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Impact of age and sex on survival outcomes in patients aged 1-45 years with acute lymphoblastic leukemia treated according to the stratification used in the NOPHO ALL2008 trial

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Short title: Survival of the NOPHO ALL2008 trial by age and sex

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Abstract

Age and sex have historically been associated with differences in acute lymphoblastic leukemia (ALL) survival. In the NOPHO ALL2008 trial, patients aged 1-45 years with *BCR*::*ABL1*-negative B-precursor and T-cell ALL were included, but neither sex nor age was integrated into risk group allocation. Among 1,771 trial patients stratified into protocol-appropriate risk groups, we estimated the impact of age and sex on survival (even after relapse) and toxicities prospectively registered at three-month intervals.

In multivariate Cox regression analysis adjusted by sex, age group, and risk group, age but not sex was an independent risk factor for reduced 5-year event-free survival (EFS), hazard ratio 1.57 (95%CI 1.15-2.14) for patients 10-17.9 years, and 2.70 (2.03-3.58) for patients 18-45 years, compared to patients <10 years at diagnosis.

The overall 5-year pEFS was 0.83. For standard-risk patients (B-lineage, white cell count $<100x10^9$/l, no risk genetics, minimal residual disease day 29 <0.1%), an inferior 5-year EFS was observed among patients 18-45 years (pEFS 0.78, p=<0.001) and 10-17.9 years (pEFS 0.86, p=0.002) compared to patients <10 years (pEFS 0.93). For the intermediate-risk and high-risk groups, EFS was worse for patients 18-45 years compared to patients <10 years, pEFS 0.69 vs 0.89 (p=<0.001) and pEFS 0.55 vs 0.71 (p=0.005), respectively.

Osteonecrosis and veno-occlusive disease were associated with the female sex in standard-risk group, and age ≥10 years was associated with osteonecrosis, thrombosis, and pancreatitis in sex- and treatment-group-adjusted analyzes.

In conclusion, this study indicates that risk-grouping and/or treatment-intensity criteria should differ across age groups, and age-adapted strategies to mitigate toxicities are needed.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in children and adolescents with an overall survival above 90% with the best contemporary treatments [1,2]. The dramatic improvements in outcome since the 1970s are mostly attributed to the evolution of multiagent chemotherapy and risk-adapted treatment strategies that include cytogenetic mapping and minimal residual disease (MRD) monitoring [3]. Among adolescents and young adults, ALL is a rare type of cancer, and outcome for these patients has lagged behind that of children despite intensified chemotherapy and frequent use of allogeneic hematopoietic stem cell transplantation (HSCT) [4–6]. After the year 2000, publications on improved survival of adolescent and young adult (AYA) ALL-patients treated with pediatric-type regimens started to emerge [7,8].

The inferior prognosis of ALL in AYAs compared to that in children can partly be explained by the age-related variations in the molecular subtypes of ALL and immunophenotypes. *ETV6*::*RUNX1* and high-hyperdiploidy are common in young children, while T-cell leukemia, *ABL*-class fusions, and *KMT2A* rearrangements become more frequent with older age [7,9,10]. Toxicities, on the other hand, remain a major challenge not least in those who undergo allogeneic HSCT [11], and some studies report 10–30% treatment-related mortality (TRM) among adolescents and young adults undergoing transplantation [12].

Contemporary, risk-based pediatric ALL treatment uses baseline risk factors such as age, white blood cell count (WBC), immunophenotype and extramedullary involvement, genetic alterations as well as treatment response by detection of MRD to tailor the treatment intensity [13]. The ultimate goal is to balance the treatment intensity to induce and maintain long-term remission and minimize the risk of serious acute and long-term side effects.

In the NOPHO ALL2008 trial, therapy was primarily guided by genetics and MRD as the most profound changes compared to previous treatment [14,15], and patients could be included up to the age of 45 years. In this study, prospectively registered data were used to analyze the effect of sex and age on survival and non-

fatal toxicities in patients stratified and treated according to the NOPHO ALL2008 protocol for non-infant and *BCR*::*ABL1*-negative B-cell precursor (BCP) and T-cell ALL.

Methods

Patients

For the analyzes in this study, we included all patients aged 1-45 years at diagnosis having BCP or T-cell ALL in Denmark, Estonia, Finland, Iceland, Lithuania, Norway, and Sweden, from July 1, 2008, to March 1, 2016, while the NOPHO ALL2008 trial was open for randomizations. Patients were followed up until June 30, 2023. Figure 1 describes the detailed inclusion criteria.

The cohort characteristics of included 1,771 patients, and their primary events are presented in Table 1 by sex and age group (1-9.9, 10-17.9, and 18-45 years at diagnosis). Central nervous system (CNS) leukemia (=CNS3; $\geq 10^6$ cells per liter with blasts; or clinical involvement by cranial nerve palsy or a leukemic mass on CNS or eye imaging) was detected at diagnosis in 72 patients (4.1%). Testicular involvement was reported in six (0.6%) male patients. Any risk group was not assigned to 21 patients due to induction death (N=18) or severe infection-driven major treatment modifications (N=3). In total, 125 patients underwent HSCT in their first complete remission (CR1). The median follow-up time of survivors was 8.3 years; 9.0 years among patients 1-9.9 years at diagnosis, 7.3 years among patients 10-17.9 years at diagnosis, and 6.6 years among patients 18-45 years at diagnosis.

