

## SUPPLEMENTAL MATERIAL

**Supplemental Table 1: Grade 3–4 toxicities within 90 days prior to initiation of metronomic therapy in descending order of frequency.**

Prior toxicity*	Grade^		
	3	4	Total
Thrombocytopenia	24	105	129
Leukopenia	27	79	106
Anemia	84	12	96
Hypophosphatemia	58	5	63
Hyperglycemia	29	1	30
Hyponatremia	29	1	30
Hypokalemia	25	3	28
Hypocalcemia	15	3	18
Fatigue	12	1	13
Gait/walking	9	3	12
Hypoalbuminemia	12	0	12
Creatinine increase	5	5	10
Dyspnea	9	1	10
SGPT (ALT) increase	9	0	9
Pain: Upper Back	7	1	8
Hypercalcemia	5	1	6
Hyperkalemia	4	1	5
Muscle weakness: whole body	5	0	5
Sensory Neuropathy	5	0	5
Renal Failure	2	2	4
SGOT (AST) increase	4	0	4
Anorexia	3	0	3
Bicarbonate decrease	1	2	3
Hearing (without monitoring program)	3	0	3
Hypotension	3	0	3

Prior toxicity*	Grade^		
	3	4	Total
Infection, Normal ANC, Lung (Pneumonia)	3	0	3
Nausea	3	0	3
Opportunistic infection associated with ≥ to Grade 2 Lymphopenia	3	0	3
Syncope	3	0	3
Bone	2	0	2
Colitis	2	0	2
Dehydration	2	0	2
Dizziness ( Includes lightheadedness, disequilibrium & vertigo)	2	0	2
Febrile neutropenia (ANC <1.0 x 10 <sup>9</sup> / L, fever > or equal to 38.5 °C)	2	0	2
HGB	2	0	2
Hypertension	2	0	2
Hypoxia	2	0	2
Pain: Lower Back	2	0	2
Vomiting	2	0	2
Acidosis	0	1	1
Alkaline phosphatase increase	1	0	1
Bilirubin increase	1	0	1
Cardiac troponin I	1	0	1
Cataract	1	0	1
Chest wall	1	0	1
Confusion	1	0	1
Cough	1	0	1
Depression	1	0	1
Diarrhea	1	0	1
Edema-limb	1	0	1
Feminization of male	1	0	1
Fever, NOS	1	0	1

Prior toxicity*	Grade^		
	3	4	Total
Fracture	1	0	1
GI Infection with normal ANC: colon	1	0	1
Hemorrhage with 3-4 thrombocytopenia	1	0	1
Hypermagnesemia	1	0	1
Hypomagnesemia	1	0	1
Incontinence, anal	1	0	1
Infection 3-4 ANC: blood	1	0	1
Insomnia	1	0	1
Lung Infection with Unknown ANC: sinus	1	0	1
Lung Infection with normal ANC: upper airway NOS	1	0	1
Memory impairment	1	0	1
Neuralgia / peripheral nerve	1	0	1
Neuropathy, Motor	1	0	1
Renal failure	0	1	1
Renal-other	1	0	1
Skin Rash / Desquamation	1	0	1
Somnolence	1	0	1
Stomatitis/pharyngitis	1	0	1
Supraventricular Arrhythmia: Sinus Tachycardia	1	0	1
Weight gain	1	0	1

\*grade 3–4 toxicities occurring within 90 days prior to initiation of metronomic therapy

^ Grading and terminology according to CTCAE v3.0

**Supplemental Table 2: Grade 3–5 toxicities within 60 days of initiation of metronomic therapy in descending order of frequency.**

