

## 1 **Patients and methods**

### 2 *Protocol treatment and definitions*

3 The treatment comprised four main components: (i) induction; (ii) consolidation (SR/IR) or HR block  
4 therapy; (iii) delayed intensifications (DIs); and (iv) maintenance therapy. Induction treatment  
5 included prednisolone on Days 1–29 (BCP-ALL and white blood cell count (WBC)  $<100 \times 10^9/L$ ) or  
6 dexamethasone on Days 1–21 (T-ALL and/or WBC  $\geq 100 \times 10^9/L$ ). Consolidation treatment in the  
7 SR/IR group included intramuscular injections of PegASP ( $1000 \text{ IU}/\text{m}^2$ ) every two weeks from Day  
8 30 (total of five doses) after which adult patients received PegASP injections every two weeks until  
9 Week 33; children were randomized to receive PegASP, administered either at two-week (control  
10 arm, 10 additional doses) versus six-week intervals (experimental arm, three additional doses) from  
11 treatment Weeks 14 to 33 (ie during DI and early maintenance-1). This randomization was closed  
12 March 01, 2016, after which all children received PegASP at six-week intervals from Week 14.<sup>1</sup>  
13 Quantification of PegASP activity measurement was performed in a subset of patients, for whom  
14 sampling took place within 16 days from PegASP administration.<sup>2</sup> SR/IR patients received oral  
15 dexamethasone  $10 \text{ mg}/\text{m}^2$  daily for two weeks during one (SR) and two (IR) DIs. The HR block  
16 therapy included one PegASP injection ( $1000 \text{ IU}/\text{m}^2$ ) at the end of each HR chemotherapy block (in  
17 total nine blocks, or seven if MRD  $<0.1\%$  after the first HR block) and an additional dose of PegASP  
18 at Weeks 99 and 101 during DI. HR patients received oral dexamethasone  $20 \text{ mg}/\text{m}^2$  daily for five  
19 days in three of the HR blocks in addition to dexamethasone  $10 \text{ mg}/\text{m}^2$  daily for two weeks during  
20 DI. Maintenance treatment included dexamethasone  $6 \text{ mg}/\text{m}^2$  daily for five days at eight-week  
21 intervals during Weeks 25–57 (SR) or Weeks 27–51 (IR). Total duration of chemotherapy was 2.5  
22 years for all non-transplanted patients.

23 The presence of a mediastinal mass at diagnosis was defined as a mediastinum  $\geq$  one-third of the  
24 diameter of the thorax at the level of the fifth thoracic vertebra; however, its presence was not a  
25 treatment stratifying factor in the ALL2008 protocol. Central nervous system (CNS) involvement at  
26 ALL diagnosis was defined as CNS1 (no blasts on cytopsin and no other signs of CNS-leukemia),  
27 CNS2 ( $>0$  and  $<5$  cells/ $\mu\text{L}$  cerebrospinal fluid (CSF) with blasts on cytopsin and no other signs of  
28 CNS-leukemia), and CNS3 ( $\geq 5$  cells/ $\mu\text{L}$  CSF with blasts on cytopsin, cranial nerve palsy,  
29 intracranial “leukemic” mass on magnetic resonance imaging (MRI), eye involvement confirmed by  
30 MRI, or a biopsy to reflect ALL). ALL relapse was defined as  $\geq 5\%$  leukemic blasts in the bone  
31 marrow,  $\geq 5 \times 10^6/\text{L}$  cells CSF with leukemic blasts on cytopsin, bulky CNS leukemia on  
32 MRI/computed tomography (CT) and confirmed histologically, or other morphologically confirmed  
33 presence of leukemia at any site. Second malignant neoplasm (SMN) was defined as the occurrence  
34 of a new malignant neoplasm.

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## 36 **References**

- 37 1. Albertsen BK, Abrahamsson J, Lund B, et al. Intermittent vs continuous asparaginase to reduce  
38 asparaginase-associated toxicities: A NOPHO ALL2008 randomized study [abstract]. *Blood*.  
39 2017;Abstract 1275.
- 40 2. Tram Henriksen L, Gottschalk Hojfeldt S, Schmiegelow K, et al. Prolonged first-line PEG-  
41 asparaginase treatment in pediatric acute lymphoblastic leukemia in the NOPHO ALL2008 protocol-  
42 Pharmacokinetics and antibody formation. *Pediatric blood & cancer*. 2017;64(12).

