

1 **Original Version dated 17 May 2013**

2 **Low Dose Chemotherapy Versus Best Supportive Care in Progressive Pediatric Malignancies:**
3 **Double Blind Placebo Controlled Randomized Study**

4 Information provided by (Principal Investigator):

5 Sameer Bakhshi, All India Institute of Medical Sciences, New Delhi

6 **ClinicalTrials.gov Identifier:NCT01858571**

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8 **Purpose of the Study:**

9 Many of the paediatric malignancies are not curable on progression on front line or 2nd line
10 chemotherapy. Further therapy with conventional drugs imposes many side effects and decreases
11 the QOL. The usual therapy offered to such patients is best supportive care. Metronomic
12 chemotherapy can induce tumor stabilization or tumor responses in patients with cancer that are
13 refractory or have relapsed after conventional chemotherapy. Whether metronomic therapy is
14 better than best supportive care is not known. In order to do so, a study is required which may
15 compare metronomic therapy with a placebo therapy on PFS and QOL in relapsed refractory cases of
16 paediatric solid tumours who have failed at least two lines of chemotherapy.

17

18 **HYPOTHESIS**

19 The investigators hypothesize that metronomic chemotherapy in progressive paediatric malignancy
20 will improve PFS and QOL. If validated, then this form for therapy will be an option for both the
21 patients and the clinicians, who are left with just an option of best supportive care in such situations
22 of progressive paediatric cancers despite multiple lines of chemotherapy.

23

24 **Condition: Malignant Childhood Neoplasm.**

25 **Intervention: Drug: Low dose chemotherapy.**

26 **Phase: Phase 3**

27 **Study Type: Interventional**

28 **Study Design: Allocation: Randomized**

29 **Endpoint Classification: Safety/Efficacy Study**

30 **Intervention Model: Parallel Assignment**

31 **Masking: Double Blind (Subject, Caregiver)**

32 **Primary Purpose: Treatment**

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34 **Primary Outcome Measures:** •Progression free survival

35 **Secondary Outcome Measures:** •Overall Survival

36 **Other Outcome Measures:** •Quality of life

37 •Bio marker of angiogenesis (VEGF), Thrombospondin-1

38 **Eligibility:**

39 Ages Eligible for Study: 5 Years to 18 Years

40 Genders Eligible for Study: Both

41 **Inclusion Criteria:**

42 1.Refractory/Progressive non hematopoietic extracranial solid tumours following treatment with at
43 least 2 lines of chemotherapy.

44 2.Good performance status(at least ambulatory)

45 3.Age: 5-18 years

46 4.Recovered from all acute toxic effects of earlier therapy

47 5.Absolute neutrophil count > $1 \times 10^9/L$

48 6.Absolute platelet count > $75 \times 10^9/L$

49 7.Normal renal functions

50 8.Serum bilirubin <1.5 times the upper limit of normal, and the serum aspartate aminotransferase
51 and alanine aminotransferase < 5 times the upper limit of normal.

52 **Exclusion Criteria:**

53 1.Uncontrolled concurrent illness or active infection

54 2.Positive serology for human immunodeficiency.

55 3.Unable to swallow oral medication

56 4.Pregnant and breast-feeding

57

58 **Arms**

59 **1. ARM 1: Experimental: Low dose chemotherapy**

60 Alternating cycles of Cycle A and B (Each cycle includes 3 weeks of drug administration) with each
61 drug rounded off to the nearest tablet/capsule size.

62 **Cycle A**

63 •Daily oral Thalidomide (at 3mg/kg)

64 •Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg
65 BID for patients > 50 kg)

66 •Daily oral Etoposide (50 mg/m²/d)

67 **Cycle B**

- 68 •Daily oral Thalidomide (at 3mg/kg)
- 69 •Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg
- 70 BID for patients > 50 kg)
- 71 •Daily oral Cyclophosphamide (2.5 mg/kg/d to a maximum of 100 mg/d) every 21 days
- 72 Drug: Low dose chemotherapy

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

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74 **Table 1: Drug schedule used in the study.**

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77 **2. ARM2: Placebo Comparator and Best supportive care**

78 **Placebo:** Alternating cycles of Cycle A and B (Each cycle includes 3 weeks of drug administration)

- 79 •Capsules of same size and colour as used in metronomic therapy

80 **Best supportive care**

- 81 •Management of pain as per WHO standard for pain management

82 **Baseline Assessment**

83

84 1. Basic Blood investigations:

- 85 • Complete Blood Counts.
- 86 • Liver and Kidney Function tests

87 2. Radiological Investigations:

- 88 • Contrast enhanced scan of chest and involved site.