Risk assessment

The details of the NOPHO ALL2008 trial design and treatment strategy are described in previous publications [15,16]. All patients received a three-drug induction and intrathecal therapy. Patients with T-cell immunophenotype or WBC $\geq 100 \times 10^9$/l (except patients with *ETV6*::*RUNX1*) received dexamethasone while all other patients received prednisolone. At the end of induction (EOI), patients were assigned to the standard-risk (SR), intermediate-risk (IR), or high-risk (HR) arms of the trial. However, patients initially treated with dexamethasone with MRD ≥25% on day 15 shifted to HR therapy already from that day.

Stratifying genetic alterations in NOPHO ALL2008 were *KMT2A*-rearrangements and modal chromosome number <45 (stratified as HR) as well as *TCF3*::*PBX1*, iAMP21, and dic(9;20) (not eligible for SR). After excluding stratifying genetic findings, BCP patients with WBC <100, no CNS3, and day 29 MRD <0.1% were stratified as SR, while T-cell and BCP patients with WBC ≥100 and MRD <0.1% as IR. Furthermore, patients with EOI MRD ≥0.1% but <5% were stratified as IR (after prednisolone induction) or HR (after dexamethasone induction). All patients having MRD ≥5% at EOI were allocated to HR treatment. HSCT was indicated for any patient with MRD ≥5% at EOI, HR patients with MRD ≥5% after block A1 or ≥0.1% after block B1, or SR and IR patients with MRD ≥0.1% at day 79.

Statistical analyzes

Differences between sexes and age groups in the distribution of individual parameters were analyzed using the Chi-square test for categorical variables. The Kaplan-Meier method was used to estimate the probability of event-free survival (pEFS) and overall survival (pOS) rates, and differences were compared with the 2-sided log-rank test. Cox regression was used for analyzing crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CI) of major outcomes EFS and OS, while competing-risks regression was used for analyzing crude and adjusted subdistribution hazard ratios (SHR) of relapse and death in first complete remission (DCR1) where the competing events were relapse, DCR1 and second malignant neoplasm (SMN). For the adjusted analyzes, the final risk group (SR, IR, HR), age (1-9.9, 10-17.9, 18-45), and sex were included in the models as explanatory factors; the results are presented as cumulative incidence rates. In all analyzes involving the trial's final risk groups, the 21 patients without an assigned risk group were excluded. Further details of statistical methods are described in supplementary data.

The above analyzes were conducted using STATA 16.1 (StataCorp, College Station, TX, USA). Cumulative incidence of single adverse outcomes and relapse types were compared between age groups and sexes using Gray's test [17]. Competing events were defined as induction failure, death in CR1, relapse (including specific relapse types), and SMN. Relapse types were defined in two ways: 1) isolated bone marrow, isolated extramedullary, or combined, and 2) CNS-involving vs. non-CNS-involving. The function 'cuminc' in package 'cmprsk' in R Version 4.1.1 (R Statistical Software v4.1.1; R Core Team 2021) was used [18,19].

Ethical statement

Written informed consent was obtained from each participant or each participant's guardian and human investigations were performed in accordance with the Helsinki Declaration, after approval by the National Medicines Agencies (Eudract no. 2008-003235-20), and relevant ethical committees. The trial is registered at www.clinicaltrials.gov (NCT00819351).

RESULTS

Baseline and response characteristics

All age groups in the study cohort included a higher proportion of male than female patients (p=0.006) (Table 1). The distribution of WBC at diagnosis, CNS status, indication for allogeneic HSCT in CR1, and primary events was similar between male and female patients (Table 1). However, T-cell immunophenotype (p<0.001), stratification to high-risk group (p=0.049), and poor EOI MRD response (p=0.001) were more frequent among males (Table 1).

The proportion of patients with T-ALL was higher (p<0.001) in the two older age groups (25.5%, 30.0%) compared to the youngest age group (9.8%). There was an age difference in genetic subgroups (p<0.001), e.g. low-risk genetics (high-hyperdiploidy, *ETV6*::*RUNX1*) were more common in patients 1-9.9 years of age (58.8%, 21.6%, 9.4%). Furthermore, the EOI MRD was lower (p<0.001) for patients <10 years at diagnosis. This translated into a higher proportion of older patients allocated to the IR and HR therapy as well as having an indication for HSCT in CR1 (Table 1).

Of the included study patients, 1699 (97.1%) achieved first complete remission (MRD <5%) after induction (N=1609) or the first high-risk blocks (post HR block A1 (including patients shifted directly to block therapy day 15; N=85), post HR block B1 (N= 1) or post HR block C1 (N=4). The continuous remission rate (CR1) at the end of follow-up was 81.7% for the whole cohort (Table 1). After a median follow-up of 8.3 years, 226 relapses (5-year cumulative risk: 12.2% (10.7-13.9%)) had occurred: 135 (5y cumulative risk: 13.1% (11.1-15.5%)) among males and 91 (5y cumulative risk: 11.1% (9.0-13.6%)) among females. The 5-year cumulative

risk of relapse was highest (28.7%) among patients 18-45 years at diagnosis (Figure 2). Twelve patients had testicular involvement at relapse (median time to relapse: 34 months, range 24-59), none of them with overt testicular involvement at primary diagnosis. The relapse patterns differed from each other by age groups and immunophenotypes (Table 2). The 5-year cumulative risk of SMN (overall 0.9%) did not differ between sex or age group.

When the frequencies of primary events were analyzed in each final risk group, there were no significant differences in the cumulative incidence of relapse between sexes (p=0.176), but age group was significantly associated with risk of relapse (<10 vs. 10-17.9 years, p<0.004; <10 vs. 18-45 years, p<0.001) (Table 3 and Figure 2 panel a-b).