Toxicity*	Grade^			
	3	4	5	Total
Thrombocytopenia	15	147	0	162
Leukopenia	47	108	0	155
Anemia	105	12	0	117
Hypophosphatemia	84	2	0	86
Hypokalemia	36	6	0	42
Hyperglycemia	38	3	0	41
Hyponatremia	40	1	0	41
Fatigue	29	2	0	31
Hypocalcemia	21	8	0	29
Gait/walking	23	2	0	25
Hypoalbuminemia	23	0	0	23
Dyspnea	13	3	0	16
Creatinine increase	12	2	0	14
SGPT (ALT) increase	10	3	0	13
Pain: Upper Back	11	0	0	11
Hyperkalemia	5	3	0	8
SGOT (AST) increase	4	4	0	8
Hypoxia	7	0	0	7
Muscle weakness: whole body	7	0	0	7
Sensory Neuropathy	7	0	0	7
Bilirubin increase	5	1	0	6
Diarrhea	6	0	0	6
Mucositis / Stomatitis (functional exam) - Upper aerodigestive tract & Lower GI Sites	6	0	0	6
Syncope	6	0	0	6
Joint-function	4	1	0	5
Lung Infection, 3-4 ANC: lung	4	1	0	5
Anorexia	4	0	0	4
Confusion	3	1	0	4
Febrile neutropenia (ANC <1.0 x 10 <sup>9</sup> / L, fever ≥ to 38.5 °C)	3	1	0	4

Toxicity*	Grade^			
	3	4	5	Total
Dehydration	3	0	0	3
Dizziness ( Includes lightheadedness, disequilibrium & vertigo)	3	0	0	3
Hypercalcemia	1	2	0	3
Hypotension	2	1	0	3
Infection, 3-4 ANC: blood	2	0	1	3
Lung Infection, normal ANC: upper airway NOS	3	0	0	3
Abdomen NOS	2	0	0	2
Blood Infection normal ANC	1	1	0	2
Diabetes	2	0	0	2
Extremity / limb	2	0	0	2
Hypermagnesemia	2	0	0	2
Infection, Other	2	0	0	2
Insomnia	2	0	0	2
Mood Alteration (Agitation, Anxiety, Depression, Euphoria)	2	0	0	2
Muscle weakness: lower extremities	2	0	0	2
Nausea	2	0	0	2
Renal Failure	1	1	0	2
Alkaline phosphatase increase	1	0	0	1
Bicarbonate decrease	1	0	0	1
Cardiac troponin I	0	1	0	1
Cardiopulmonary arrest	0	1	0	1
Cholesterol	1	0	0	1
Cognitive disturbance	1	0	0	1
Constipation	1	0	0	1
Depression	1	0	0	1
Dermatology-other	1	0	0	1
Diarrhea without colostomy	1	0	0	1
Esophagitis/dysphagia	1	0	0	1

Toxicity*	Grade^			
	3	4	5	Total
Fever (in the absence of neutropenia)	1	0	0	1
GI Hemorrhage: rectum	0	1	0	1
GI-other	1	0	0	1
Hearing (without monitoring program)	0	1	0	1
Hemorrhage with 3-4 thrombocytopenia	1	0	0	1
Hemorrhage with surgery	0	0	1	1
Hypertriglyceridemia	0	1	0	1
Hypomagnesemia	1	0	0	1
Liver dysfunction	0	1	0	1
Lung Infection, Unknown ANC: bronchus	1	0	0	1
Melena/GI bleeding	1	0	0	1
Memory impairment	1	0	0	1
Mental status	1	0	0	1
Musculoskeletal-other	1	0	0	1
Neurology-other	1	0	0	1
Opportunistic infection associated with $\geq$ to Grade 2 Lymphopenia	1	0	0	1
Pain NOS	1	0	0	1
Pneumonitis	1	0	0	1
Rash/desquamation	1	0	0	1
Skin Rash / Desquamation	1	0	0	1
Stomatitis/pharyngitis	1	0	0	1
Thrombotic microangiopathy	0	1	0	1

\*grade 3–4 toxicities occurring within 60 days of initiation of metronomic therapy

^ Grading and terminology according to CTCAE v3.0

**Supplemental Table 3: Distribution of hematological toxicity of metronomic therapy according to the level of cytopenias prior to therapy.**

