

**Impact of central nervous system involvement in adult patients with philadelphia-negative acute lymphoblastic leukemia – a GRAALL-2005 study**

**Supplementary data**

## Supplementary Methods

High-risk patients < 55 years eligible for allogeneic SCT in first CR were defined by one or more of the following criteria: CNS involvement, a white blood cell (WBC) count of 30 G/l or higher, a CD10-negative immature immunophenotype, poor cytogenetic abnormalities (t(4;11) or other *KMT2A* gene rearrangement, t(1;19), or complex karyotype), poor early peripheral blood (PB) blast clearance, defined by a PB blast count  $>1 \times 10^9/L$  at the end of the pre-phase, poor early bone marrow (BM) blast clearance, defined by  $>5\%$  blasts in the BM on day 8 of induction, or late complete remission, defined by a need for salvage reinduction to achieve complete remission.<sup>18</sup> Since the initial GRAALL-2005 publications, criteria defining high-risk patients for whom allogeneic SCT is recommended have been modified in the ongoing GRAALL-2014 trial and now only include patients with insufficient MRD response during initial treatment.

**Supplementary table 1.** Classification of CNS involvement. *Adapted from Winick et al.*

<b>Classification</b>	<b>Definition</b>
<b>CNS-1</b>	No blast in the CSF, regardless of WBC or RBC
<b>CNS-2</b>	
a	<5 WBC/ $\mu$ l + CC positive for blasts + < 10 RBC/ml
b	<5 WBC/ $\mu$ l + CC positive for blasts + $\geq$ 10 RBC/ml
c	$\geq$ 5 WBC/ $\mu$ l + CC positive for blasts + $\geq$ 10 RBC/ml, excess WBC proportional to RBC*
<b>CNS-3</b>	
a	$\geq$ 5 WBC/ $\mu$ l + CC positive for blasts + <10 RBC/ml
b	$\geq$ 5 WBC/ $\mu$ l + CC positive for blasts + $\geq$ 10 RBC/ml, excess WBC not proportional to RBC*
c	Clinical signs

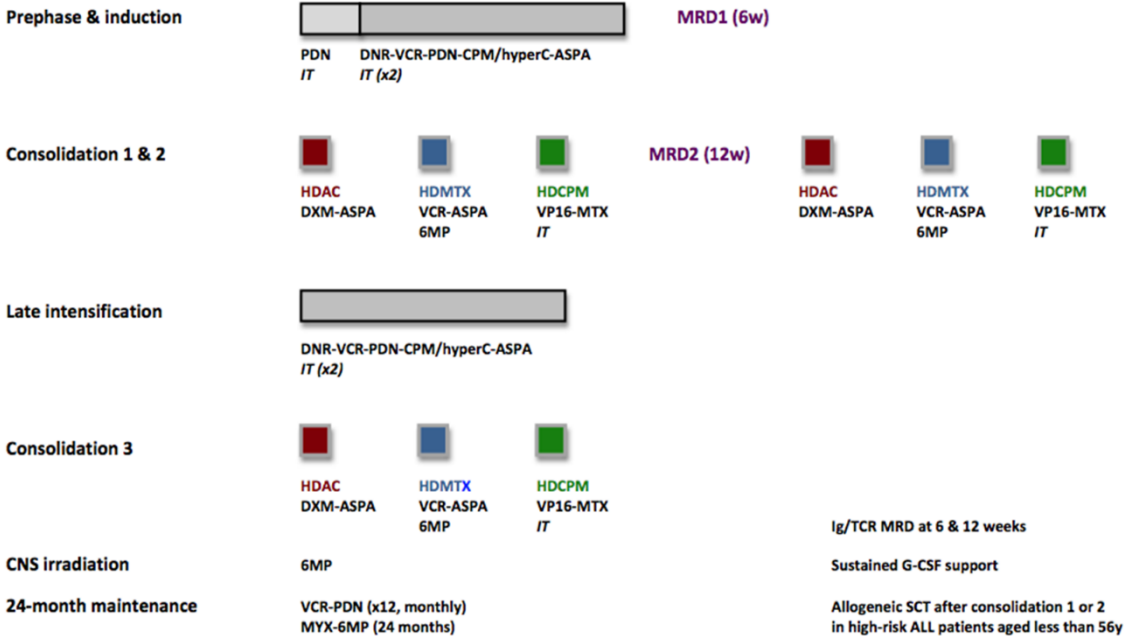
Abbreviations: CC, conventional cytospin; CNS, central nervous system; CSF, cerebrospinal fluid; RBC, red blood cells; WBC, white blood cells. \*Proportional is defined as CSF WBC less than two times blood WBC.

