Impact of central nervous system involvement in adult patients with Philadelphia-negative acute lymphoblastic leukemia: a GRAALL-2005 study

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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 x 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.[18] 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.*

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

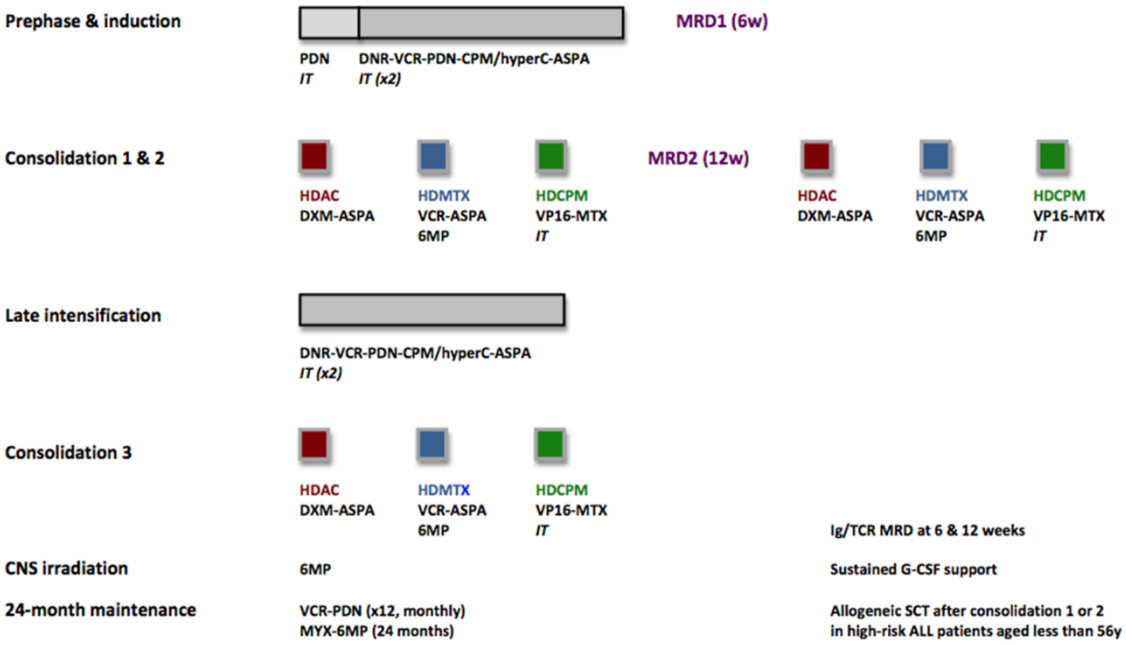
Abbreviations: CC, conventional cytospin; CNS, central nervous system; CSF, cerebrospinal fluid; RBC, red blood cells; WBC, white blood cells. *Proportional is defined as CSF WBC less than two times blood WBC.

