SUPPLEMENTAL MATERIAL

Table S1: Definitions of outcomes

Outcome	*Definition of event*	*Time at risk*	*Cased censored at*	*Competing risk*
Toxicity	See methods section under definition and statistics	From 7 days after start of protocol (administration of first course completed) to 9 months after diagnosis	Relapse and HSCT in CR1	Death
Treatment related mortality	Death unrelated to relapse, refractory or progressive disease	From 7 days after start of protocol to 9 months after diagnosis	Relapse and HSCT in CR1	Non-treatment related death
Event-free survival	Resistant disease, death during induction, death in remission, relapse or second malignancy	From 7 days after start of protocol to event or end of follow-up (7 May 2015)		None
Overall survival	Death from any cause	From 7 days after start of protocol to event or end of follow-up (7 May 2015)		None

HSCT: hematopoietic stem cell transplantation, CR1: first complete remission

Table S2. Toxicity after each block.

	AIET n=318	*AM*[1)] *n=312*	*HA_1M n=288*	*HA_2E1 n=269*	*HA_3 n=244*	*HA_2E2 n=235*
Days to absolute neutrophil count recovery median (range)[2)]	27 (8-84)[3)]	23 (0-56)	26 (5-199)	22 (0-127)	21 (0-42)	20 (0-38)
Infection requiring intravenous antibiotics n (%)[4)]	310 (97)	287 (92)	261 (91)	228 (85)	185 (76)	202 (87)
At least one grade 3 or 4 toxicity n (%)	200 (63)	131 (42)	145 (50)	105 (39)	65 (27)	88 (37)

[1)] AM or alternative second induction (figure 1).

[2)] Absolute neutrophil count recovery was defined as days from start of block to last date with ANC< 0.5 $x10^9$/L.

[3)] Includes 221 patients only, who reached remission after first induction, because according to protocol those who did not, should proceed immediately to AM.

[4)] Including both episodes with known pathogen and fever of unknown origin.

Table S3. Information on the 14 treatment-related deaths during standard treatment.

Case	*Age*	*Body-weight group*	*Sex*	*After*	*Days after course start*	*Cause of death*
1	0	-	F	AM	12	Intensive care unit from the beginning. AM in CR1 during dialysis. Multi-organ failure.
2	1	-	F	HA_2E2	35	Respiratory syncytial virus infection.
3	1	-	M	AIET	39	Sepsis, pneumonia and ARDS
4	1	-	M	AIET	11	Acute circulatory arrest during neutropenic septicemia under control; probably GI-bleeding.
5	1	-	F	AIET	18	Intracranial bleeding
6	4	Healthy weight	F	HA_2E1	12	Ileus, typhlitis, clostridium septicum infection
7	5	Healthy weight	M	AIET	37	Acute respiratory distress syndrome and multiorgan failure
8	5	Healthy weight	F	AIET	15	Toxic leukoencephalopathy. Mitochondrial disease suspected.
9	12	Healthy weight	M	HA_1M	22	Sepsis. Pleural puncture caused hepatic bleeding and death.
10	13	Healthy weight	F	AM	45	Disseminated fungal infection (Fusarium) and pulmonary hemorrhage
11	14	Healthy weight	F	FLAG2	12	Respiratory insufficient (virus?) with sudden cardiac arrest during anesthesia
12	16	Healthy weight	M	AM	22	Necrotic appendix, died from peritonitis, sepsis and coagulopathy after surgery
13	16	Underweight	M	FLAG	142	Pneumonia
14	17	Healthy weight	M	HA_1M	28	E. coli sepsis

M: male, F: female

Table S4. Toxicity analyses after first course (AIET) only by weight group.

Toxicity	*Age/body-weight group*	*No of events*	*Crude hazard ratio (95%-CI)*	*P value*	*Adjusted* hazard ratio (95%-CI)*	*P value*
Any grade 3 or 4 toxicity	Healthy weight	98	1	-	1	-
	Overweight	37	1.1 (0.8-1.7)	0.5	1.2 (0.8-1.8)	0.4
Bedridden and in need of care (general condition grade 3 and 4)	Healthy weight	76	1	-	1	-
	Overweight	32	1.3 (0.8-1.9)	0.3	1.3 (0.9-2.1)	0.2
Intensive care unit (general condition grade 4) §	Healthy weight	12				
	Overweight	7				
Requiring supplemental oxygen (Hypoxia grade 3 and 4)	Healthy weight	12	1	-	1	-
	Overweight	9	2.3 (1.0-5.4)	0.06	2.6 (1.0-6.7)	0.04
Continuous positive airway pressure or assisted ventilation (Hypoxia grade 4) §	Healthy weight	6				
	Overweight	3				
Infection with an identified pathogen (infection grade 3 and 4)	Healthy weight	56	1	-	1	-
	Overweight	21	1.1 (0.7-1.9)	0.6	1.2 (0.7-2.0)	0.5
Sepsis/hypotension (Infection grade 4) §	Healthy weight	6				
	Overweight	4				
Abdominal pain severely interfering with activities of daily life (Abdominal pain grade 3 and 4)	Healthy weight	27	1	-	1	-
	Overweight	14	2.3 (1.0-5.4)	0.06	2.6 (1.0-6.6)	0.04

