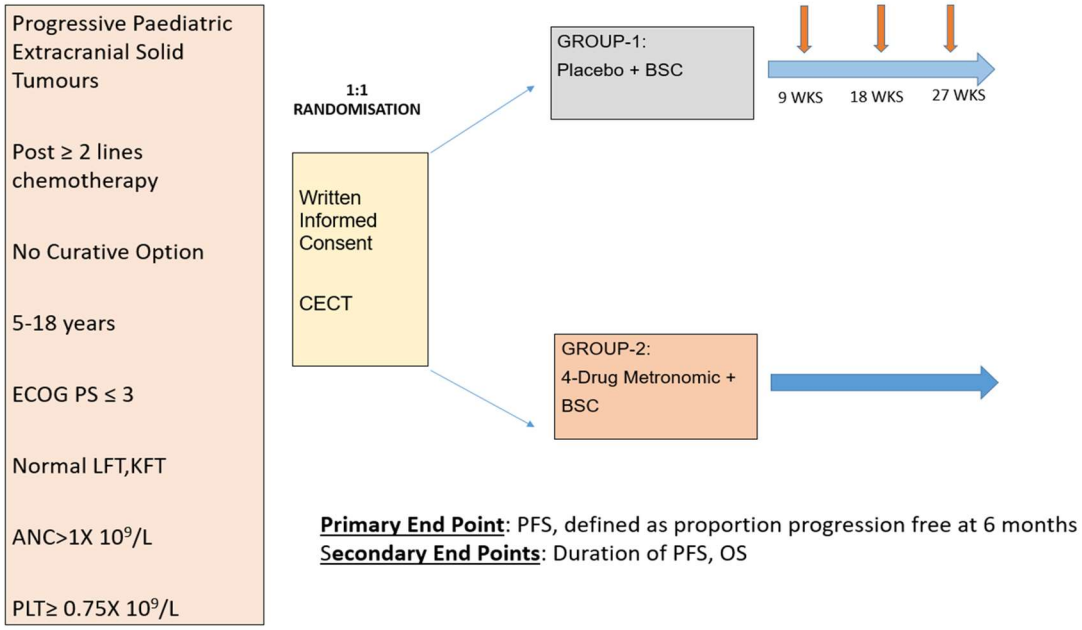
Supplementary Online Content

Pramanik R, Agarwala S, Gupta YK, et al. Metronomic chemotherapy vs best supportive care in progressive pediatric solid malignant tumors: a randomized clinical trial. *JAMA Oncol.* Published online April 6, 2017. doi:10.1001/jamaoncol.2017.0324

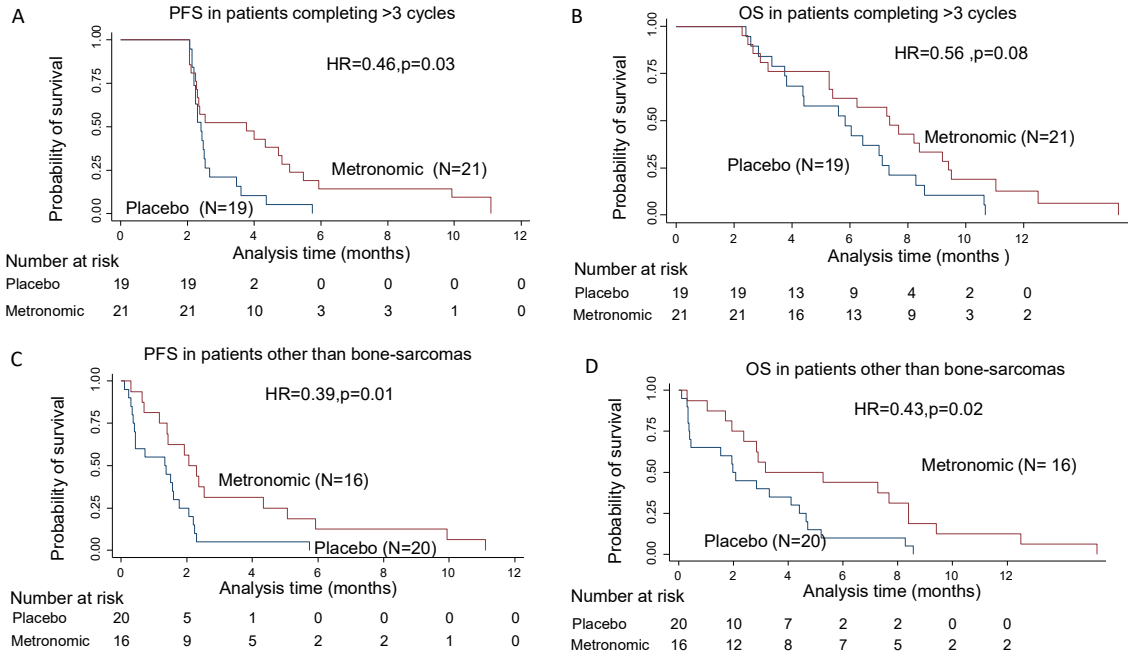
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Study Design