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

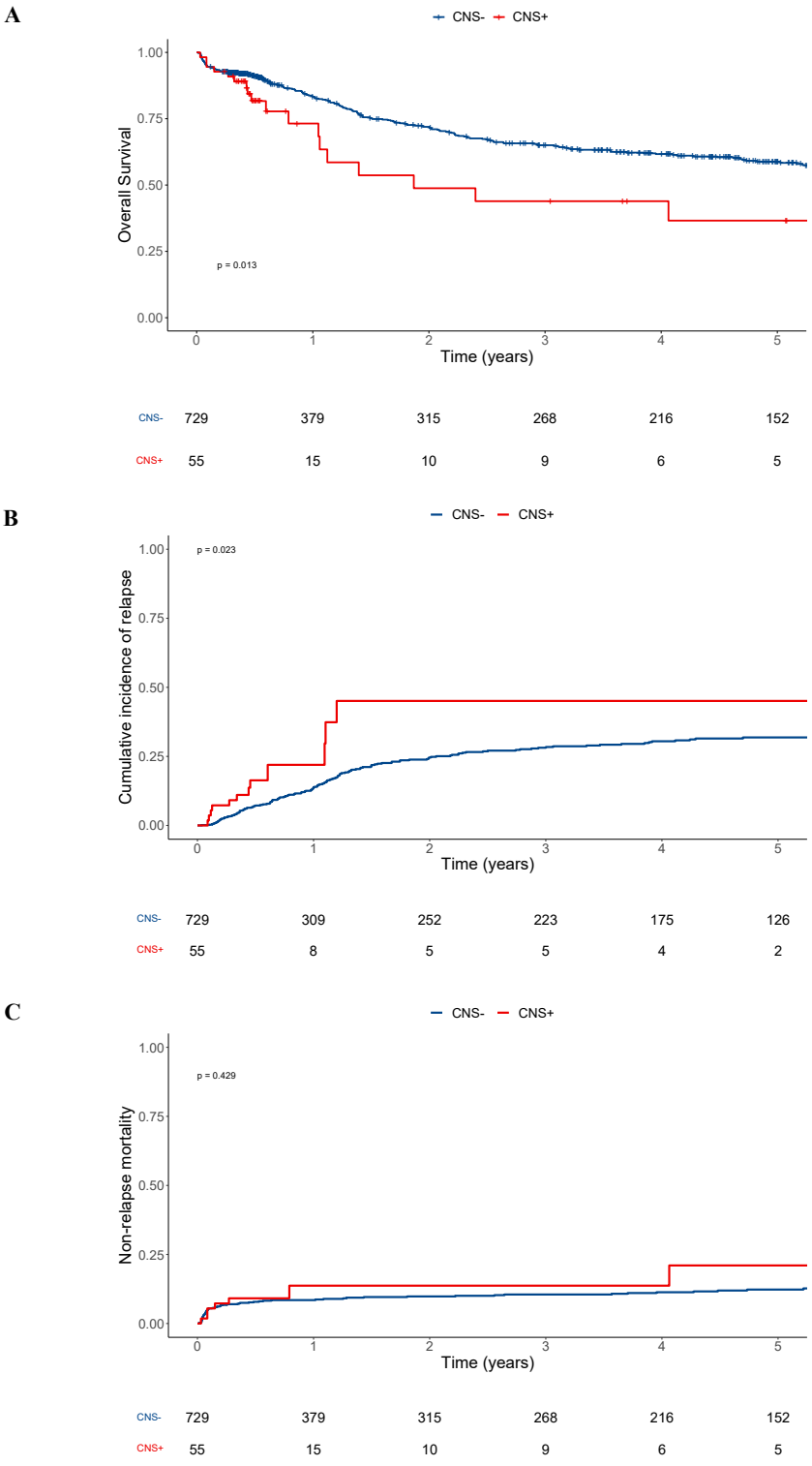
Characteristic	CNS-positive (n=55)	Standard-C (n=30)	Hyper-C (n=25)
Age, median (IQR), years	30 (24 - 44)	29 (23 - 43)	30 (27 - 53)
Female, n (%)	18 (33%)	7 (23%)	11 (44%)
BMI, median (IQR), kg/m2	24 (21 - 26)	23 (21 - 26)	24 (22 - 27)
Phenotype, n (%)			
B-cell	27 (49%)	15 (50%)	12 (48%)
T-cell	28 (51%)	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%)
Not evaluable	*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%)
Not evaluable	*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.