*The analysis was adjusted for sex, age group and ethnicity and only included children 2 years or older.

§ Too few events to perform analyses.

Table S5. Weight and age group interaction analysis for patients 2 years or older.

Toxicity	*Age and body weight group*	*No of first events*	*Adjusted* hazard ratio (95%-CI)*	*RERI§ (95%-CI)*
Any grade 3 or 4 toxicity	2-9 healthy weight	92	1	-0.2 (-1.0 - 0.5)
	10-17 healthy weight	60	0.9 (0.7-1.3)	
	2-9 overweight	19	1.4 (0.8-2.2)	
	10-17 overweight	32	1.0 (0.7-1.6)	
Bedridden and in need of care (general condition grade 3 and 4)	2-9 healthy weight	57	1	-0.3 (-1.5 - 0.8)
	10-17 healthy weight	42	1.2 (0.8-1.7)	
	2-9 overweight	16	1.8 (1.0-3.2)	
	10-17 overweight	29	1.7 (1.0-2.6)	
Intensive care unit (general condition grade 4)	2-9 healthy weight	13	1	-0.3 (-3.3 - 2.6)
	10-17 healthy weight	13	1.7 (0.8-3.6)	
	2-9 overweight	5	2.4 (0.8-6.8)	
	10-17 overweight	10	2.7 (1.2-6.4)	
Requiring supplemental oxygen (Hypoxia grade 3 and 4)	2-9 healthy weight	16	1	-1.8 (-4.9 -1.4)
	10-17 healthy weight	18	1.9 (1.0-3.7)	
	2-9 overweight	8	3.3 (1.4-7.9)	
	10-17 overweight	11	2.5 (1.1-5.5)	
Continuous positive airway pressure or assisted ventilation (Hypoxia grade 4)	2-9 healthy weight	7	1	-1.1 (-4.9 - 2.7)
	10-17 healthy weight	10	2.4 (0.9-6.2)	
	2-9 overweight	2	1.8 (0.4-8.6)	
	10-17 overweight	4	2.1 (0.6-7.3)	
Infection with an identified pathogen (infection grade 3 and 4)	2-9 healthy weight	80	1	0.2 (-0.6 - 0.9)
	10-17 healthy weight	50	0.9 (0.6-1.2)	
	2-9 overweight	16	1.1 (0.6-1.9)	
	10-17 overweight	29	1.2 (0.7-1.8)	
Sepsis/hypotension (Infection grade 4)	2-9 healthy weight	8	1	1.2 (-2.7 - 5.1)
	10-17 healthy weight	11	2.2 (0.9-5.6)	
	2-9 overweight	3	2.1 (0.6-8.1)	
	10-17 overweight	11	4.6 (1.8-11.8)	
Abdominal pain severely interfering with activities of daily life (Abdominal pain grade 3 and 4)	2-9 healthy weight	20	1	-1.6 (-4.3 - 1.1)
	10-17 healthy weight	24	2.1 (1.2-3.8)	
	2-9 overweight	9	2.9 (1.3-6.4)	
	10-17 overweight	14	2.4 (1.2-4.9)	

RERI: Relative excess risk due to interaction

*The multivariate analysis is adjusted for sex and ethnicity

§ RERI was calculated as $HR_{11}-HR_{10}-HR_{01}+1$ using the algorithm of Andersson et al.[1] HR_{11} is the hazard ratio for both 10-17 and overweight, HR_{10} is the hazard ratio for 2-9 and overweight, and HR_{01} is the hazard ratio for 10-17 and healthy weight. RERI of 0 indicates no interaction, values > 0 indicate a positive additive interaction and values < 0 indicates a negative additive interaction.

1. Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol. 2005 Jul;20(7):575–9.