**Platelets \*:**

		Within 60 days after start of metronomic therapy			
		No-Mild thrombocytopenia	Moderate thrombocytopenia	Severe thrombocytopenia	Total
Within 90 days prior to start of metronomic therapy	No-Mild thrombocytopenia	3 (1.7%)	12 (6.6%)	19 (10.4%)	34 (18.7%)
	Moderate thrombocytopenia	3 (1.7%)	6 (3.3%)	35 (19.2%)	44 (24.2%)
	Severe thrombocytopenia	3 (1.7%)	3 (1.7%)	98 (53.9%)	104 (57.1%)
	Total	9 (5.0%)	21 (11.5%)	152 (83.5%)	182 (100.0%)

**White blood cells \*:**

		Within 60 days after start of metronomic therapy			
		No-Mild leukopenia	Moderate leukopenia	Severe leukopenia	Total
Within 90 days prior to start of metronomic therapy	No-Mild leukopenia	5 (2.8%)	10 (5.5%)	16 (8.8%)	31 (17.0%)
	Moderate leukopenia	3 (1.7%)	30 (16.5%)	40 (22.0%)	73 (40.1%)
	Severe leukopenia	3 (1.7%)	16 (8.8%)	59 (32.4%)	78 (42.9%)
	Total	11 (6.0%)	56 (30.8%)	115 (63.2%)	182 (100.0%)

**Hemoglobin \*:**

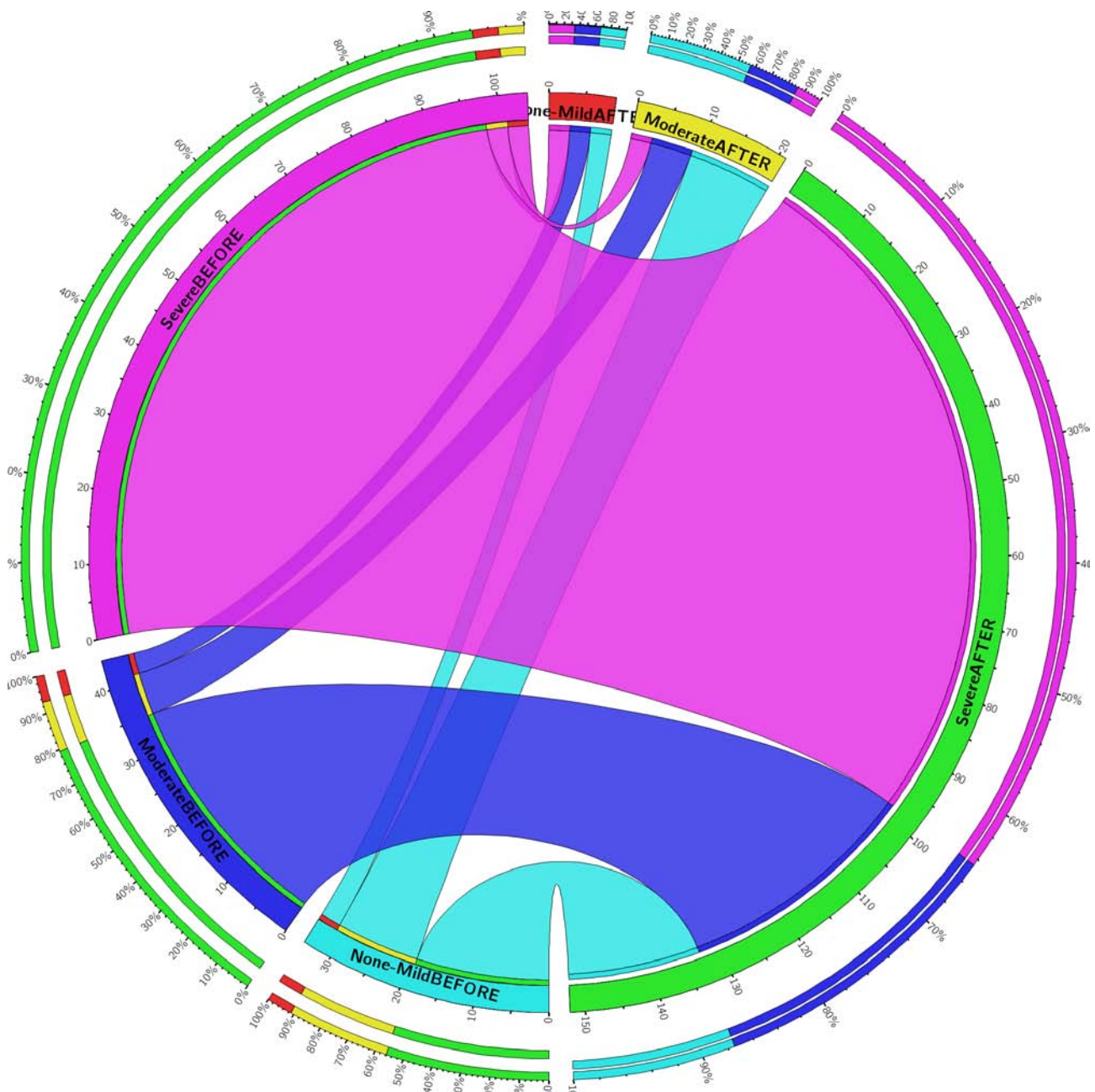
		Within 60 days after start of metronomic therapy			
		No-Mild anemia	Moderate anemia	Severe anemia	Total
Within 90 days prior to start of metronomic therapy	No-Mild anemia	7 (3.9%)	27 (14.8%)	0 (0.0%)	34 (18.7%)
	Moderate anemia	1 (0.6%)	133 (73.1%)	7 (3.9%)	141 (77.5%)
	Severe anemia	0 (0.0%)	6 (3.3%)	1 (0.6%)	7 (3.9%)
	Total	8 (4.4%)	166 (91.2%)	8 (4.4%)	182 (100.0%)

