated Ewing sarcoma	HDCT	Intervention	–	Trials
NCT00078988	[No author]. High-dose chemotherapy plus autologous stem cell transplantation compared with intermediate-dose chemotherapy plus autologous stem cell transplantation with or without isotretinoin in treating young patients with recurrent high-grade gliomas	Gliomas	Population	–	Trials
NCT01858571	[No author]. Low-dose chemotherapy versus best supportive care in progressive pediatric malignancies	Related to Pramanik 2017 [17]	Registry	–	Trials
CTRI/2013/06/003734	[No author]. Low-dose chemotherapy versus best supportive care in progressive and/or refractory pediatric malignancies	Related to Pramanik 2017 [17]	Registry	–	Trials
EudraCT: 2018-000096-32	[No author]. Metro-PD1: A phase I/II trial evaluating anti-PD1 (Nivolumab) in combination with metronomic chemotherapy in children and teenagers with refractory /relapsing solid tumors or lymphoma.	MC vs MC + Nivolumab	Comparator	–	Trials
NCT01467986	[No author]. Multimodal molecular targeted therapy to treat relapsed or refractory high-risk neuroblastoma (RIST-rNB-2011)	Comparing two molecular targeted therapies	Intervention	–	Trials
NCT03585465	[No author]. Nivolumab in combination with metronomic chemotherapy in paediatrics refractory / relapsing solid tumors or lymphoma.	MC vs MC + Nivolumab	Comparator	–	Trials
NCT00688376; EUCTR2007-005442-20-GB.	[No author]. Randomized, double-blind, placebo-controlled study of efficacy and safety of donepezil hydrochloride in preadolescent and adolescent children with attention impairment following cancer treatment - amend 02.	Attention Impairment; Donepezil vs Placebo	Population	–	Trials
–	Andre N, Rome A, Coze C, Padovani L, Pasquier E, Camoin L, et al. Metronomic etoposide/cyclophosphamide/celecoxib regimen given to children and adolescents with refractory cancer: a preliminary monocentric study. Clin Ther. 2008;30(7):1336-1340.	MC in a single-arm study	Study type	–	Trials
–	Andre N, Corradini N, Shaked Y. Metronomic maintenance therapy for rhabdomyosarcoma. Trends Cancer. 2019;5(12):756-759.	Letter relates to NCT00339118	Study type	PM	–
NCT00526318	Berthold F, Boos J, Burdach S, Erttmann R, Henze G, Hermann J, et al. Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: A randomised controlled trial. Lancet Oncol. 2005;6(9):649-658.	MC vs HDCT	Comparator	PM	Trials
NCT00526318	Berthold F, Ernst A, Hero B, Klingebiel T, Kremens B, Schilling FH, et al. Long-term outcomes of the GPOH NB97 trial for children with high-risk neuroblastoma comparing high-dose chemotherapy with autologous stem cell transplantation and oral chemotherapy as consolidation. Br J Cancer. 2018;119(3):282-290.	MC vs HDCT	Comparator	PM	Trials
2018 ASCO Meeting	Bisogno G, De-Salvo GL, Bergeron C, Jenney M, Merks JHM, Minard-Colin V, et al. Maintenance low-dose chemotherapy in patients with high-risk (HR) rhabdomyosarcoma (RMS): A report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). J Clin Oncol. 2018;36(18_suppl).	Related to Bisogno 2019 [16]	Meeting	–	Trials

