SUPPLEMENTARY APPENDIX

Dexamethasone (6 mg/m^2/day) and prednisolone (60 mg/m^2/day) were equally effective as induction therapy for childhood acute lymphoblastic leukemia in the EORTC CLG 58951 randomized trial

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 doi:10.3324/haematol.2014.103507
Manuscript received on January 7, 2014. Manuscript accepted on April 4, 2014.
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Appendix

Patients:

Patients were assigned to different risk groups: very low risk (VLR), average risk (AR) and very high risk (VHR). VLR was defined as B-lineage ALL with no VHR criteria, with WBC counts below $10x10^9$/L, and with hyperdiploid karyotype (51-66 chromosomes) or DNA index >1.16 and <1.5, in the absence of CNS and gonadal involvement. VHR criteria consisted of blast count in peripheral blood ≥ $1x10^9$/L at completion of the prephase (day 8), presence of t(9;22), t(4;11) or another MLL rearrangement, near-haploidy (< 34 chromosomes), acute undifferentiated leukemia (AUL), minimal residual disease (MRD) $\geq 10^{-2}$ at completion of induction (day 35)[12] or failure to achieve complete remission (CR).[13,14] AR patients had no VLR and VHR characteristics. Patients with B-cell lineage ALL, with WBC <$100x10^9$/L and without gonadal and CNS involvement were AR1. The others, including T-cell lineage, were classified as AR2. Patients with CNS-2 or with hemorrhagic cerebrospinal fluid (CSF) becoming negative on day 4 of the prephase were included in AR1 group whereas non-equivocal CNS involvement at diagnosis (CNS-3) or any CNS involvement on day 4 were considered as AR2.

Definitions:

Complete remission (CR) was defined as disappearance of all symptoms related to the leukemia, in combination with fewer than 5% leukemic cells in the bone marrow with signs of recovering hematopoiesis and absence of blasts in the CSF.

Remission failure was defined as failure to reach CR at the completion of consolidation. Relapse was defined as the reappearance of more than 20% leukemic cells in the bone marrow or of any leukemic cell at any extramedullary site.

Statistical analysis:

In order to detect an increase of the 5-year EFS rate from 80% (PRED arm) to 85.5% (DEXA arm), corresponding to hazard ratio (HR) of 0.70, 358 patients had to be followed until an EFS event (logrank test, 2-sided alpha=5%, power=90%). So, a total of approximately 2000 patients had to be randomized. Two interim analyses were foreseen to be done and evaluated by the EORTC Independent Data Monitoring Committee.

Randomization, performed centrally at the EORTC Headquarters, was stratified according to patient's age, WBC count at diagnosis, start of prephase (N/Y) and center, using a minimization technique.

Survival distributions were estimated according to the Kaplan-Meier technique; SEs of the estimates were obtained via the Greenwood formula. The two-sided, log-rank test was used for comparisons of treatment outcome. The forest plot technique was used to estimate the treatment HR and its 95% or 99% Confidence Interval, and to assess heterogeneity of HRs.[18] For EFS endpoint, Cox model was used to adjust treatment comparison by important prognostic factors. For patients who reached CR, Fine and Gray model was used to compare cumulative incidences of CNS relapses (isolated or combined), considering non-CNS relapses and deaths in CR as competing risks. All analyses were performed according to the intent-to-treat principle.

The following investigators/biologists participated to this study:

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Supplemental tables on line

Table 1: EORTC-CLG treatment protocol for VLR patients

Table 2: EORTC-CLG treatment protocol for AR (AR1 and AR2) patients

Table 3: EORTC-CLG treatment protocol for VHR patients

Supplemental figures on line

Figure 1: Cumulative incidence of CNS relapse (isolated or combined) according to the randomized arm

Figure 2: Event-free survival (Figure 2A) and overall survival (Figure 2B) for precursor B-cell ALL according to the randomized arm

Figure 3: Event-free survival (Figure 3A) and overall survival (Figure 3B) for T-cell ALL according to the randomized arm

Figure 4: Event-free survival (Figure 4A) and overall survival (Figure 4B) for precursor B-cell ALL according to the 4 different risk groups of EORTC 58951

Figure 5: Event-free survival (Figure 4A) and overall survival (Figure 4B) for precursor B-cell ALL with Standard Risk NCI criteria, and Event-free survival (Figure 4C) and overall survival (Figure 4D) for precursor B-cell ALL with High Risk NCI criteria according to the randomized arm