**Supplementary table 2.** Characteristics of patients with CNS involvement according to randomization arm (Standard-C versus Hyper-C).

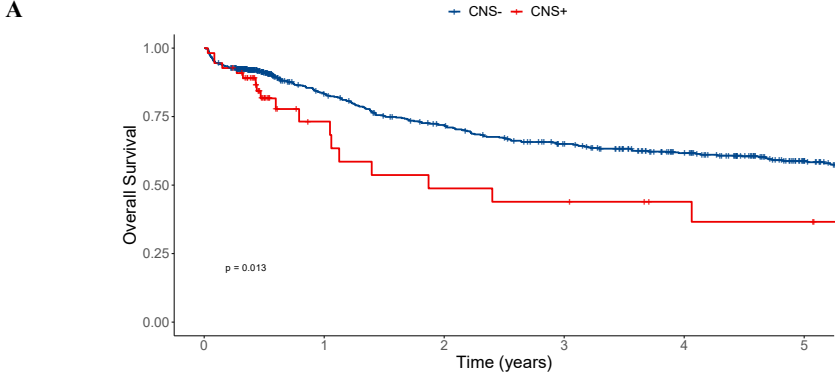
Characteristic	CNS-positive (n=55)	Standard-C (n=30)	Hyper-C (n=25)
Age, median (IQR), years	30 (24 - 44)	29 (23 - 43)	30 (27 - 53)
Female, n (%)	18 (33%)	7 (23%)	11 (44%)
BMI, median (IQR), kg/m <sup>2</sup>	24 (21 - 26)	23 (21 - 26)	24 (22 - 27)
Phenotype, n (%)			
B-cell	27 (49%)	15 (50%)	12 (48%)
T-cell	28 (51%)	15 (50%)	13 (52%)
WBC count at diagnosis, median (IQR), G/l	23 (9 - 66)	36 (14 - 73)	18 (8 - 36)
Hemoglobin level at diagnosis, median (IQR), g/dl	11.1 (8.8 - 13)	11.1 (8.9 - 12.5)	11.1 (8.8 - 13.2)
Platelet count at diagnosis, median (IQR), G/l	78 (36 - 137)	72 (35 - 113)	94 (37 - 150)
Poor early PB blast clearance, n (%)	15 (27%)	9 (30%)	6 (24%)
Poor early BM blast clearance, n (%)	25 (46%)	12 (40%)	13 (52%)
<i>Not evaluable</i>	4	2	2
CR, n (%)	50 (91%)	28 (93%)	22 (88%)
Induction death, n (%)	3 (6%)	1 (3%)	2 (8%)
MRD1 negativity, n (%)	7 (27%)	3 (20%)	4 (36%)
<i>Not evaluable</i>	29	15	14
Allogeneic SCT in first CR, n (%)	29 (53%)	16 (53%)	14 (56%)

**Abbreviations:** BM, bone marrow; BMI, body mass index; CNS, central nervous system; CR, complete remission; IQR, interquartile range; PB, peripheral blood; SCT, stem cell transplantation; WBC, white blood cells.

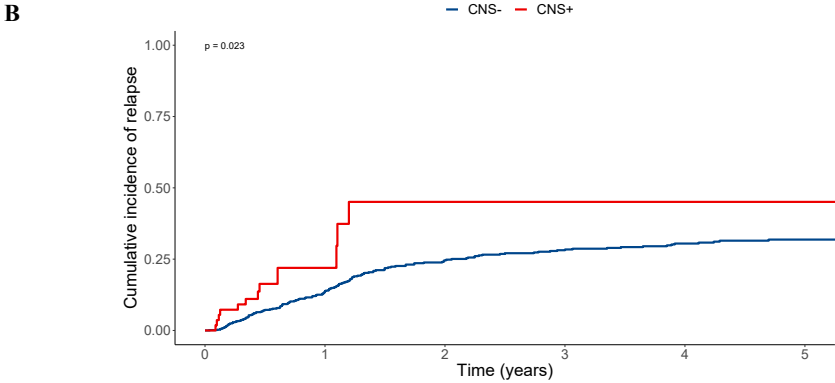
Supplementary figure 1. The GRAALL-2005 protocol.