Toxicity

A slightly higher (p=0.06) proportion of females (N=12; 1.5%) suffered induction death than males (N=6; 0.6%) (Table 1), which was not significant when the analysis was stratified by induction glucocorticosteroid type (0.9% (prednisolone) vs 4.4% (dexamethasone) for females, and 0.4% vs 1.3% for males respectively; p=0.08).

Concerning the 19 predefined toxicities in NOPHO ALL2008 trial [16], females had significantly more osteonecrosis (ON, p=0.001), veno-occlusive disease (VOD, p=0.009), and posterior reversible encephalopathy syndrome (PRES, p=0.040) than males (Table S1). The frequencies of toxicities by age group are presented in Table S1 and by risk group in Table S2. When stratified by risk group (Table S3), females had increased OR for ON and VOD only in the SR group. Odds ratios for thrombosis were significantly increased in all risk groups for patients ≥10 years, and for ON in all risk groups for adolescents and in SR and IR groups for adults (Table S3). Adolescents had an elevated OR for seizures in the SR group and in the IR group for severe hyperlipidemia and severe kidney dysfunction. Adults had elevated odds for PJP in the SR group and for pancreatitis in the SR and IR groups. Figure 3 illustrates the sex and risk group adjusted OR by age group for the eleven toxicities with ≥50 observations. Table S4 shows the adjusted results for all 19 toxicities.

Event-free survival

The 5-year event-free survival (EFS) was 0.83±0.01 for the whole cohort, 0.91±0.01 for patients stratified as SR, 0.85±0.01 for IR, and 0.66±0.03 for HR patients (0.64±0.03 for HR-chemo, 0.67±0.04 for HR-HSCT). We did not observe a sex difference in the EFS (p=0.48) for the whole cohort or within any risk group (Figure S1).

When analyzing the 5-year EFS by age, patients 1-9.9 years at diagnosis had significantly better outcome than those 10-17.9 years (HR 1.54 (95% CI 1.15-2.07), p=<0.001) or 18-45 years (HR 2.70 (95% CI 2.03-3.58), p<0.001) (Figure 4). This difference was most pronounced for patients stratified as SR where a statistically significant difference was observed between patients 1-9.9 years and each older age group, but for patients stratified as IR and HR, we only observed a significant difference between patients 18-45 years and the youngest age groups (Figure 4).

When the 5-year EFS was analyzed in Cox regression models, there were no significant interactions between the final risk group and sex or age (Table S5). The hazard ratios and 95% confidence intervals for EFS in multivariate Cox regression analyzes adjusted by sex, age group, and risk group are presented in Table 4. Results are also illustrated as cumulative incidence curves for events by age group and risk group in Figure S2 (panel a-b). When we estimated the EFS for the HR patients separately and stratified by the HSCT status, the lower EFS in the oldest age group was only significant for patients that had an indication for HSCT in CR1 (age 18-45 compared to 1-9.9 years; HR 3.94, 95% CI 1.78-8.75) (Figure 4).

When the risk of DCR1 was analyzed in competing-risks regression models, there were no significant interactions between the final risk group and sex or age (Table S5). Subdistribution hazard ratio (SHR) for DCR1 was significantly higher for patients 18-45 years in the intermediate-risk group, 3.65 (95% CI 1.30-10.23), compared to age 1-9.9 years, but in the adjusted multivariable regression analysis, the SHR for DCR1 reached significance only in 10-17.9-year-old patients (Table 4). Figure S2c illustrates the cumulative incidence of DCR1 for the adjusted model by risk group. These curves showed that the effect on DCR1 was more pronounced in HR patients than in the other groups. The adjusted SHR for DCR1 was also analyzed

within the final risk groups; the IR group had SHR 2.26 (95% CI 1.01-5.05) and the HR group 8.56 (95% CI 3.98-18.41) when compared with the SR group.

Concerning the risk of relapse, there was no significant interaction between the final risk group and sex, but a trend (p=0.06) was found between age and the final risk group (Table S5). This trend of interaction was explained by patients aged 10-17.9 years treated in the SR group having significantly elevated HR 2.83 (95%CI 1.48-5.40) compared to the patients <10 years (p=0.002), which was not the case for IR (p=0.213) or HR patients (p=0.332). Patients aged 18-45 years had a significantly elevated risk of relapse in all treatment groups. In the adjusted multivariable regression analysis, both IR and HR compared to the SR group as well as the 18-45-year-old group compared to the younger groups had a significantly increased risk of relapse (Table 4). These results are illustrated in Figure S2d as cumulative incidence for the three risk groups separately, where all three groups had an increasing incidence over time, with the HR group having the highest incidence rates.

Overall survival

The 5-year overall survival (OS) for the whole cohort was 0.89±0.01. The 5-year OS estimates by final risk group were 0.96±0.01 for SR, 0.92±0.01 for IR, and 0.70±0.02 for HR patients (0.68±0.03 in HR-chemo, 0.74±0.04 in HSCT). The OS for males and females was similar (p=0.475). When analyzing the 5-year OS by age groups, patients 1-9.9 years at diagnosis had a better outcome (OS 0.94±0.01) than those 10-17.9 years (OS 0.86±0.02) (p=0.001) or 18-45 years (OS 0.73±0.02) (p<0.001).