O = Observed number of events

N = Number of patients randomized

%: 8-year EFS, OS or cumulative incidence estimate, followed by SE

Table 1: EORTC-CLG treatment protocol for VLR patients

Drug	Dose	Days of administration
Induction: protocol IA		
Methotrexate (IT)[€]		1 (prephase)
According to randomization		
PRED (PO)	60 mg/m²	1-7 (prephase)
DEXA (PO)	6 mg/m²	1-7 (prephase)
According to randomization		
PRED (PO)	60 mg/m²	8-28, tapered over 9 days
DEXA (PO)	6 mg/m²	8-28, tapered over 9 days
Vincristine (IV)	1.5 mg/m² (max 2 mg)	8,15,22,29
Daunorubicin (IV)	30 mg/m²	8,15
Methotrexate (IT)[€]		12,25
E coli asparaginase	10,000 IU/m²	12,15,18,22,25,29,32,35
Consolidation: protocol IB		
Cytarabine (IV)	75 mg/m²	38-41,45-48,52-55,59-62
MTX chemotherapy (IT)[€]		38,52
6-mercaptopurine (PO)	60 mg/m²	36-63
According to randomisation		
No asparaginase		
E coli asparaginase	5,000 IU/m²	38,41,45,48,52,55,59,62
Interval therapy		
6-mercaptopurine (PO)	25 mg/m²	1-56
Methotrexate (24 h)[†]	5000 mg/m²	8,22,36,50
MTX chemotherapy (IT)[€]		9,23,37,51
Late intensif.: protocol II		
DEXA (PO)	6 mg/m²	1-21, taper over 9 days
Vincristine (IV)	1.5 mg/m² (max 2 mg)	8,15,22,29
Doxorubicin (IV)	30 mg/m²	8,15
Methotrexate (IT)[€]		38
Cytarabine (IV)	75 mg/m²	38-41,45-48
6-thioguanine (PO)	60 mg/m²	36-49
According to randomisation		
E coli asparaginase	10,000 IU/m²	8,11,15,18
E coli asparaginase	10,000 IU/m²	8,11,15,18
and	5,000 IU/m²	22,25,29,32
Maintenance (74 weeks)		
6-mercaptopurine (PO)	50 mg/m²	Daily
Methotrexate (PO)	20 mg/m²	Weekly

IT indicates intrathecally; PO, orally; PRED, prednisolone; DEXA, Dexamethasone; IV, intravenously;.

[€] Methotrexate: For age less than 1 year: 6 mg, 1 year 8 mg, 2 years 10 mg, 3 years and more: 12 mg

[†] Leucovorin rescue 12 mg/m²/6h starts at H36.

Table 2: EORTC-CLG treatment protocol for AR (AR1 and AR2) patients

Drug	Dose	Days of administration
Induction: protocol IA		
Methotrexate (IT)[e]		1
According to randomization		
PRED (PO)	60 mg/m²	1-7 (prephase)
DEXA (PO)	6 mg/m²	1-7 (prephase)
According to randomization		
PRED (PO)	60 mg/m²	8-28, tapered over 9 days
DEXA (PO)	6 mg/m²	8-28, tapered over 9 days
AR1		
Vincristine (IV)	1.5 mg/m² (max 2 mg)	8,15,22,29
Daunorubicin (IV)	30 mg/m²	8,15,22,29
Triple chemotherapy (IT)[e]		12,25
E coli asparaginase	10,000 IU/m²	12,15,18,22,25,29,32,35
AR2		
Cyclophosphamide	1000 mg/m²	9
Methotrexate (24 h)[†]	5 g/m²	8
Triple chemotherapy (IT)[e]		9,25
Vincristine (IV)	1.5 mg/m² (max 2 mg)	8,15,22,29
Daunorubicin (IV)	40 mg/m²	15,22,29
E coli asparaginase	10,000 IU/m²	12,15,18,22,25,29,32,35
Consolidation: protocol IB		
Cyclophosphamide (IV)	1000 mg/m²	36,63
Cytarabine (IV)	75 mg/m²	38-41,45-48,52-55,59-62
Triple chemotherapy (IT)[e]		38,52
6-mercaptopurine (PO)	60 mg/m²	36-63
According to randomisation		
No asparaginase		
E coli asparaginase	5,000 IU/m²	38,41,45,48,52,55,59,62
Interval therapy		
6-mercaptopurine (PO)	25 mg/m²	1-56
Methotrexate (24 h)[†]	5000 mg/m²	8,22,36,50
Triple chemotherapy (IT)[e]		9,23,37,51
Late intensif.: protocol II		
DEXA (PO)	6 mg/m²	1-21, taper over 9 days
Vincristine (IV)	1.5 mg/m² (max 2 mg)	8,15,22,29
Doxorubicin (IV)	30 mg/m²	8,15,22,29
Triple chemotherapy (IT)[e]		38
Cyclophosphamide (IV)	1000 mg/m²	36
Cytarabine (IV)	75 mg/m²	38-41,45-48
6-thioguanine (PO)	60 mg/m²	36-49
According to randomisation		