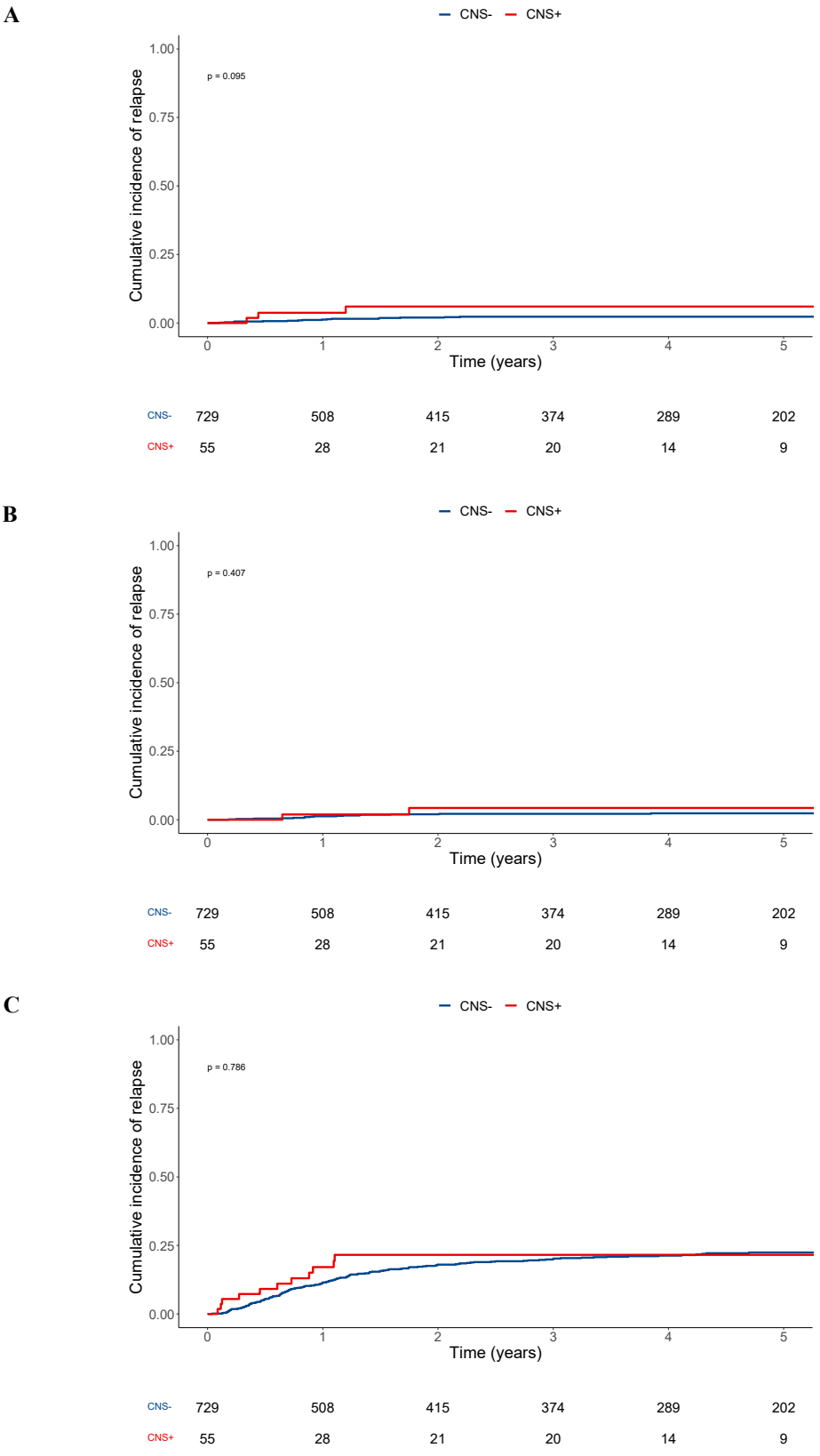
Supplementary figure 1. The GRAALL-2005 protocol.