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**Table S1. Multiple analyses of TE subtypes (N=1750)**

		TE-specific HRa	95% CI	P
<b>PE</b>				
<b>Mediastinal mass</b>	No	1.00 [ref.]		
	Yes	1.6	0.5–4.9	.4
<b>Age groups</b>	1.0–9.9 years	1.00 [ref.]		
	10.0–17.9 years	2.4	0.6–10.0	.2
	18.0–45.9 years	11.6	4.0–33.7	<.0001
<b>Sex</b>	Female	1.00 [ref.]		
	Male	1.9	0.7–5.4	.2
<b>CSV T</b>				
<b>Mediastinal mass</b>	No	1.00 [ref.]		
	Yes	1.1	0.3–3.8	.8
<b>Age groups</b>	1.0–9.9 years	1.00 [ref.]		
	10.0–17.9 years	3.3	1.5–7.3	.003
	18.0–45.9 years	1.9	0.7–5.2	.2
<b>Sex</b>	Female	1.00 [ref.]		
	Male	0.9	0.4–1.8	.7
<b>Supra-diaphragmatic TE</b>				
<b>Mediastinal mass</b>	No	1.00 [ref.]		
	Yes	2.2	1.0–4.8	.05
<b>Age groups</b>	1.0–9.9 years	1.00 [ref.]		
	10.0–17.9 years	2.8	1.3–6.0	.006
	18.0–45.9 years	3.8	1.8–7.9	.0004
<b>Sex</b>	Female	1.00 [ref.]		
	Male	0.9	0.5–1.7	.8
<b>Infra-diaphragmatic TE</b>				
<b>Mediastinal mass</b>	No	1.00 [ref.]		
	Yes	1.9	0.7–5.1	.2
<b>Age groups</b>	1.0–9.9 years	1.00 [ref.]		
	10.0–17.9 years	10.1	3.59–28.6	<.0001
	18.0–45.9 years	6.5	2.0–20.9	.002
<b>Sex</b>	Female	1.00 [ref.]		
	Male	1.4	0.6–3.3	.4
<b>TE at multiple sites</b>				
<b>Mediastinal mass</b>	No	1.00 [ref.]		
	Yes	2.0	0.6–6.2	.2
<b>Age groups</b>	1.0–9.9 years	1.00 [ref.]		
	10.0–17.9 years	8.9	2.3–34.6	.002
	18.0–45.9 years	10.4	2.7–41.2	.0008
<b>Sex</b>	Female	1.00 [ref.]		
	Male	3.0	0.9–10.5	.09