An interaction age*risk group was found regarding the risk of lower OS (Table S5). This interaction was explained by patients aged 10-17.9 years at diagnosis treated as SR (hazard ratio 4.42 (95% CI, 1.92-10.16)) or IR (hazard ratio 3.01 (95% CI, 1.42-6.41)) group having statistically significantly lower OS compared to patients aged 1-9.9 years at diagnosis, but not if they were allocated to HR therapy (hazard ratio 1.19 (95% CI, 0.71-2.01)). The HRs and 95% CIs for OS in multivariate Cox regression analyzes adjusted by sex, age group, and risk group are presented in Table 4. In addition, the sex and age-adjusted hazard ratios were estimated for HR patients and stratified by HSCT status. This analysis showed that age group had a

significant effect on OS impairment (age 10-17.9, HR 1.93, 95% CI 0.67-5.53; age 18-45 years, HR 4.33, 95% CI 1.76-10.67) only in the HSCT group as respective HRs in the high-risk chemotherapy group were 1.08 (95% CI 0.59-1.99) for age 10-17.9 years and 1.43 (95% CI 0.82-2.51) for age 18-45 years compared with age group 1-9.9 years.

In a subanalysis where we only included patients stratified as intermediate risk and made further adjustments for immunophenotype, WBC count, and EOI MRD, patients ≥10 years at diagnosis had worse OS than patients 1-9.9 years, and adult patients had worse EFS and OS as well as higher risk of relapse and DCR1 compared to children 1-9.9 years (Table S6).

Survival after first relapse

For the whole relapse cohort, the 5-year pOS was 0.47±0.03. We found significant differences between the age groups: 10-17.9 years (pOS 0.38±0.08; p=0.021) and 18-45 years (pOS 0.28±0.05; p<0.001) compared to patients 1-9.9 years at primary diagnosis (pOS 0.65±0.05) (Table S7). The age-group associations among the relapse patients were very similar to the primary treatment where patients ≥10 years primarily stratified as SR or IR had worse pOS than patients 1-9.9 years but not if stratified as high-risk (chemo-only or HSCT in CR1). The OS was similar between the age groups 10-17.9 years and 18-45 years for the different primary risk groups (SR, IR, HR). We did not observe differences in the pOS after the first relapse between females and males, in general, or by risk group. Relapses occurring very early (<18 months from primary diagnosis) had significantly poorer survival than the others overall, but time to relapse did not have a significant effect on survival in HR patients (Table S7).

Discussion

The results from the NOPHO ALL2008 trial are among the best reported for younger adults with ALL, demonstrating that pediatric-inspired therapy is both feasible and effective for this age group.

In general, males are considered to have worse overall survival after childhood cancer than females [20,21]. This has been shown specifically for ALL [22,23] and in earlier Nordic studies [24,25] although not in the NOPHO-ALL2000 trial [14]. In a recent large study, the 5-year OS in childhood ALL was 85% in males compared to 88% in females (hazard ratio 1.24, 95% CI 1.12-1.37) [21]. Other studies have also reported worse survival for male patients with ALL [26,27] but without further information on, e.g., relapse rate or TRM. To counter the effect of sex on survival, some ALL trials allocate males to longer maintenance therapy than females [28].

In the NOPHO ALL2008 trial, we abandoned all non-CNS extramedullary involvement (testicular, mediastinal, liver, spleen enlargements) at diagnosis in the risk-group assignment. Testicular involvement at diagnosis was a rare finding and none of the affected males relapsed during follow-up. In addition, the incidence of testicular relapse did not differ from that in previous NOPHO trials.

Even though T-cell immunophenotype and poor MRD response, both of which are associated with inferior survival, were more common among males in the NOPHO ALL2008 trial, we did not find statistically significant sex differences in the 5-year pEFS or pOS. The results from the NOPHO ALL2008 trial therefore indicate that stratification of treatment by cytogenetics and MRD will provide similar survival probabilities for females and males.

Concerning severe toxicity, induction failures were slightly more common in females than males. However, the higher proportion of males with relapse abolished the effect of females' higher susceptibility to toxicity on impaired EFS and OS. In previous NOPHO trials, females were twice as likely to experience treatment-related mortality than males [29], which confirms reports from the US Children's Oncology Group, where female HR patients experienced significantly more TRMs [30], and the MRC UKALL X trial, where female sex was associated with infection-related deaths during induction therapy [31]. The underlying biological mechanisms for these sex differences are still poorly understood and warrant further study.

With regard to the frequency of non-fatal toxicities evaluated in the NOPHO ALL2008 trial, osteonecrosis, VOD, and PRES were more common in female than male patients. However, when adjusted for age, we only found an increased risk of ON and VOD among females stratified as SR. The adverse effect of female

sex has not been a consistent finding in previous publications of ON [32,33]. Furthermore, the alternate-week dexamethasone administration during delayed intensification instead of continuous treatment has been reported to reduce the risk of ON in all patient groups [32]. This strategy was also utilized in the NOPHO ALL08 trial, and the SR group got the lowest cumulative dose of dexamethasone despite age. Thus, our finding confirms the independent effect of female sex on the risk of developing ON. Concerning VOD, treatment with 6-thioguanine has been identified as a risk factor [34] and seems to be associated with *TPMT* heterozygosity [35], but the effect of prolonged exposure to pegylated asparaginase during the maintenance phase of SR and IR patients is a novel finding from the NOPHO ALL2008 trial [36]. The association between female sex and the risk of VOD has to our knowledge not been described previously. However, the pattern of non-fatal toxicities differing by age (<10 vs ≥10 years) when adjusting for sex and trial risk group (like ON, thrombosis, pancreatitis) warrants further attention. Osteonecrosis, in addition to higher age, has been stated to be associated with, e.g., hypertriglyceridemia, and host germline polymorphisms of genes encoding, e.g., proteins involved in thrombosis, fibrinolysis, and lipid homeostasis [37]. Hence, preemptive measures for older patients such as thrombo-prophylaxis [38] and lipid-lowering measures [39] might be worth testing in prospective clinical trials.