LFT= Liver Function Tests, KFT= Kidney Function Tests, ECOG PS= Eastern Cooperative Oncology Group Performance Status, BSC= Best Supportive Care, ANC= Absolute Neutrophil count, PLT= platelet count, CECT= Contrast Enhanced Compute tomography, PFS= Progression free survival, OS= Overall survival.

eFigure 2. Kaplan-Meier Curves for Progression-Free Survival (A) and Overall Survival (B) in Patients Completing More Than 3 Cycles of Therapy (n = 40) and Kaplan-Meier Curves for Progression-Free Survival (C) and Overall Survival (D) in Patients With Histologic Subtypes Other Than Bone Sarcomas (n = 36)



HR= Hazard ratio, PFS=progression free survival, OS= overall survival

eTable 1. Drug Schedule Used in the Study

Drug Code	Drugs	Cycle A (3 weeks)	Cycle B (3 weeks)
Cap1	Thalidomide (3mg/kg) o.d.	Daily	Daily
Cap2	Celecoxib 100 mg b.i.d for patients < 20 kg, 200 mg b.i.d for patients 20–50 kg, 400 mg b.i.d for patients > 50 kg,	Daily	Daily
Cap3	Etoposide (50mg/m^2) o.d.	Daily	----
Tab4	Cyclophosphamide (2.5mg/kg)(max=100mg) o.d.	----	Daily

One cycle consists of 3 weeks of drug therapy (Either A or B). Cycle A alternates with Cycle B every three weeks. b.i.d = twice a day. o.d = once a day.

Rationale of various drugs used in metronomic chemotherapy

This metronomics regimen was a combination of various drugs of different class having antiangiogenic, immunostimulatory as well as apoptotic properties. This regimen was used by Kieran et al in their feasibility study as the drugs were cheap, oral, easily available, had good safety profile and the regimen embodied the principles of metronomics.(1) Cyclophosphamide, an alkylating agent, has selective toxicity on T–reg cells. Celecoxib, a Cyclo-oxygenase 2 (COX 2) inhibitors also show antitumor activity, caused partly by inhibition of angiogenesis. Thalidomide, an immunomodulator is known to have powerful anti-angiogenic activity by degrading mRNA of a number of peptide-signalling molecules such as fibroblast growth factor and tumour necrosis factor- alpha (TNF-α). It also inhibits VEGF and b-FGF induced angiogenesis. It has been proposed that having a break from low dose continuous drugs prevents the development of resistance and also may have a therapeutic benefit according to the 4D effect (drug driven dependency and deprivation).(2)**These principles of metronomic inspired us to adopt this regimen for our protocol.**

eTable 2. Rationale of the 4-Drug Antiangiogenic Regimen[1]

	Thalidomide	**Celecoxib**	**Etoposide**	**Cyclophosphamide**
Oral	**Yes**	**Yes**	**Yes**	**Yes**
Mechanism of Action	Inhibits VEGF & b-FGF induced neovascularisation	Inhibits Cox in immature endothelial cells	Inhibits Topoisomerase-II in dividing endothelial cells	Alkylates DNA in immature endothelial cells.
Toxicity as a single agent	Constipation, sedation	Stomach upset, renal damage	Myelosuppression, second malignancies	Myelosuppression, second malignancies
Tolerability as a single agent	Good	Good	Good	Good
Human Clinical data demonstrating clinical activity	Good	Good	Good	Good