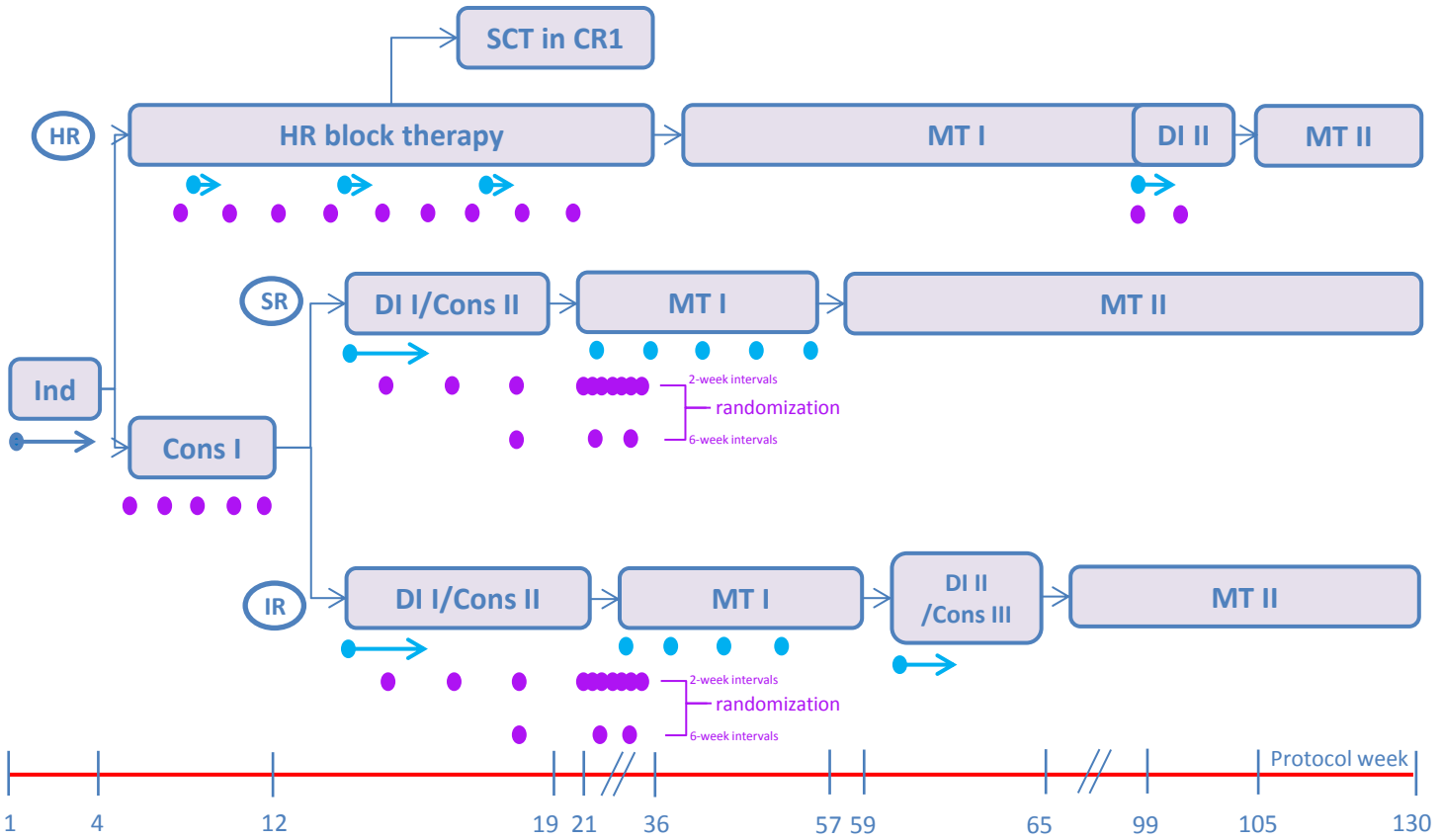
49 **Figure S1. The NOPHO ALL2008 Protocol.** Protocol overview for standard risk (SR),  
50 intermediate risk (IR), and high risk (HR) patients with highlighted administrations of  
51 corticosteroids and PegASP.

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53 **Figure S2. The cumulative incidence of symptomatic TE.** The cumulative incidence of  
54 symptomatic TE by age groups with 95% CIs and patients at risk. The 2.5-year cumulative  
55 incidences were: 3.6% for 1.0–9.9 years (CI, 2.5–4.6); 13.5% for 10.0–17.9 years (CI, 9.5–17.2);  
56 17.0% for 18.0–45.9 years (CI, 12.2–21.5).