–	Bisogno G, Minard-Colin V, Zanetti I, Ferrari A, Gallego S, Davila Fajardo R, et al. Nonmetastatic Rhabdomyosarcoma in Children and Adolescents: Overall Results of the European Pediatric Soft Tissue Sarcoma Study Group RMS2005 Study. J Clin Oncol. 2023;41(13):2342-2349.	Related to Bisogno 2019 [16]	Study type	PM	–
–	Bisogno G, Minard-Colin V, Jenney M, Ferrari A, Chisholm J, Di Carlo D, et ak. Maintenance Chemotherapy for Patients with Rhabdomyosarcoma. Cancers (Basel). 2023;15(15):4012.	Review related to Bisogno 2019 [16]	Study type	PM	–
NCT00278070	Briasoulis E, Aravantinos G, Kouvatseas G, Pappas P, Biziota E, Sainis I, et al. Dose selection trial of metronomic oral vinorelbine monotherapy in patients with metastatic cancer: a hellenic cooperative oncology group clinical translational study. BMC Cancer. 2013;13:263.	Breast, Prostate, and Non Small Cell Lung Cancer	Population	–	Trials
–	Casanova M, Ferrari A, Bisogno G, Merks JH, De-Salvo GL, Meazza C, et al. Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European rhabdomyosarcoma protocol. Cancer. 2004;101(7):1664-1671.	MC + HDCT in a single-arm study	Study type	–	Trials
NCT00643565	Chisholm JC, Merks JHM, Casanova M, Bisogno G, Orbach D, Gentet JC, et al. Open-label, multicentre, randomised, phase II study of the EpSSG and the ITCC evaluating the addition of bevacizumab to chemotherapy in childhood and adolescent patients with metastatic soft tissue sarcoma (the BERNIE study). Eur J Cancer. 2017;83:177-184.	CT + Bevacizumb (monoclonal antibody) vs CT	Intervention	PM	–
NCT00061893	Felgenhauer JL, Nieder ML, Krailo MD, Bernstein ML, Henry DW, Malkin D, et al. A pilot study of low-dose anti-angiogenic chemotherapy in combination with standard multiagent chemotherapy for patients with newly diagnosed metastatic Ewing sarcoma family of tumors: A Children's Oncology Group (COG) Phase II study NCT00061893. Pediatr Blood Cancer. 2013;60(3):409-414.	MC + standard chemotherapy in a single-arm study	Study type	–	Trials
NCT00538239; 2012, ASPHO Meeting	Iannone R, Yang Y, Elias A, Peylan-Ramu N, Judson I, Nunes J, et al. Ridaforolimus as maintenance therapy in advanced sarcoma patients following clinical benefit from prior chemotherapy: Pediatric data from the phase 3 sarcoma multi-center clinical evaluation of the efficacy of ridaforolimus (SUCCEED) trial. Pediatr Blood Cancer. 2012,58(7),1081	Ridaforolimus (protein inhibitor) vs Placebo	Intervention	–	Trials
–	Klingebiel T, Boos J, Beske F, Hallmen E, Int-Veen C, Dantonello T, Treuner J, Gadner H, Marky I, Kazanowska B, Koscielniak E. Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial. Pediatr Blood Cancer. 2008;50(4):739-745.	MC vs HDCT	Comparator	–	Trials
–	Koscielniak E, Blank B, Vokuhl C, Kazanowska B, Ladenstein R, Niggli F, et al. Long-term clinical outcome and prognostic factors of children and adolescents with localized rhabdomyosarcoma treated on the CWS-2002P protocol. Cancers (Basel). 2022;14(4):899.	MC vs no therapy, based on the decision of the treating physician	Study type	PM	–
2017 GPOH Meeting	Koscielniak E, Sparber-Sauer M, Scheer M, Klingebiel T. CWS-2007-HR A randomised phase-III trial for localised high-risk rhabdomyosarcoma and rhabdomyosarcoma-like soft tissue sarcoma (STS) in children, adolescents, and young adults. Status update. Monatsschr Kinderheilkd. 2017;165(7):645. CN-01572093.	MC vs no therapy, parents refused randomization	Study type	–	Trials
–	Kyr M, Polaskova K, Kuttnerova Z, Merta T, Neradil J, Berkovcova J, et al. Individualization of treatment improves the survival of children with high-risk solid tumors: Comparative patient series analysis in a real-life scenario. Front Oncol. 2019;9:644.	Comparative case series analysis including MC	Study type	PM	–
NCT01704716	Ladenstein R, Pötschger U, Pearson ADJ, Brock P, Luksch R, Castel V, et al. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): An international, randomised, multi-arm, open-label, phase 3 trial. Lancet Oncol. 2017;18(4):500-514.	Two HDCT arms, all patients received MC	Intervention	PM	Trials
NCT03585465	Leblond P, Probst A, Entz-Werle N, Defachelles AS, Aerts I, Bogart E, et al. Metro-Pd1: A phase-1 feasability study evaluating anti-Pd1 (nivolumab) in combination with metronomic chemotherapy in children and teenagers with refractory/relapsing solid tumors or lymphoma.	MC vs MC + Nivolumab	Comparator	–	Trials
–	Longhi A, Cesari M, Serra M, Mariani E. Long-term follow-up of a randomized study of oral etoposide versus viscum album fermentatum pini as maintenance therapy in osteosarcoma patients in complete surgical remission after second relapse. Sarcoma. 2020;2020:8260730.	MC vs European mistletoe	Comparator	–	Trials