Since several studies have confirmed higher age to be a risk factor for lower EFS and OS [1,14,28,40], age is commonly used as a stratifying factor for risk-group allocation in childhood ALL. In addition to AYA patients being more likely to have subtypes of ALL associated with worse outcomes [3,41], outcome differences could also reflect age-related differences in pharmacokinetics and treatment adherence [42]. Some favorable prognosis-related cytogenetic markers, such as the chromosomal rearrangement *ETV6*::*RUNX1* and high-hyperdiploidy, peak at preschool age [43]. Similarly, older children and young adults have a higher proportion of T-cell immunophenotype, *ABL*-class fusions, as well as a higher frequency of prednisone-poor response, all factors associated with inferior outcomes [41,44,45]. Furthermore, especially adolescent patients may have problems with treatment adherence as they are more independent in their daily lives compared to small children [46]. In young adults, age-dependent changes in body composition and drug distribution, co-medication, and hormonal changes may also influence treatment efficacy and toxicity [47].

Following previous findings, T-cell immunophenotype, worse EOI MRD response, and HR cytogenetics were more common among the older patients in NOPHO ALL2008. Although age was not a stratifying factor in the NOPHO ALL2008 trial, our study shows that despite the risk-stratification strategy used in this trial, age ≥10 years is associated with worse EFS and OS compared to younger age, including a higher risk of relapse among adult patients. Furthermore, the interaction analyses (age*risk-group) for risk of relapse and pOS showed that the effect of age is still different in risk groups despite taking into account the known age-related factors (immunophenotype, cytogenetics, EOI-MRD) in patient stratification.

An analysis of survival after relapsed childhood ALL primarily treated within NOPHO trials was recently published [48]. In our study analyzing the whole trial cohort, the 5-year OS after the first relapse was significantly worse for patients ≥10 years compared to those <10 years at primary diagnosis. This supports that age ≥10 years at diagnosis predicts worse outcome both for the primary disease and relapse. The age difference we found was seen in patients primarily stratified as SR and IR but not in those stratified as HR. This effect of age could also explain the finding in interaction analysis of pOS for the adolescent age group where the hazards of relapse or DCR1 were not significantly elevated. One of the underlying factors for the large outcome difference after the first relapse could be a selection of treatment-resistant leukemic clones after high-risk upfront treatment. Furthermore, no association of survival with time to relapse was found after primary high-risk treatment.

Limitations of the study: age-related factors such as differences in pharmacokinetics, treatment adherence, or effects of toxicity on possible changes in treatment, were not possible to analyze.

In conclusion, treatment based on the NOPHO ALL2008 risk-stratification system abolished the previously reported sex differences on EFS and OS in patients aged 1-45 years with *BCR*::*ABL1*-negative B-precursor and T-cell ALL and demonstrated the benefits of pediatric-inspired therapy for young adults. However, despite most AYAs being stratified to higher risk groups, the age differences observed in this study suggest that de-intensifying the treatment for some AYAs might be problematic. In upcoming trials, more extensive inclusion of genetic mapping, addressing age-related factors such as adherence to oral chemotherapy,

possible toxicity-driven treatment adaptations, and differences in pharmacokinetics, as well as evaluating whether MRD cut-offs for risk groups should differ between age groups, could be of interest.

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Table 1. Description of the patients included in the study, by sex and age at diagnosis.