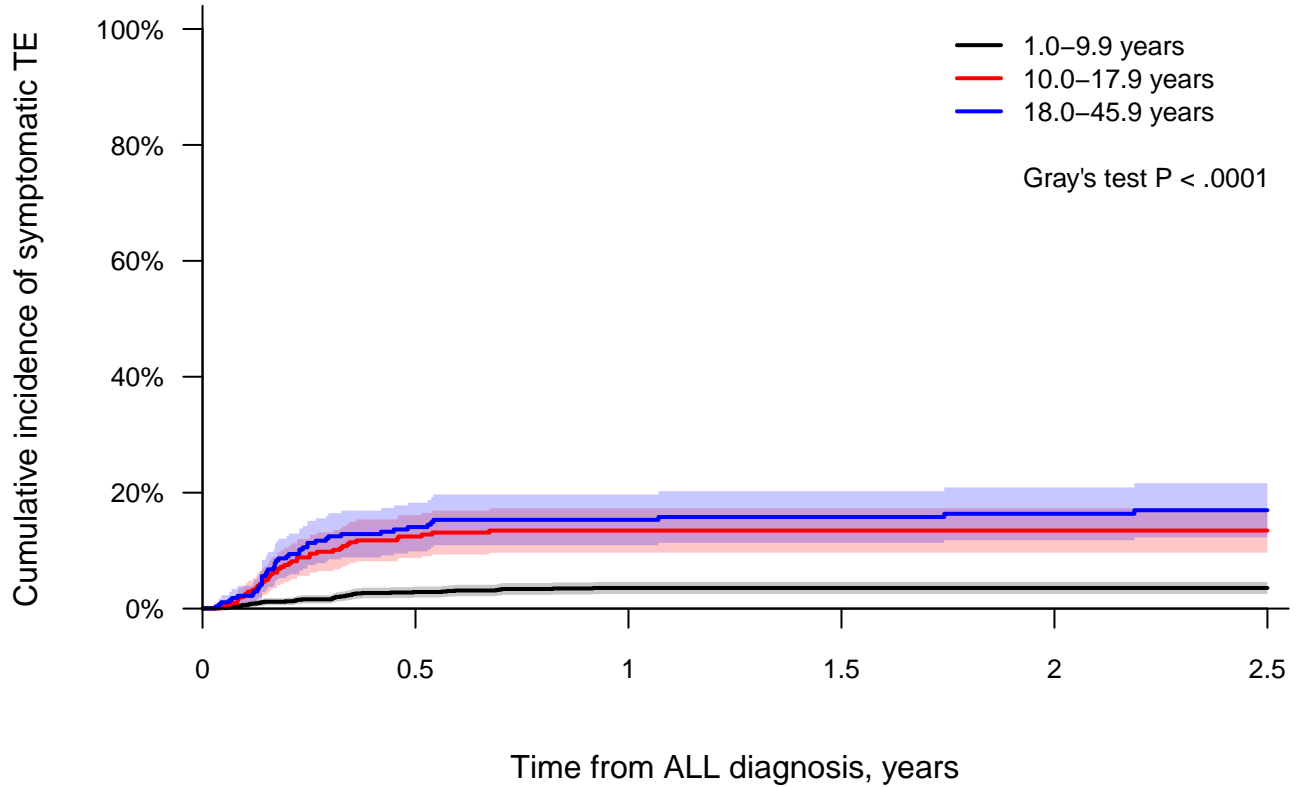
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58 **Figure S3. The predicted cumulative incidence of TE.** The predicted cumulative incidence of TE  
59 by combinations of the TE risk factors from the absolute risk model: age  $\geq 10$  years of age, presence  
60 of mediastinal mass, and enlarged lymph nodes at ALL diagnosis.



Ind = induction  
 Cons = consolidation  
 DI = delayed intensification  
 MT = maintenance therapy  
 SCT in CR1 = hematopoietic stem cell transplantation in first complete remission

Ind: Dexamethasone 10 mg/m<sup>2</sup>/day for 21 days (WBC ≥100 x 10<sup>9</sup>/L or T-ALL) or Prednisolone 60 mg/m<sup>2</sup>/day for 29 days (WBC <100 x 10<sup>9</sup>/L and BCP-ALL).  
 corticosteroids (2-week blocks, 10 mg/m<sup>2</sup>/day (SR/IR/HR) and 5-day block, 20 mg/m<sup>2</sup>/day (HR block therapy))     asparaginase (1000 IU/m<sup>2</sup>/dosis, i.m.)  
 corticosteroids (5-day pulses, 6 mg/m<sup>2</sup>/day)



At risk:

1.0–9.9 years :	1192	1158	1111	1076	1059	1026	993	955	915	876	834
10.0–17.9 years :	306	272	250	236	225	215	207	200	188	179	172
18.0–45.9 years :	274	228	195	168	150	141	133	122	113	108	100