VEGF= Vascular endothelial growth factor, b-FGF= beta fibroblastic growth factor, Cox= cyclooxygenase, DNA= deoxyribonucleic acid.

eREFERENCES

1. Kieran MW, Turner CD, Rubin JB, Chi SN, Zimmerman MA, Chordas C, et al. A feasibility trial of antiangiogenic (metronomic) chemotherapy in pediatric patients with recurrent or progressive cancer. J PediatrHematolOncol. 2005 Nov;27(11):573–81.

2. Pasquier E, Kavallaris M, André N. Metronomic chemotherapy: new rationale for new directions. Nat Rev ClinOncol. 2010 Aug;7(8):455–65.

eTable 3. Comparison of Baseline Characteristics of the 2 Study Groups

	Placebo	Metronomic	P- value
Total no. of Patients	52	56	
Median Age (range) years	15 (5-18)	13 (5-18)	0.362
Sex (M:F) Males: Females:	3.3:1 40 12	3:1 42 14	0.82
Performance Status 0 1 2 3	 1 (2%) 19 (36%) 21 (40%) 11 (21%)	 3 (5%) 18 (32%) 25 (44%) 10 (17%)	0.73
Diagnosis: **Bone Sarcoma(PNET*/Osteosarcoma)** **Neuroblastoma** **Rhabdomyosarcoma** **Esthesioneuroblastoma** **Non-rhabdomyosarcoma Soft –tissue sarcoma** **Others** **Retinoblastoma**	 32 (61%) 5 (10%) 6 (11%) 1 (2%) 4 (8%) 3 (6%) 1 (2%)	 40 (71%) 5 (9%) 3 (5%) 1 (2%) 2 (4%) 3 (5%) 2 (4%)	0.44
Mean Haemoglobin(g/dl) (SD)	10.7 ± 1.4	10.61 ± 1.3	0.86
Mean Platelets (X 10^9/l) SD	2.14 ± 0.66	2.54 ± 2.2	0.21
Mean albumin (g/dl) SD	4.04 ± 0.46	4.15 ± 0.56	0.25
Mean ANC$ (X 10^9/l) **SD**	4.72 ± 2.963	5.03 ± 4.06	0.46
No. of previous lines: **2** **3** **4**	 48 4 0	 53 2 1	0.43

*PNET: primitive neuroectodermal tumour,$ ANC: Absolute Neutrophil Count. (All percentage points have been showed rounded to the nearest whole number)

eTable 4. Results of the Primary and Secondary End Points of the Study

Outcome Variables	Placebo (N=52)	Metronomic (N=56)	P-value
A) **Primary End Point**			
Patients progressed at/before 6 months	52 (100%)	53 (94.6%)	0.24
Patients not progressed at 6 months	0	3	
B) **Response Rates:**			
Complete Response (CR)(%)	0/52	0/56	
Partial Response (PR) (%)	0/52	2/56 (3.5%)	
Stable Disease (for > 3months) (%)	0/52	8/56 (14.2%)	
Overall Response Rate(ORR)	0/52	2/56 (3.5%)	
Disease Control Rate (DCR)*	0/52	10/56(17.8%)	*0.27
Best Response @ 9 weeks	SD=5	PR=2, SD=8	
Best Response @ 18 weeks	SD=1	PR=0, SD=3	
C) Progression Free Survival(PFS)			
Median PFS (months)	(1.53 mon)	(1.63 mon)	0.07
(Days)	46	49	
[95% CI]	(33-58)	(43-59)	
D) Overall Survival(OS)			
Median OS (months)	(2.83 mon)	(2.83 mon)	0.13
(Days)	85	85	
[95% CI]	(61-123)	(69-113)	

ORR= overall response rate= CR+PR, DCR= Disease control rate= CR+PR+SD.