E coli asparaginase	10,000 IU/m²	8,11,15,18
E coli asparaginase	10,000 IU/m²	8,11,15,18
and	5,000 IU/m²	22,25,29,32
Maintenance (74 weeks)		
AR1		
6-mercaptopurine (PO)	50 mg/m²	Daily
Methotrexate (PO)	20 mg/m²	Weekly
Triple chemotherapy (IT)[e]		Every 70 days, starting D22, 6 times
According to randomisation		
No pulses		
PRED (PO)[‡]	60 mg/m²	Every 70 days, for 7 days, starting D57-63, 6 times
DEXA (PO)[‡]	6 mg/m²	Every 70 days, for 7 days, starting D57-63, 6 times
Vincristine	1.5 mg/m² (max 2 mg)	Every 70 days, on D57 and D63, 6 times
AR2		
6-mercaptopurine (PO)	50 mg/m²	Daily
Methotrexate (PO)	20 mg/m²	Weekly
Methotrexate (24 h)[†]	5000 mg/m²	Every 70 days, starting D22, 6 times
Triple chemotherapy (IT)[e]		Every 70 days, starting D23, 6 times
E Coli asparaginase	25,000 IU/m²	Every 70 days, starting D23, 6 times
According to randomization		
No pulses		
PRED (PO)[‡]	60 mg/m²	Every 70 days, for 7 days, starting D57-63, 6 times
DEXA (PO)[‡]	6 mg/m²	Every 70 days, for 7 days, starting D57-63, 6 times
Vincristine (IV)	1.5 mg/m² (max 2 mg)	Every 70 days, on D57 and D63, 6 times

IT indicates intrathecally; PO, orally; PRED, prednisolone; DEXA, Dexamethasone; IV, intravenously; D X, day X.

[e] Methotrexate: Less than 1 year: 6 mg, 1 year 8 mg, 2 years 10 mg, 3 years and more: 12 mg
Cytarabine: Less than 1 year: 15 mg, 1 year 20 mg, 2 years 25 mg, 3 years and more: 30 mg
Hydrocortisone: Less than 1 year: 7.5 mg, 1 year 10 mg, 2 years 12.5 mg, 3 years and more: 15 mg

[†] Leucovorin rescue 12 mg/m²/6h starts at H36.

[‡] Same corticosteroid as initial randomisation (protocol IA).

Table 3: EORTC-CLG treatment protocol for VHR patients

Drug	Dose	Days of administration
Induction: protocol IA		
Methotrexate (IT)[e]		1
According to randomization		
PRED (PO)	60 mg/m²	1-7 (prephase)
DEXA (PO)	6 mg/m²	1-7 (prephase)
According to randomization		
PRED (PO)	60 mg/m²	8-28, tapered over 9 days
DEXA (PO)	6 mg/m²	8-28, tapered over 9 days
Cyclophosphamide	1000 mg/m²	9
Methotrexate (24 h)[†]	5 g/m²	8
Triple chemotherapy (IT)[e]		9,25
Vincristine (IV)	1.5 mg/m² (max 2 mg)	8,15,22,29
Daunorubicin (IV)	40 mg/m²	15,22,29
E coli asparaginase	10,000 IU/m²	12,15,18,22,25,29,32,35
Consolidation: protocol IB'		
DEXA	10 mg/m²/12h	36-40,50-54
6-mercaptopurine (PO)	100 mg/m²	36-40
Vincristine	1.5 mg/m² (max 2 mg)	36,41
Methotrexate (24 h)[†]	5 g/m²	36,50
Cytarabine (IV)	2 g/m²/12h	40
Triple chemotherapy (IT)[e]		37,51
E coli asparaginase	10,000 IU/m²	41, 43,45,55,57,59
6-thioguanine (PO)	100 mg/m²	50-54
Vindesine (IV)	3 mg/m² (max 4 mg)	50
Daunorubicin (IV)	50 mg/m²	54
Cyclophosphamide (IV)	500 mg/m²	52,53
VANDA		
DEXA (PO)	10 mg/m²/12h	1-5
Cytarabine (IV)	2 g/m²/12h	1,2
Etoposide (IV)	150 mg/m²	3,4,5
Triple chemotherapy (IT)[e]		5
Mitoxantrone (IV)	8 mg/m²	3,4
E coli asparaginase	10,000 IU/m²	7,9,11,13
Interval therapy		
6-mercaptopurine (PO)	25 mg/m²	1-42
Methotrexate (24 h)[†]	5000 mg/m²	8,22,36
Triple chemotherapy (IT)[e]		9,23,37
Block R1		
DEXA (PO)	10 mg/m²/12h	1-5
6-mercaptopurine (PO)	100 mg/m²	1-5
Vincristine (IV)	1.5 mg/m² (max 2 mg)	1,6