–	Minard-Colin V, Ichante JL, Nguyen L, Paci A, Orbach D, Bergeron C, et al. Phase II study of vinorelbine and continuous low doses cyclophosphamide in children and young adults with a relapsed or refractory malignant solid tumour: good tolerance profile and efficacy in rhabdomyosarcoma--a report from the Societe Francaise des Cancers et leucemies de l'Enfant et de l'adolescent (SFCE). Eur J Cancer. 2012 Oct;48(15):2409-2416.	MC in a single-arm study	Study type	–	Trials
2017 ASPHO Meeting	Ortiz D, Harden A, Ruiz-Mesa C, Podda A. Combination of bevacizumab and taxane containing regimen, hyperthermic intraperitoneal chemotherapy (HIPEC) and tyrosine kinase inhibitor (TKI) trametenib for the treatment of aggressive metastatic pediatric angiosarcoma. Pediatr Blood Cancer. 2017;64:S82.	Case report on bevacizumab (monoclonal antibody) for angiosarcoma	Intervention	–	Trials
2011 ASCO Meeting	Petrilli AS, Macedo CR, Toledo SRC, Pavoni-Ferreira PC, Grings M, Scopinaro M, et al. Preliminary safety and outcome report of the metronomic chemotherapy from the Latin American osteosarcoma treatment protocol 2006. J Clin Oncol. 2011;29(15_suppl):10032.	Related to Senerchia 2017 [18]	Meeting	–	Trials
2016 ASCO Meeting	Pramanik R, Bakhshi S, Agarwala S, Gupta YK, Thulkar S, Vishnubhatla S, et al. Metronomic chemotherapy versus best supportive care in progressive pediatric solid malignancies: A double-blind placebo controlled randomized study. J Clin Oncol. 2016;34(15_suppl).	Related to Pramanik 2017 [17]	Meeting	–	Trials
2017 SIOP Meeting	Pramanik R, Batra A, Bakhshi S, Thulkar S, Sreenivas V, Dhawan D, et al. Progressive paediatric solid tumours other than bone-sarcomas benefit from metronomic chemotherapy: A subgroup analysis from a double-blind placebo controlled randomized study. Pediatr Blood Cancer. 2016;63:S7-S8.	Related to Pramanik 2017 [17]	Meeting	–	Trials
NCT01858571	Pramanik R, Tyagi A, Agarwala S, Vishnubhatla S, Dhawan D, Bakhshi S. Evaluation of vascular endothelial growth factor (VEGF) and thrombospondin-1 as biomarkers of metronomic chemotherapy in progressive pediatric solid malignancies. Indian Pediatr. 2020;57(6):508-511.	Related to Pramanik 2017 [17]	Outcome	PM	–
NCT00643565	Schoot RA, Chisholm JC, Casanova M, Minard-Colin V, Geoerger B, Cameron AL, et al. Metastatic rhabdomyosarcoma: Results of the European Paediatric Soft Tissue Sarcoma study group MTS 2008 study and pooled analysis with the concurrent BERNIE study. J Clin Oncol. 2022;40(32):3730-3740.	CT + Bevacizumb (monoclonal antibody) vs CT	Intervention	PM	–
–	Simon T, Hero B, Faldum A, Handgretinger R, Schrappe M, Klingebiel T, et al. Long term outcome of high-risk neuroblastoma patients after immunotherapy with antibody ch14.18 or oral metronomic chemotherapy. BMC Cancer. 2011;11:21.	MT vs no therapy, not randomized	Study type	–	Trials
–	Traore F, Togo B, Pasquier E, Dembele A, Andre N. Preliminary evaluation of children treated with metronomic chemotherapy and valproic acid in a low-income country: Metro-Mali-02. Indian J Cancer. 2013;50(3):250-253.	MC in a single-arm study	Study type	–	Trials
–	Zapletalova D, Andre N, Deak L, Kyr M, Bajciova V, Mudry P, et al. Metronomic chemotherapy with the COMBAT regimen in advanced pediatric malignancies: a multicenter experience. Oncology. 2012;82(5):249-260.	MC in a single-arm study	Study type	–	Trials