	Total N (%)	Sex N (%)			Age at diagnosis N (%)			
		female	male	*p*-value	1-9.9 years	10-17.9 yrs	18-45 yrs	*p*-value
Total	1771							
Median follow-up	8.3 years				9.0 years	7.3 years	6.6 years	
Age at diagnosis				0.006				
1 – 9 yrs	1188 (67.1)	559 (70.9)	629 (64.0)		-	-	-	
10 – 17 yrs	306 (17.3)	125 (15.9)	181 (18.4)		-	-	-	
18 – 45 yrs	277 (15.6)	104 (13.2)	173 (17.6)					
Sex				<0.001				0.006
female	788 (44.5)	-	-		559 (47.1)	125 (40.8)	104 (37.5)	
male	983 (55.5)	-	-		629 (52.9)	181 (59.2)	173 (62.5)	
WBC at diagnosis				0.21				0.10
<100 x 10^9/L	1535 (86.7)	692 (87.8)	843 (85.8)		1044 (87.9)	257 (84.0)	234 (84.5)	
≥100 x 10^9/L	236 (13.3)	96 (12.2)	140 (14.2)		144 (12.1)	49 (16.0)	43 (15.5)	
Immunophenotype				<0.001				<0.001
BCP	1493 (84.3)	707 (89.7)	786 (80.0)		1071 (90.2)	228 (74.5)	194 (70.0)	
T-ALL	278 (15.7)	81 (10.3)	197 (20.0)		117 (9.8)	78 (25.5)	83 (30.0)	
Cytogenetics*				<0.001				<0.001
LR	790 (44.6)	382 (48.5)	408 (41.5)		698 (58.8)	66 (21.6)	26 (9.4)	
IR	117 (6.6)	62 (7.9)	55 (5.6)		75 (6.3)	26 (8.5)	16 (5.8)	
HR	82 (4.6)	43 (5.5)	39 (4.0)		45 (3.8)	16 (5.2)	21 (7.6)	
other	439 (24.8)	192 (24.4)	247 (25.1)		225 (18.9)	111 (36.3)	103 (37.2)	
missing	65 (3.7)	28 (3.6)	37 (3.8)		28 (2.4)	9 (2.9)	28 (10.1)	
T-cell patients	*278 (15.7)*	*81 (10.3)*	*197 (20.0)*		*117 (9.8)*	*78 (25.5)*	*83 (30.0)*	
MRD d29 (EOI)				0.001				<0.001
≥25%	22 (1.2)	3 (0.4)	19 (1.9)		9 (0.8)	9 (2.9)	4 (1.4)	
≥5% <25%	70 (4.0)	35 (4.4)	35 (3.6)		24 (2.0)	17 (5.6)	29 (10.5)	
≥0.1% <5%	431 (24.4)	197 (25.0)	234 (23.8)		265 (22.3)	82 (26.8)	84 (30.3)	
<0.1%	552 (31.1)	249 (31.6)	303 (30.8)		399 (33.6)	83 (27.1)	70 (25.3)	
negative <0.1%	626 (35.4)	277 (35.2)	349 (35.5)		460 (38.7)	102 (33.3)	64 (23.1)	
no sample	4 (0.2)	3 (0.4)	1 (0.1)		3 (0.3)	0	1 (0.4)	
no marker	6 (0.3)	3 (0.4)	3 (0.3)		2 (0.2)	1 (0.3)	3 (1.1)	
death before d29	17 (1.0)	12 (1.5)	5 (0.5)		11 (0.9)	3 (1.0)	3 (1.1)	
d15 >25%	43 (2.4)	9 (1.1)	34 (3.5)		15 (1.3)	9 (2.9)	19 (6.9)	

	Total N (%)	Sex N (%)			Age at diagnosis N (%)			
		female	male	*p*-value	1-9.9 years	10-17.9 yrs	18-45 yrs	*p*-value
CNS status				0.16				0.131
CNS1	1549 (87.5)	677 (85.9)	872 (88.7)		1027 (86.4)	267 (87.3)	255 (92.1)	
CNS2	148 (8.4)	73 (9.3)	75 (7.6)		110 (9.3)	22 (7.2)	16 (5.8)	
CNS3	72 (4.1)	36 (4.6)	36 (3.7)		50 (4.2)	16 (5.2)	6 (2.2)	
Missing	2 (0.1)	2 (0.3)	0 (0)		1 (0.1)	1 (0.3)	0 (0)	
Final risk group**				0.049				<0.001
Standard risk	792 (44.7)	354 (44.9)	438 (44.6)		636 (53.5)	94 (30.7)	62 (22.4)	
Intermediate risk	628 (35.5)	289 (36.7)	339 (34.5)		389 (35.5)	127 (41.5)	112 (40.4)	
High risk	330 (18.6)	131 (16.6)	199 (20.2)		149 (12.5)	81 (26.5)	100 (36.1)	
No risk group	21 (1.2)	14 (1.8)	7 (0.7)		14 (1.2)	4 (1.3)	3 (1.1)	
HSCT in CR1				0.074				<0.001
yes	125 (7.1)	46 (5.8)	79 (8.0)		45 (3.8)	34 (11.1)	46 (16.6)	
no	1646 (92.9)	742 (94.2)	904 (92.0)		1143 (96.2)	272 (88.9)	231 (83.4)	
Primary events				0.24				<0.001
CR1	1447 (81.7)	650 (82.5)	797 (81.1)		1036 (87.2)	237 (77.5)	174 (62.8)	
induction failure	18 (1.0)	12 (1.5)	6 (0.6)		12 (1.0)	3 (1.0)	3 (1.1)	
DCR1	65 (3.7)	29 (3.7)	36 (3.7)		27 (2.3)	19 (6.2)	19 (6.9)	
SMN	15 (0.8)	6 (0.8)	9 (0.9)		10 (0.8)	4 (1.3)	1 (0.4)	
relapse	226 (12.8)	91 (11.5)	135 (13.7)		103 (8.7)	43 (14.1)	80 (28.9)	

*Only including BCP ALL, ** Intention-to-treat. Six male patients had testicular involvement at diagnosis (3 BCP, 3 T-cell). Abbreviations: WBC = white blood cell count, MRD = minimal residual disease, EOI = end of induction, BCP = B-cell precursor, T-ALL = T-cell acute lymphoblastic leukemia, LR = low-risk genetics (high-hyperdiploidy, t(12;21)), IR = intermediate risk genetics (t(1;19), iAMP21, dic(9;20)), HR = high-risk genetics (KMT2A-rearrangement, hypodiploidy), CNS = central nervous system, CR1 = first complete remission, DCR1 = death in first complete remission, SMN = second malignant neoplasm.

Table 2. Description of the types of relapses in total and by immunophenotype.