\*No-Mild: Grade 0-1 cytopenia, Moderate: Grade 2-3 cytopenia, Severe: Grade 4 cytopenia. Grading according to the CTCAE v3 criteria.

^note: Of the 186 patients that received metronomic therapy, 4 did not have lab measurements within 60 days after the start of metronomic therapy; these tables compare results for the 182 patients with both pre and post MT lab measurements.

**Supplemental Figure 1**  
**Dynamics of Thrombocytopenia before and after metronomic therapy.**

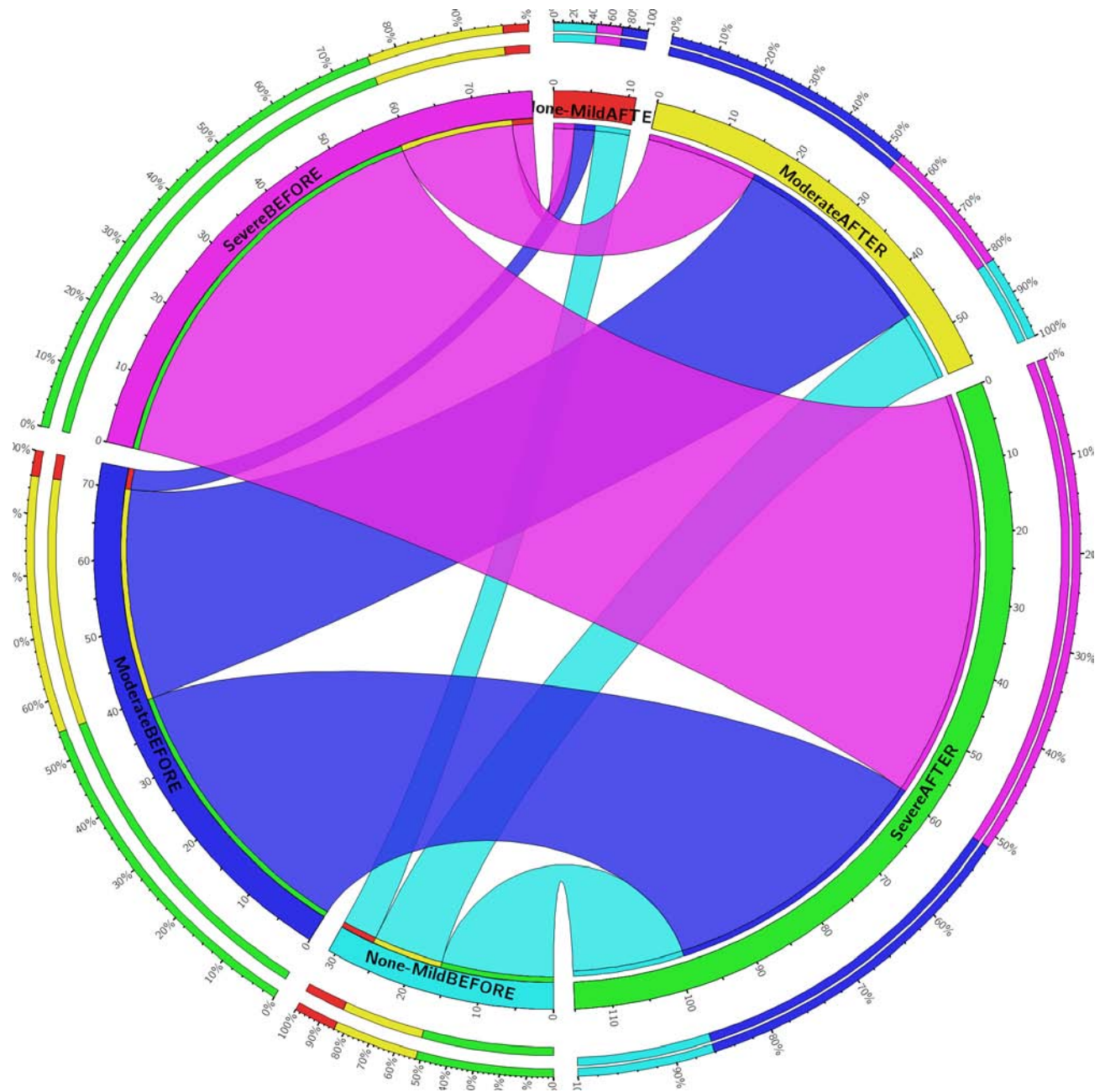
None-Mild Thrombocytopenia **Before** Treatment, Moderate Thrombocytopenia **Before** Treatment, Severe Thrombocytopenia **Before** Treatment, None-Mild Thrombocytopenia **After** Treatment, Moderate Thrombocytopenia **After** Treatment, Severe Thrombocytopenia **After** Treatment. Circularly arranged segments represent respective groups. Angular value of the segment, proportional to the size of the respective group. Ribbons with the respective color of the group before treatment ending (without touching) to the group after treatment proportionally to the percentage. Outer circularly arranged stacked bars representing the relative contribution of each group (before or after treatment) to the formation of another group (after or before treatment respectively).