Abbreviation. ACTRN: Australian New Zealand Clinical Trials Registry (ANZCTR) registration number; ASCO: American Society of Clinical Oncology; ASPHO: American Society of Pediatric Hematology/Oncology; CT: chemotherapy; EUCTR: European Union Clinical Trials Register; EudraCT: European Union Drug Regulating Authorities Clinical Trials Database; GPOH: Gesellschaft für Pädiatrische Onkologie und Hämatolgie (Society for Pediatric Oncology and Hematology); HDCT: high-dose chemotherapy; MC: Metronomic chemotherapy; NCT: ClinicalTrials.gov identifier (National Clinical Trial number); PM: retrieved from PubMed; SIOP: Societe Internationale d'Oncologie Pediatrique (International Paediatric Oncology Congress); Trials: retrieved from Trials, the Cochrane Central Register of Controlled Trials (CENTRAL)

Supplemental Table S5 Characteristics of interventions

	Bisogno 2019[(a)] [16]	**Pramanik 2017**[(b)] [17]	**Senerchia 2017**[(c)] [18]
Pretreatment before randomization	Concerning both groups: Standard chemotherapy comprised nine cycles of the IVA or IVADo chemotherapy, and surgery or radiotherapy, or both. IVA Ifosfamide 3 g/sqm days 1 and 2 Vincristine 1.5 mg/sqm weekly during the first 7 weeks then only on day 1 of each cycle (maximum dose 2 mg) Actinomycin D (= Dactinomycin) 1.5 mg/sqm on day 1 (maximum dose 2 mg) IVADo IVA plus doxorubicin 30 mg/sqm on days 1 and 2 in the initial four cycles of chemotherapy. Surgery: Marginal resection was acceptable, provided it was followed by radiotherapy. Radiotherapy 41.4 Gy to 50.4 Gy)	n.r.	Concerning both groups: Induction with two 5-week MAP chemotherapy cycles during weeks 1 to 10 followed by complete resection of the primary tumor in week 11 or 12. MAP Methotrexate 12 g/sqm Adriamycin (= doxorubicin) 75 mg/sqm Platinum (= cisplatin) 120 mg/sqm Adriamycin (= doxorubicin) and platinum (= cisplatin) were administered in weeks 1 and 6, and methotrexate was administered in weeks 4, 5, 9, and 10.
Pretreatment after randomization	n.r.	n.r.	Concerning both groups: After surgery, consenting patients were randomly assigned to complete 31 weeks of MAP with cisplatin replaced by intravenous dexrazoxane (375 mg/sqm on days 1 and 2) in the last 2 cycles.
Metronomic chemotherapy after randomization	Metronomic chemotherapy (n=185): Six 4-week cycles of intravenous vinorelbine 25 mg/sqm on days 1, 8, and 15; during the same time: oral cyclophosphamide 25 mg/sqm per day given continuously for 24 weeks on an outpatient basis.	Metronomic chemotherapy (n=56): Alternating cycles of cycle A and B (each cycle included 3 weeks of drug administration) and best supportive care[(a)] Cycle A: Daily oral thalidomide (3mg/kg), daily oral celecoxib 200 mg to 800 mg, and daily oral etoposide (50 mg/sqm). Cycle B: Daily oral thalidomide (3mg/kg), daily oral celecoxib 200 mg to 800 mg, and daily oral cyclophosphamide 2.5 mg/kg to a maximum of 100 mg/day.	Treatment continued after 31 weeks chemotherapy. Metronomic chemotherapy was applied from week 32 to week 104: oral cyclophosphamide (25 mg/sqm daily) and oral methotrexate (1.5 mg/sqm twice daily twice per week)
Comparator after randomization	Stop treatment (n=186)	Placebo (n=52): Capsules of same size and color as used in metronomic chemotherapy and best supportive care[(a)]	Treatment stopped after 31 weeks chemotherapy.