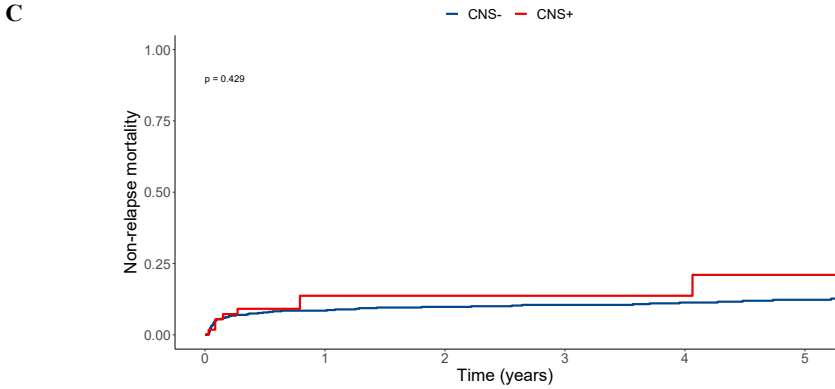
**Supplementary figure 2.** Overall survival (A), cumulative incidence of relapse (B), and cumulative incidence of non-relapse mortality (C) according to CNS involvement at diagnosis after censoring patients at the time of allogeneic SCT.



CNS-	729	379	315	268	216	152
CNS+	55	15	10	9	6	5

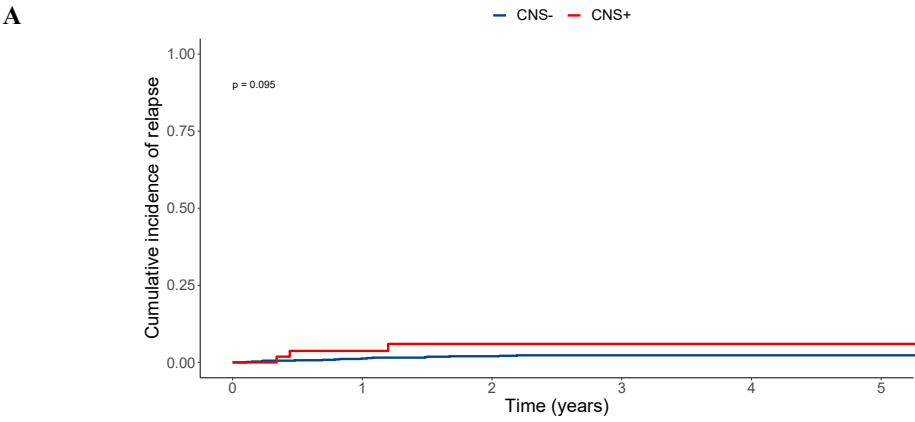


CNS-	729	309	252	223	175	126
CNS+	55	8	5	5	4	2

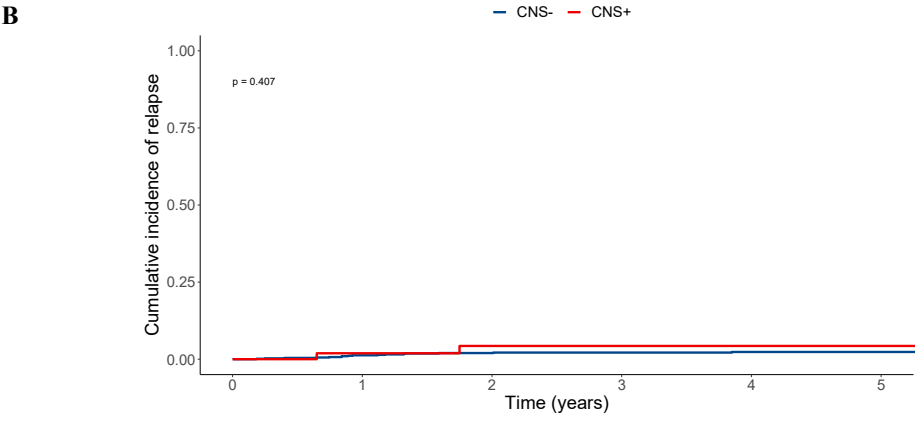


CNS-	729	379	315	268	216	152
CNS+	55	15	10	9	6	5

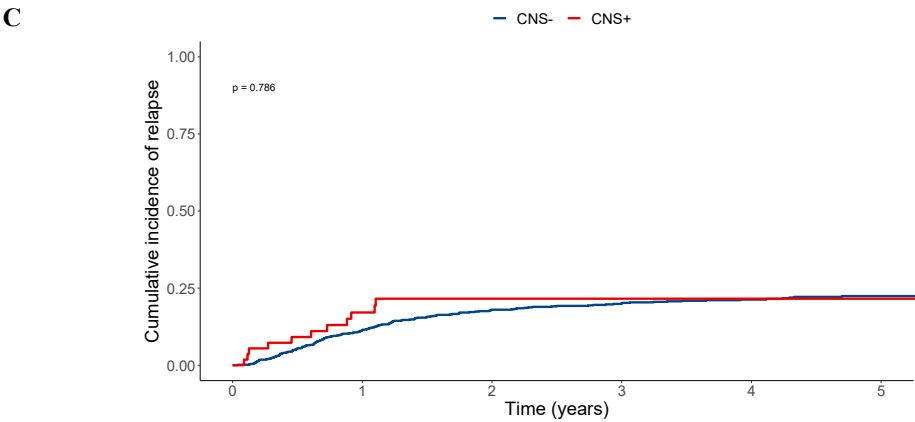
**Supplementary figure 3.** Cumulative incidence of CNS relapse (A), combined relapse (B), and isolated bone marrow relapse (C) according to CNS involvement at diagnosis.