	Sex N (%)			Age at diagnosis N (%)			
	female	**male**	***p*-value**	**1-9.9 yrs**	**10-17.9 yrs**	**18-45 yrs**	***p*-value**
Relapse type (total)			0.16				<0.001
isolated BM	63 (69.2)	74 (54.8)		59 (56.7)	27 (62.8)	51 (63.8)	
combined	14 (15.4)	28 (20.7)		25 (24.0)	6 (14.0)	11 (13.7)	
isolated EM*	14 (15.4)	32 (23.7)		18 (17.5)	10 (23.3)	18 (22.2)	
missing		1 (1.0)		1 (1.0)	0 (0.0)	0 (0.0)	
Relapse type (total)			0.51				<0.001
CNS-involving	22 (24.2)	39 (28.9)		35 (33.7)	15 (34.9)	12 (14.8)	
non-CNS	69 (75.8)	95 (70.4)		67 (65.0)	28 (65.1)	68 (85.0)	
missing		1 (0.7)		1 (1.0)	0 (0.0)	0 (0.0)	
BCP relapse	80 (87.9)	103 (76.3)		84 (81.6)	37 (86.0)	62 (77.5)	
BCP relapse type			0.66				0.73
isolated BM	53 (66.3)	61 (59.2)		49 (58.3)	23 (62.2)	42 (67.7)	
combined	13 (16.3)	19 (18.4)		18 (21.4)	5 (13.5)	9 (14.5)	
isolated EM	14 (17.5)	22 (21.4)		16 (19.0)	9 (24.3)	11 (17.7)	
Missing	0 (0.0)	1 (1.0)		1 (1.2)	0 (0.0)	0 (0.0)	
BCP relapse type			0.67				0.007
CNS-involving	21 (26.3)	26 (25.2)		28 (33.3)	13 (35.1)	6 (9.7)	
non-CNS	59 (73.8)	76 (73.8)		55 (65.5)	24 (64.9)	56 (90.3)	
Missing	0 (0.0)	1 (1.0)		1 (1.2)	0 (0.0)	0 (0.0)	
T-cell relapse	11 (12.1)	32 (23.7)		19 (18.4)	6 (14.0)	18 (22.5)	
T-cell relapse type			0.014				0.18
isolated BM	10 (91.0)	13 (41.0)		10 (53.0)	4 (67.0)	9 (50.0)	
combined	1 (9.0)	9 (28.0)		7 (37.0)	1 (17.0)	2 (11.0)	
isolated EM	0 (0.0)	10 (31.0)		2 (11.0)	1 (17.0)	7 (39.0)	
T-cell relapse type			0.054				0.99
CNS-involving	1 (9.0)	13 (41.0)		6 (32.0)	2 (33.0)	6 (33.0)	
non-CNS	10 (91.0)	19 (59.0)		13 (68.0)	4 (67.0)	12 (67.0)	

*12 testicular relapses (11 BCP, 1 T-cell), 34 isolated CNS relapses. Abbreviations: BM = bone marrow, EM = extramedullary, CNS = central nervous system, BCP = B-cell precursor, T-cell = T-cell acute lymphoblastic leukemia

Table 3. Frequencies of all primary events by sex and age group in each final risk group (patients without assigned risk group excluded, N=21).

	Sex			Age at diagnosis			
	Male N (%)	**Female** N (%)	***p-value***	**1-9 years** N (%)	**10 -17 years** N (%)	**18-45 years** N (%)	***p-value***
Total N	983[1]	788[2]		1188[3]	306[4]	277[5]	
Standard risk	438	354	0.79	636	94	62	**<0.001**
CR1	392 (89.5)	322 (91.0)		588 (92.5)	78 (83.0)	48 (77.4)	
DCR1	5 (1.1)	4 (1.1)		6 (0.9)	2 (2.1)	1 (1.6)	
Relapse	34 (7.8)	25 (7.1)		33 (5.2)	13 (13.8)	13 (21.0)	
SMN	7 (1.6)	3 (0.8)		9 (1.4)	1 (1.1)	0 (0.0)	
Intermediate risk	339	289	0.18	389	127	112	**<0.001**
CR1	275 (81.1)	245 (84.8)		341 (87.7)	107 (84.3)	72 (64.3)	
DCR1	8 (2.4)	10 (3.5)		7 (1.8)	4 (3.1)	7 (6.3)	
Relapse	56 (16.5)	33 (11.4)		40 (10.3)	16 (12.6)	33 (29.5)	
SMN	0 (0.0)	1 (0.3)		1 (0.3)	0 (0.0)	0 (0.0)	
High risk	199	131	0.93	149	81	100	**0.005**
CR1	130 (65.3)	82 (62.6)		106 (71.1)	52 (64.2)	54 (54.0)	
DCR1	23 (11.6)	15 (11.5)		14 (9.4)	13 (16.0)	11 (11.0)	
Relapse	44 (22.1)	32 (24.4)		29 (19.5)	13 (16.0)	34 (34.0)	
SMN	2 (1.0)	2 (1.5)		0 (0.0)	3 (3.7)	1 (1.0)	

7 males[1] and 14 females[2] could not be assigned a risk group. 14 patients <10 years[3], 4 patients 10-17.9 years[4], and 3 patients aged 18-45 years[5] could not be assigned a risk group. CR1 = first complete remission, DCR1 = death in first complete remission, SMN = second malignant neoplasm

Table 4. The hazard ratios (HR) or sub-distribution hazard ratio (SHR) and 95% confidence intervals (CI) for the studied outcomes in multivariate Cox and competing-risks regression analysis adjusted by sex, age group, and risk group (patients without assigned risk group excluded, N=21).