Methotrexate (24 h) †	5000 mg/m²	1
Triple chemotherapy (IT) ε		2
Cytarabine (IV)	2 g/m²/12h	5
E coli asparaginase	25,000 IU/m²	6
Block R2		
DEXA (PO)	10 mg/m²/12h	1-5
6- thioguanine (PO)	100 mg/m²	1-5
Vindesine (IV)	3 mg/m² (max 4 mg)	1
Methotrexate (24 h) †	5000 mg/m²	1
Triple chemotherapy (IT) ε		2
Cyclophosphamide (IV)	500 mg/m²	3,4
Daunorubicin (IV)	50 mg/m²	5
E coli asparaginase	25,000 IU/m²	6
Block R3		
DEXA (PO)	10 mg/m²/12h	1-5
Cytarabine (IV)	2 g/m²/12h	1,2
Etoposide (IV)	150mg/m²	3,4,5
Triple chemotherapy (IT) ε		2
E coli asparaginase	25,000 IU/m²	6
Maintenance (50 weeks)		
6-mercaptopurine (PO)	50 mg/m²	Daily
Methotrexate (PO)	20 mg/m²	Weekly
Triple chemotherapy (IT) ε		Every 70 days, starting D22

IT indicates intrathecally; PO, orally; PRED, prednisolone; DEXA, Dexamethasone; IV, intravenously; D X, day X.

ε Methotrexate: Less than 1 year: 6 mg, 1 year 8 mg, 2 years 10 mg, 3 years and more: 12 mg
Cytarabine: Less than 1 year: 15 mg, 1 year 20 mg, 2 years 25 mg, 3 years and more: 30 mg
Hydrocortisone: Less than 1 year: 7.5 mg, 1 year 10 mg, 2 years 12.5 mg, 3 years and more: 15 mg

† Leucovorin rescue 12 mg/m²/6h starts at H36.

Figure 1: Cumulative incidence of CNS relapse (isolated or combined) according to the randomized arm