CNS-	729	508	415	374	289	202
CNS+	55	28	21	20	14	9

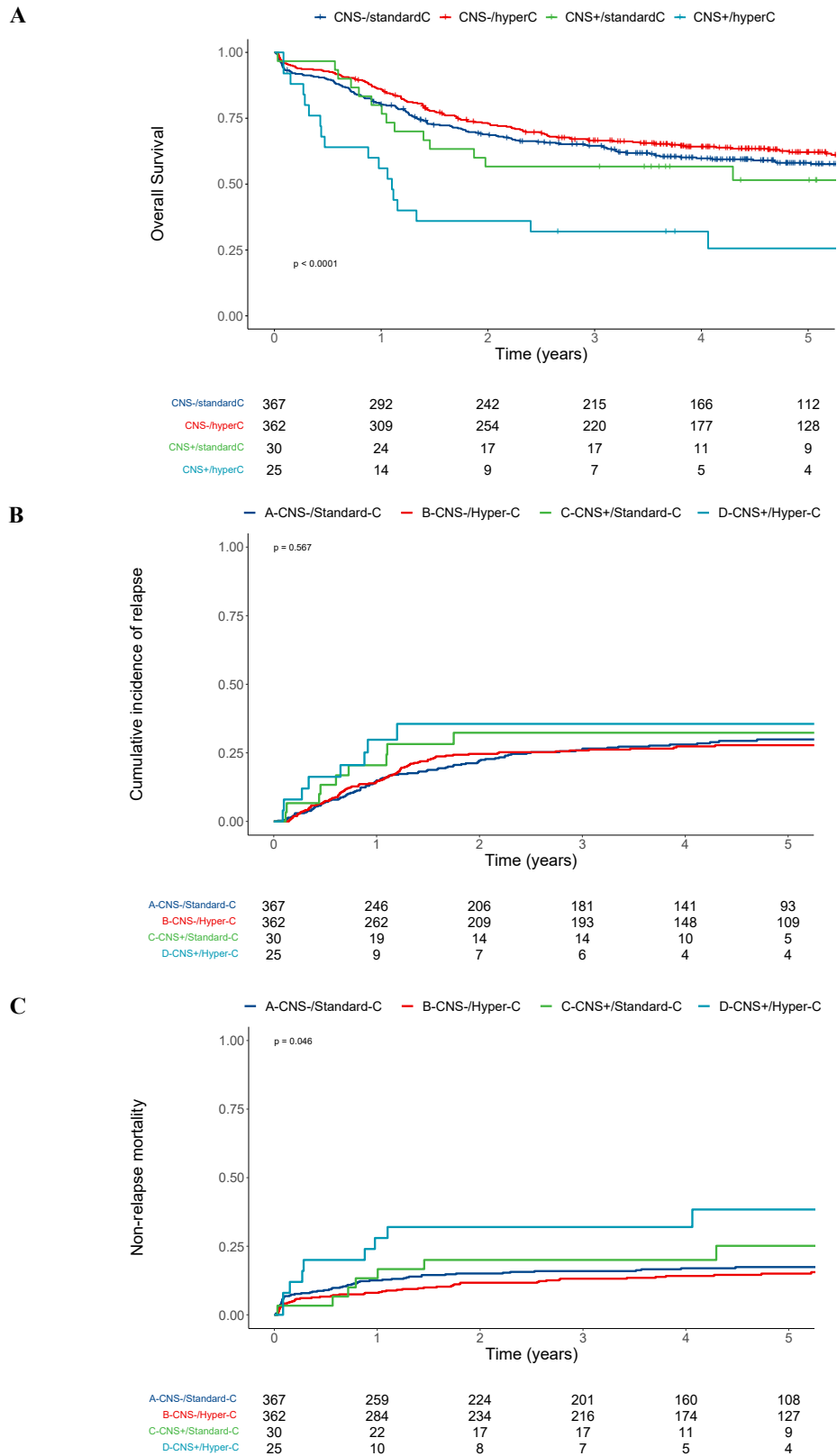


CNS-	729	508	415	374	289	202
CNS+	55	28	21	20	14	9



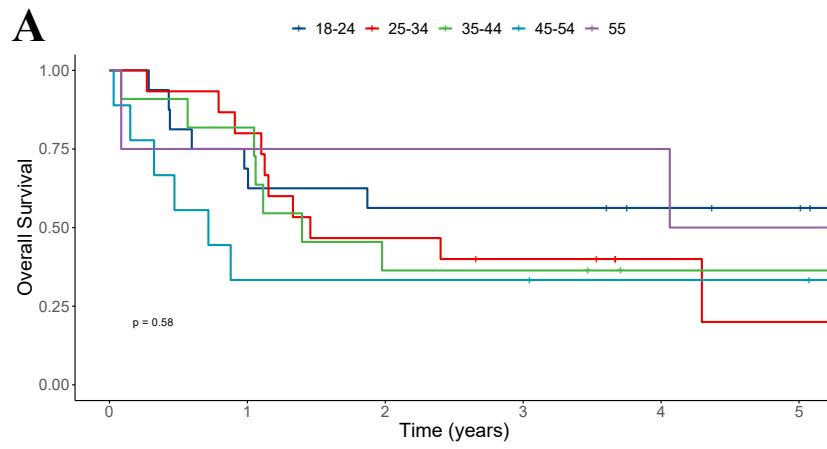
CNS-	729	508	415	374	289	202
CNS+	55	28	21	20	14	9

**Supplementary Figure 4.** Overall survival (A), cumulative incidence of relapse (B), and cumulative incidence of non-relapse mortality (C) according to