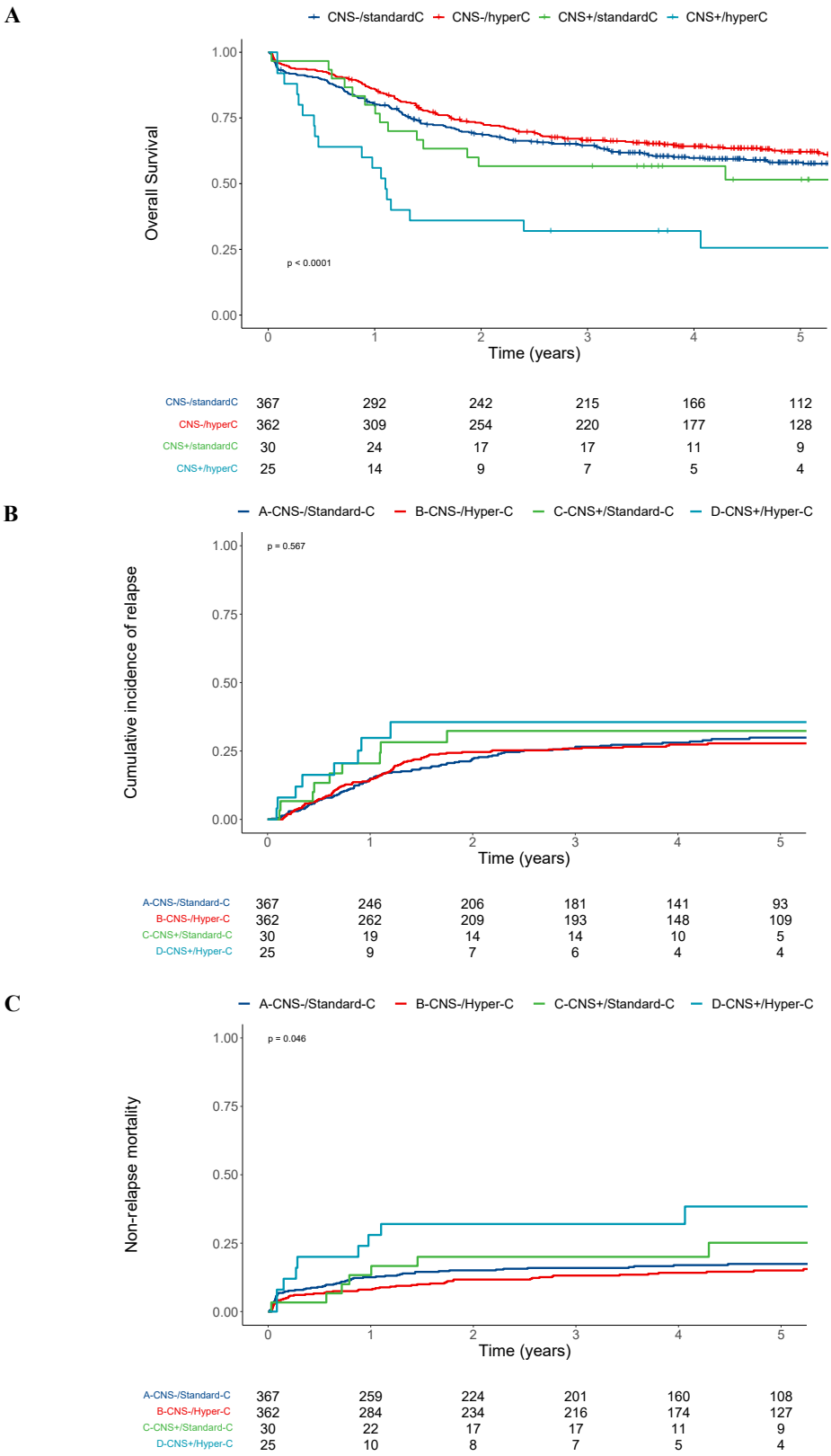
Supplementary figure 2. Overall survival (A), cumulative incidence of relapse (B), and cumulative incidence of non-relapse mortality (C) according to CNS involvement at diagnosis after censoring patients at the time of allogeneic SCT.



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



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.