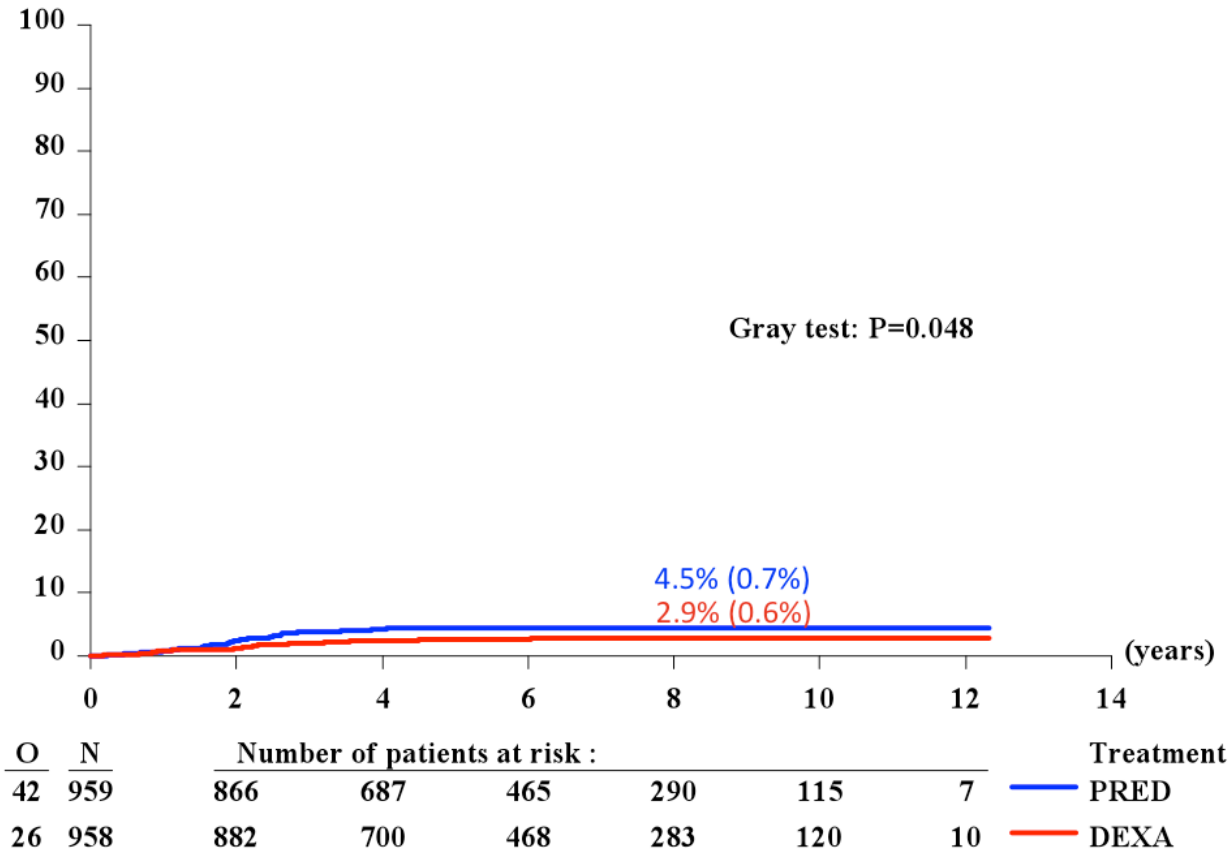
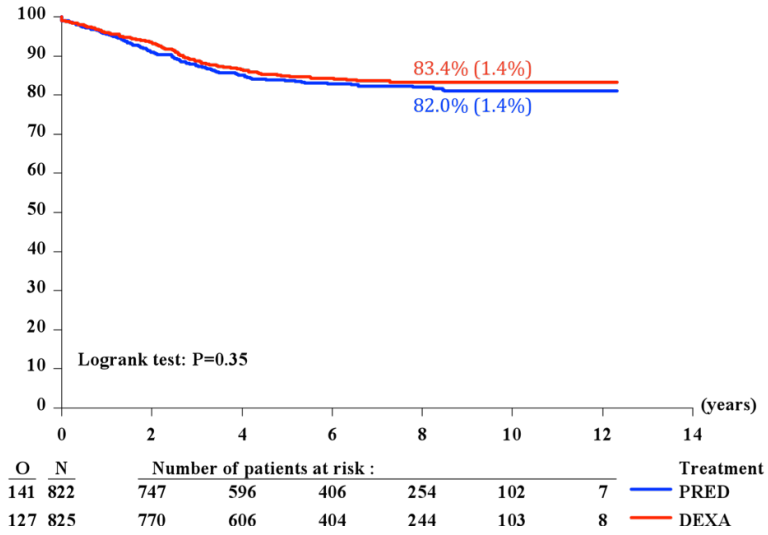


Figure 2: Event-free survival (Figure 2A) and overall survival (Figure 2B) for precursor B-cell ALL according to the randomized arm



B.