CNS involvement at diagnosis and randomization arm (standard-C versus hyper-C).

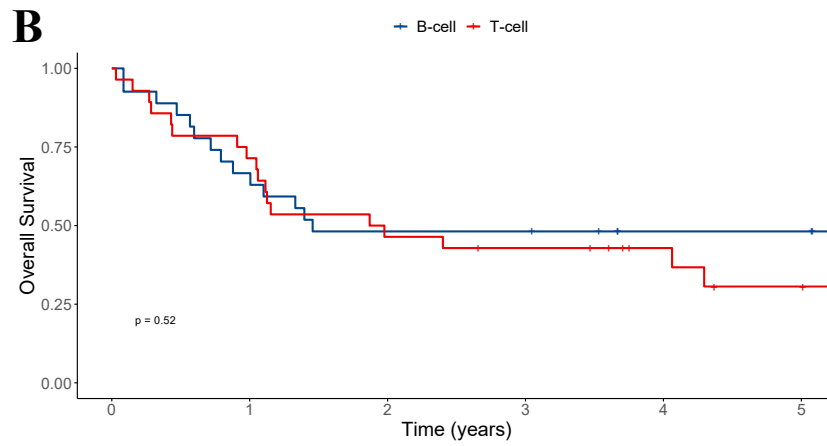




**Supplementary Figure 5.** Overall survival in CNS-positive patients according to (A) age categories and to (B) ALL subtype.



18-24	16	11	9	9	7	6
25-34	15	12	7	5	2	1
35-44	11	9	4	4	2	2
45-54	9	3	3	3	2	2
55	4	3	3	3	3	2



B-cell	27	18	13	13	9	9
T-cell	28	20	13	11	7	4