**Supplemental Figure 2**  
**Dynamics of Leukopenia before and after metronomic therapy.**

None-Mild Leukopenia **Before** Treatment, Moderate Leukopenia **Before** Treatment, Severe Leukopenia **Before** Treatment, None-Mild Leukopenia **After** Treatment, Moderate Leukopenia **After** Treatment, Severe Leukopenia **After** Treatment. Circularly arranged segments represent respective groups. Angular value of the segment proportional to the size of the respective group. Ribbons with the respective color of the group before treatment ending (without touching) to the group after treatment proportionally to the percentage. Outer circularly arranged stacked bars representing the relative contribution of each group (before or after treatment) to the formation of another group (after or before treatment respectively).



### Supplemental Figure 3

Dynamics of Anemia before and after metronomic therapy.

None-Mild Anemia **Before** Treatment, Moderate Anemia **Before** Treatment, Severe Anemia **Before** Treatment, None-Mild Anemia **After** Treatment, Moderate Anemia **After** Treatment, Severe Anemia **After** Treatment. Circularly arranged segments represent respective groups. Angular value of the segment proportional to the actual size of the respective group. Ribbons with the respective color of the group before treatment ending (without touching) to the group after treatment proportionally to the percentage of contribution. Outer circularly arranged stacked bars representing the relative contribution of each group (before or after treatment) to the formation of another group (after or before treatment respectively).