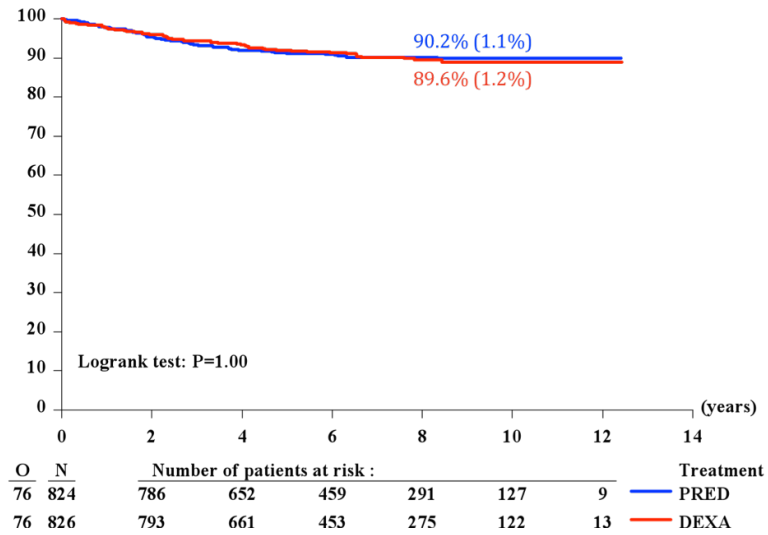
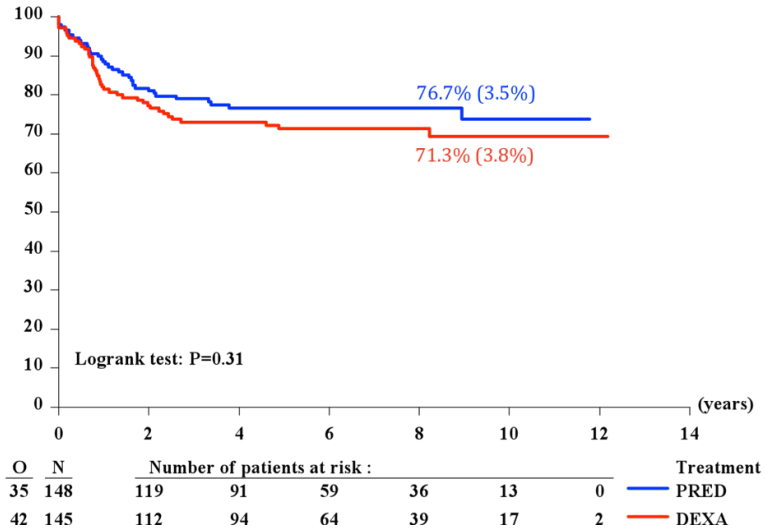


Figure 3: Event-free survival (Figure 3A) and overall survival (Figure 3B) for T-cell ALL according to the randomized arm

A.



B.

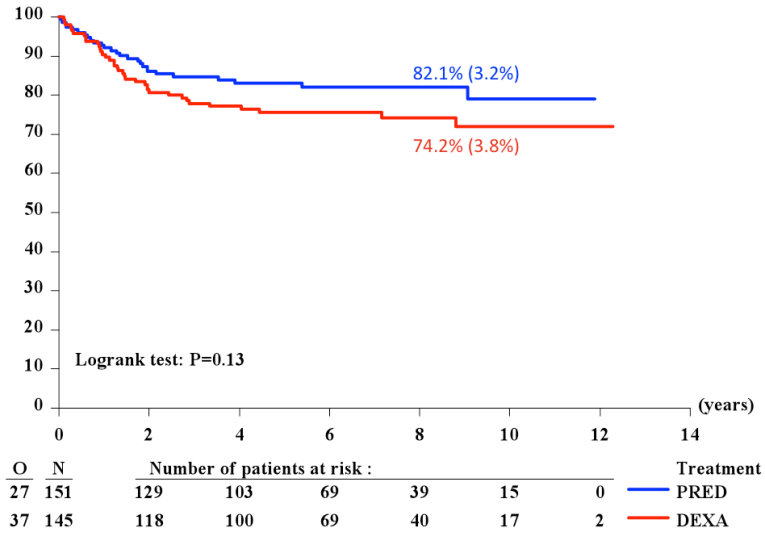
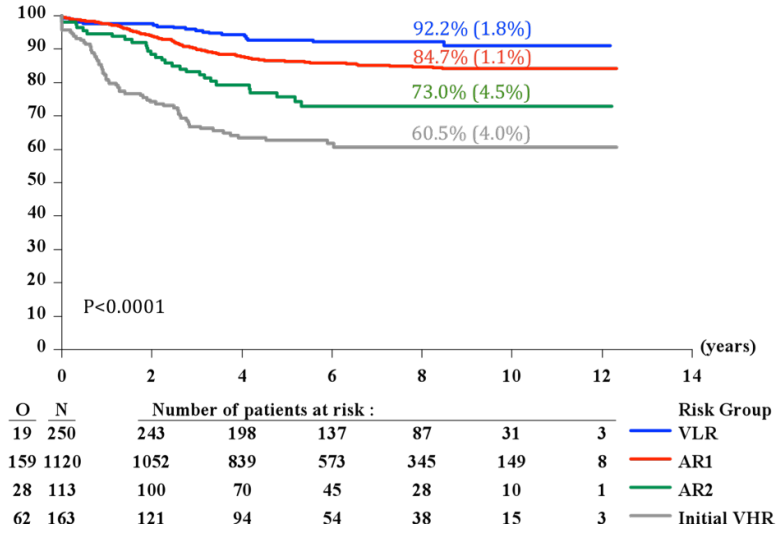