89 3. Assessment of biomarkers of angiogenesis

- 90 • Serum/ plasma sample to measure VEGF, bFGF, endostatin, and thrombospondin-1 levels.

91 4. Assessment of QOL by PedsQL- Cancer Module (version 3)

92

93 **Before Each Cycle**

94 1. Basic Blood investigations:

- 95 • Complete Blood Counts.
- 96 • Liver and Kidney Function tests

97 **Interim (Post 3 cycles: at 9 weeks) and (Post 6 cycles: at 18 weeks)**

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99 1. Basic Blood investigations:

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108 Further Assessments: Every 3 monthly till Progression

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115 **Assessment at Time of Progression**

116 Assessment of biomarkers of angiogenesis

- 117 • Serum/ plasma sample to measure VEGF and thrombospondin-1 levels.

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123 **Statistical analysis:**

124 Descriptive statistics such as mean, median, standard deviation and range will be used to describe
125 baseline demographic and clinical profile of all patients. To see association between two categorical
126 variables, Chi-square test will be used. To see association between two continuous variables, t-test
127 or Wilcoxon rank sum test will be used. Survivals will be depicted using Kaplan Meier plots.
128 Difference between groups will be analysed using log-rank test. Proportional survival at specific
129 times will be determined using Kaplan Meier survival analysis. P-value <0.05 will be considered as
130 significant. Data analyses will be performed using statistical software packages Stata 11.2.

131 **Sample Size Calculation:**

132 From an exhaustive review of literature, data on PFS in solid extracranial tumours paediatric
133 tumours after failing two lines of treatment, without any further therapy is not available from
134 anywhere. From our experience we know that most of such advanced patients will progress within
135 few weeks to months time. Therefore, we make the modest assumption that 95% of such patients
136 will progress by 6 months without therapy and a 20% improvement is a standard parameter for
137 efficacy in oncology patients. With a 2 sided α of 5% and power of 80%, a sample size of 49 in each
138 group would detect a 20% difference between the proportion of progression at 6 months between
139 placebo arm (group 1) and metronomic (group 2) (95% vs 75%). Assuming loss to follow up of 15%,
140 54 subjects per group will be required. So, total of 108 patients are proposed to be randomized.

141

142 **Ethics and Registration:**

143 The study protocol was submitted to the Institute Ethics Committee and approval has been
144 obtained. All patients were included in the study after informed written consent.

145

146 **Enrollment: 108**

147 **Study Start Date: October 2013**

148 First received: May 17, 2013

149 Last updated: July 12, 2016

150 Last verified: July 2016

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160 **Study Protocol Version 2: (dated 17 June 2014)**

161 **Changes highlighted in yellow.**

162

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178 better than best supportive care is not known. In order to do so, a study is required which may
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207 least 2 lines of chemotherapy.

208 2. ECOG performance status (≤ 3) (at least patients ambulating with crutches or on wheel chair)

209 3. Age: 5-18 years

210 4. Recovered from all acute toxic effects of earlier therapy

211 5. Absolute neutrophil count $> 1 \times 10^9/L$

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215 and alanine aminotransferase < 5 times the upper limit of normal.

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223 **2. ARM1: Experimental: Low dose chemotherapy**

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225 drug rounded off to the nearest tablet/capsule size.

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229 BID for patients > 50 kg)

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231 **Cycle B**

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238 **Table 1: Drug schedule used in the study.**

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241 **3. ARM2: Placebo Comparator and Best supportive care**

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243 •Capsules of same size and colour as used in metronomic therapy

244 **Best supportive care**

245 •Management of pain as per WHO standard for pain management

246 The dose of medications in capsules have to be rounded off to the nearest capsule size. Instead of
247 rounding off on the daily dose, the total dose over the week would be calculated and rounded off
248 and divided over 5-6 days in a week. This is being done so as to prevent any extra dosing.

249 If any grade 3-4 toxicity occurs in the first course, then the dose for chemotherapy would be reduced
250 in the subsequent course by 20%.

251 All toxicities and adverse effects of the drugs would be graded according to NCI common
252 terminology criteria for Adverse Events version 4.03 (June 2010).

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324 **Primary Completion date (last date for data collection)**

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