eTable 5. Toxic Effects Recorded During the Study

	Placebo(N=52) (Grade1-2)	Metronomic(N=56) (Grade 1-2)	Placebo(N=52) (Grade 3-4)	Metronomic (N=56) (Grade 3-4)
Anaemia	43 (82.6%)	34 (60%)	4 (7.1%)	11(11.7%)
Neutropenia	0	1 (1.7%)	0	6 (10.7%)
Thrombocytopenia	1 (1.9%)	7 (12.4%)	0	6 (10.7%)
Febrile Neutropenia	0	0	0	5 (8.8%)
Oral Mucositis	0	5 (8.8%)	0	3(5.3%)
Diarrhoea	0	2 (3.5%)	0	0
Non-neutropenic fever	0	13 Episodes	0	0
Peripheral Neuropathy	0	0	0	0
Toxic Deaths	0	0	0	0
Deep Vein Thrombosis	0	0	0	0
Vomiting	0	4 (7%)	0	0
Altered Liver Function Tests	1(1.9%)	1(1.7%)	0	0
Altered Renal Function Tests	0	0	0	0
Alopecia	0	5 (8.8%)	0	0

eTable 6. Supportive Care Provided in the Study

Intervention	**Placebo (N=52)**	**Metronomic (N=56)**
Number of patients requiring visits to Emergency	7(13.4%)	11(12.5%)
Number of patients requiring admission in ward	2 (3.8%)	7 (12.5%)
Dose decreased	0	8 (14.2%)
Dose interrupted due to patient compliance	2 (3.8%)	1 (1.7%)
Dose Delayed	2 (3.8%)	9 (16%)
Packed Red Blood Cells during treatment phase	4 (2 patients)	24(11 patients)
Packed Red bold cells after Progression	5 (2 patients)	18(8 patients)
Random Donor platelet units during Treatment Phase	0	8 (2 patients)
Intercostal chest tube drain insertion	5 (9.6%)	3 (5.3%)
Antibiotics Numberof patients Oral Intravenous Average duration per patient **Number of patients requiring Granulocyte Colony stimulating factor**		 11 (19.6%) 5 (8.9%) 6 (10.7%) 5 days 6 (10.7%)

eTable 7. Comparison of Toxicity Profiles in the Subsets That Benefited From Metronomic Therapy (ie, Patients Tolerating Metronomic Therapy for ≥3 Cycles and the Nonbone Sarcomas)

	Placebo	Metronomic	P –value*
Patients tolerating ≥3 cycles of therapy			
Neutropenia (grade ¾)	0	3	0.14
Thrombocytopenia (grade ¾)	0	3	0.14
Anaemia(grade ¾)	2	3	0.59
Mucositis	0	2	0.27
Diarrhoea	0	0	-
Febrile neutropenia	0	2	0.27
Toxic deaths	0	0	-
Non –bone sarcomas			
Neutropenia(grade ¾)	0	3	0.14
Thrombocytopenia(grade ¾)	0	1	0.52
Anaemia(grade ¾)	1	4	0.20
Mucositis	0	0	-
Diarrhoea	0	0	-
Febrile neutropenia	0	2	0.27
Toxic deaths	0	0	-

* Fisher's exact test was used to compare the groups.

eAppendix. Evidence Implications

Evidence before this study:

Metronomic chemotherapy is often used in a palliative setting in relapsed progressive tumours, but scepticism and empiricism flank its usage due to lack of level 1 evidence. Majority of studies are retrospective or small single arm studies and anecdotal case reports, and that too in extremely heterogeneous population. Certain patients may remain stable on their own while others progress rapidly. So to truly appreciate the effects of metronomics in the palliative setting we need a randomized controlled study, which is an unmet need in medical literature on metronomics.

Added value of this study:

This is the first randomized comparison of low dose oral antiangiogenic chemotherapy (metronomic therapy) versus placebo in paediatric population. Never before has this been compared to best supportive care in the palliative setting. Our study is a PI initiated "double blind" and placebo controlled RCT giving answer to an important unanswered clinical question.

Implications of all the available evidence:

It has significant clinical implications in oncology clinical practice in general and paediatric tumours in particular. Metronomic chemotherapy is not an effective blanket palliative treatment for every relapsed refractory paediatric solid tumour. Histology does matter in this setting. Tumours other than osteosarcomas and PNETs benefit from this therapy.