Figure 4: Event-free survival (Figure 4A) and overall survival (Figure 4B) for precursor B-cell ALL according to the 4 different risk groups of EORTC 58951

A.



B.

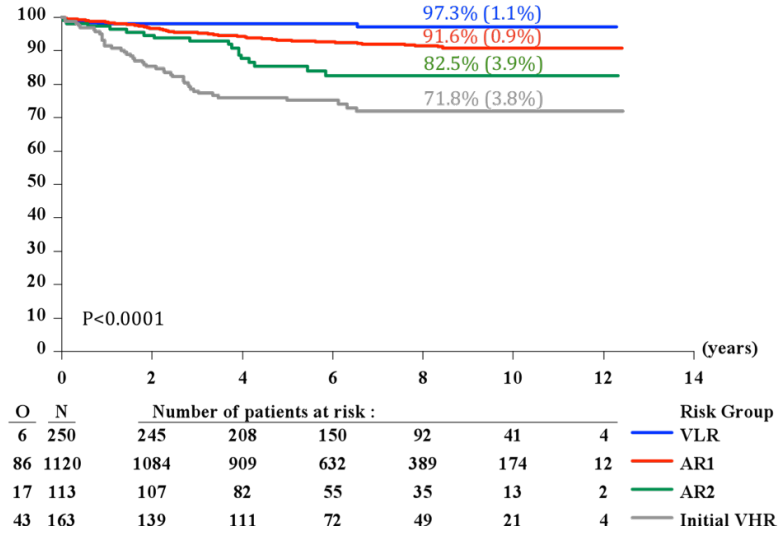
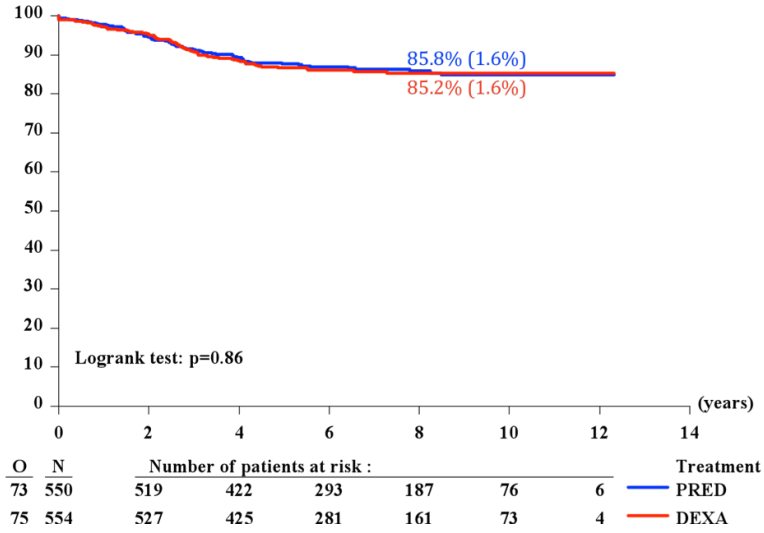


Figure 5: Event-free survival (Figure 4A) and overall survival (Figure 4B) for precursor B-cell ALL with Standard Risk NCI criteria, and Event-free survival (Figure 4C) and overall survival (Figure 4D) for precursor B-cell ALL with High Risk NCI criteria according to the randomized arm

A.