Abbreviations. IVA: ifosfamide, vincristine, and actinomycin D (= dactinomycin); IVADo: ifosfamide, vincristine, actinomycin D (= dactinomycin), and doxorubicin; MAP: methotrexate, adriamycin (= doxorubicin), and platinum (= cisplatin); sqm: square meter = m^2;

[(a)] Pramanik 2017 [17]: Best supportive care included management of pain as per the World Health Organization standard for pain management, blood product transfusion, management of infection, and malodorous necrotic masses.

Supplemental Table S6 Risk of bias assessment results

Item	**Bisogno 2019** [16]	**Pramanik 2017** [17]	**Senerchia 2017** [18]
Random sequence generation (selection bias)	Randomisation was done with a web-based system provided by CINECA (Bologna, Italy), a non-profit, inter-university consortium thus LOW.	Randomization was based on a computer-generated table of random numbers, thus LOW.	Not reported, thus UNCLEAR.
Allocation concealment (selection bias)	Not reported, thus UNCLEAR.	Not reported, thus UNCLEAR.	Not reported, thus UNCLEAR.
Blinding of participants and personnel (performance bias)	Neither investigators nor patients were masked to treatment allocation, but we believe that these issues may not influence the results, thus UNCLEAR.	Masking was double blind (subject, caregiver), thus LOW.	Not reported, thus UNCLEAR.
Blinding of outcome assessment (detection bias)	Not reported, thus UNCLEAR.	Not reported, thus UNCLEAR.	Not reported, thus UNCLEAR.
Incomplete outcome data (attrition bias)	Attrition rates (lost other than death) were low and comparable between groups, thus LOW.	Attrition rates (lost other than death) were low and comparable between groups, thus LOW.	Attrition (lost other than death) was more than 20% in a single arm. We are unsure whether this affects the outcome since the authors applied an intention-to-treat analysis. Thus, we judged the risk of bias to be UNCLEAR.
Selective reporting (reporting bias)	Patient flow and primary/secondary patient-centered outcomes were provided, characteristics were balanced, and intention-to-treat analysis was applied, thus LOW.	Patient flow and primary/secondary patient-centered outcomes were provided, characteristics were balanced, and intention-to-treat analysis was applied, thus LOW.	Patient flow and primary/secondary patient-centered outcomes were provided, characteristics were balanced, and intention-to-treat analysis was applied, thus LOW.
Other bias	Sponsor was the European paediatric Soft tissue sarcoma Study Group (EpSSG), thus LOW.	Sponsor was All India Institute of Medical Sciences (AIIMS), thus LOW.	Sponsor was the Federal University of Sao Paulo (Portuguese: Universidade Federal de Sao Paulo, UNIFESP), thus LOW.