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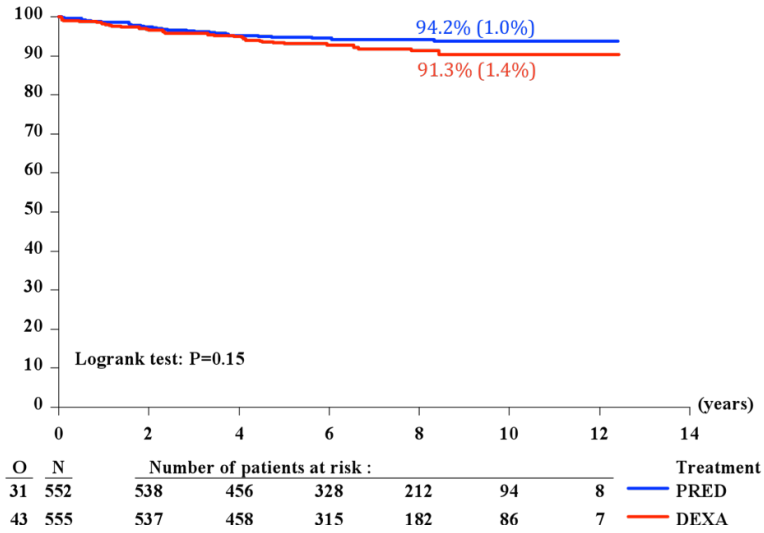
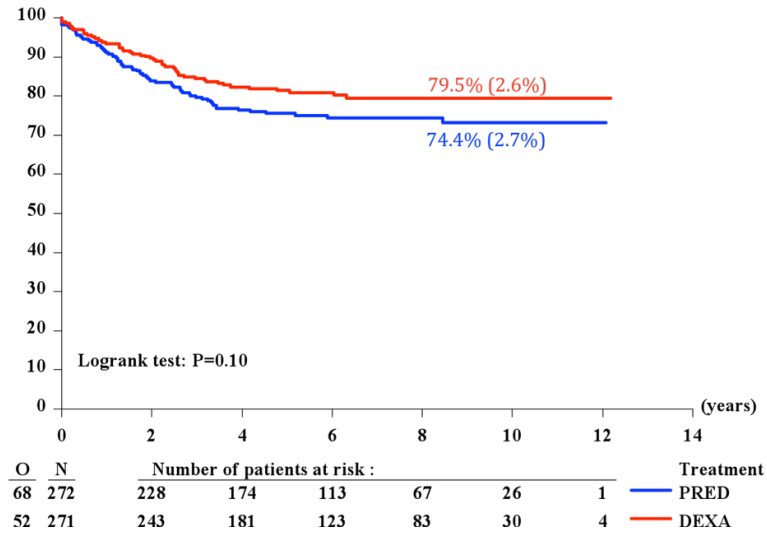
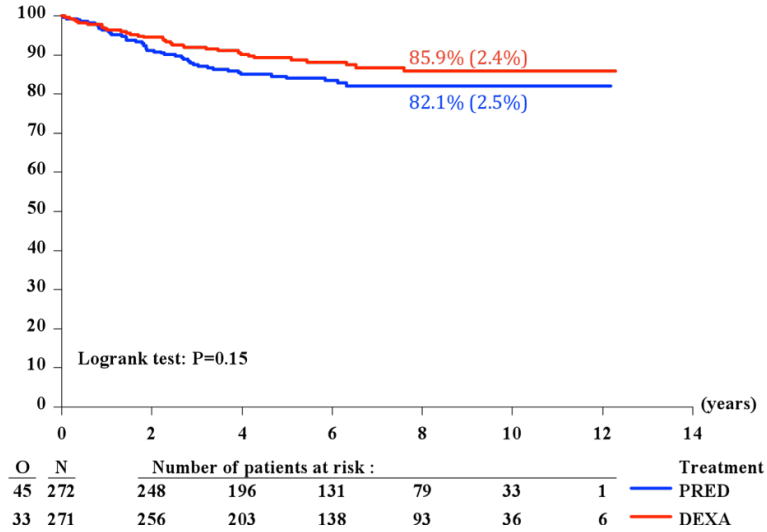


C.


100
90
80
70
60
50
40
30
20
10
0
79.5% (2.6%)
74.4% (2.7%)
Logrank test: P=0.10
(years)
0 2 4 6 8 10 12 14
O N Number of patients at risk : Treatment
68 272 228 174 113 67 26 1 PRED
52 271 243 181 123 83 30 4 DEXA

D.


100
90
80
70
60
50
40
30
20
10
0
85.9% (2.4%)
82.1% (2.5%)
Logrank test: P=0.15
(years)
0 2 4 6 8 10 12 14
O N Number of patients at risk : Treatment
45 272 248 196 131 79 33 1 PRED
33 271 256 203 138 93 36 6 DEXA