	EFS		**Relapse***		**Death in CR1***		**OS**	
	HR	**95% CI**	**SHR**	**95% CI**	**SHR**	**95% CI**	**HR**	**95% CI**
Standard risk	1		1		1		1	
Intermediate risk	**1.54**	**(1.15-2.07)**	**1.63**	**(1.17-2.29)**	**2.26**	**(1.01-5.05)**	**1.77**	**(1.14-2.75)**
High risk	**3.33**	**(2.44-4.56)**	**2.52**	**(1.72-3.69)**	**8.56**	**(3.98-18.41)**	**5.92**	**(3.82-9.17)**
Age <10 y	1		1		1		1	
Age 10-17.9 y	**1.57**	**(1.15-2.14)**	1.40	(0.95-2.05)	**1.90**	**(1.04-3.45)**	**2.04**	**(1.36-3.06)**
Age 18-45 y	**2.70**	**(2.03-3.58)**	**3.04**	**(2.19-4.21)**	1.75	(0.94-3.25)	**3.67**	**(2.54-5.31)**
Female	1		1		1		1	
Male	1.02	(0.81-1.29)	1.07	(0.81-1.41)	0.87	(0.53-1.40)	0.91	(0.68-1.22)

*Competing risks (death in CR1, SMN, relapse) were considered in the analyzes. CR1 = first complete remission, SMN = second malignant neoplasm, EFS = event-free survival, OS = overall survival.

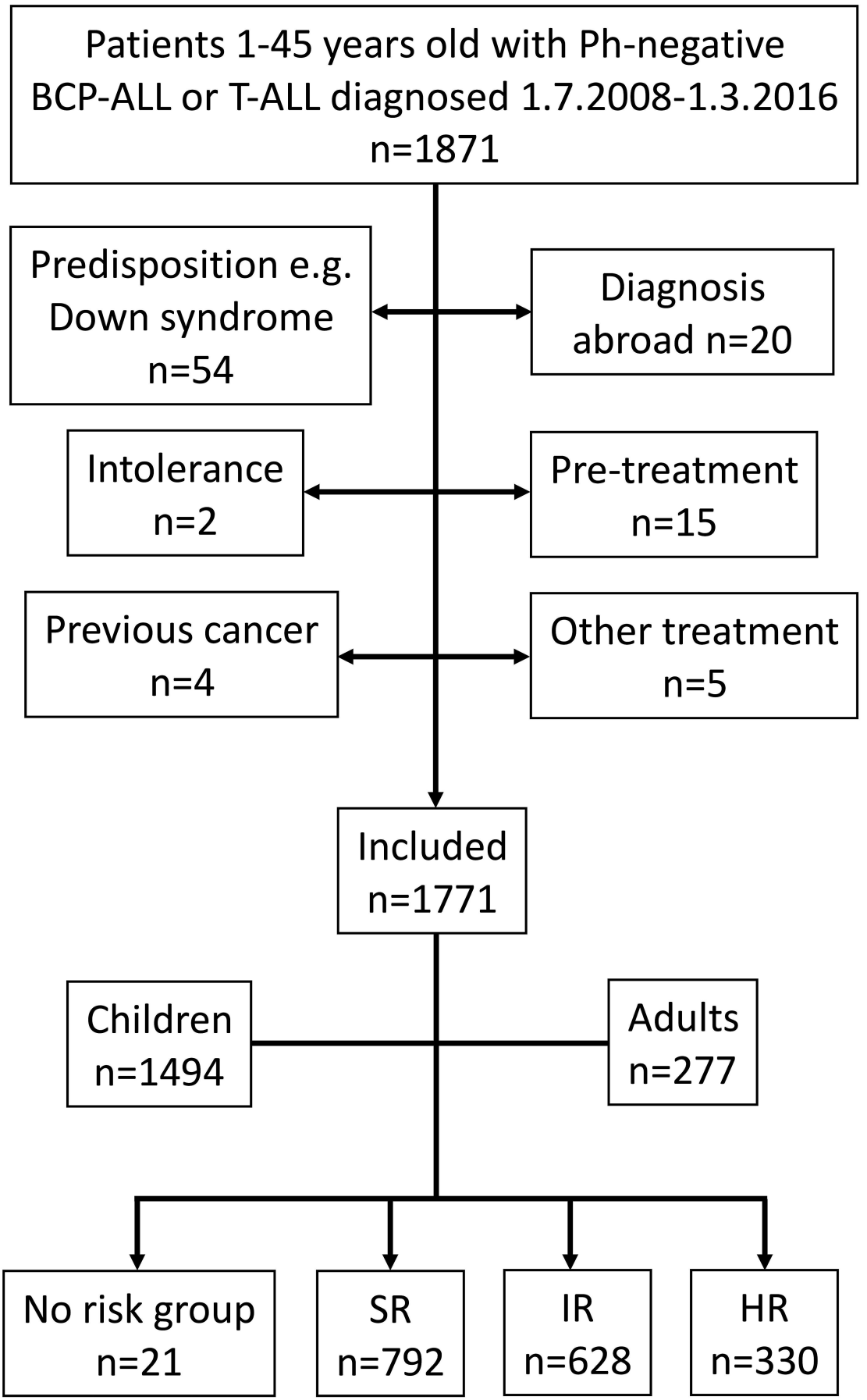
Figure legends

Figure 1. Consort diagram ALL patients 1-45 years at diagnosis. Patients with BCR::ABL1-positive or multiple-lineage ALL, Down's syndrome, previous cancer, diagnosis outside a NOPHO country, pre-treatment beyond one week, intolerance to leukemia medication, or insufficient registration were excluded from the current analyzes. (BCP = B-cell precursor; ALL = acute lymphoblastic leukemia; n = number; SR = standard risk; IR = intermediate risk; HR = high risk.)

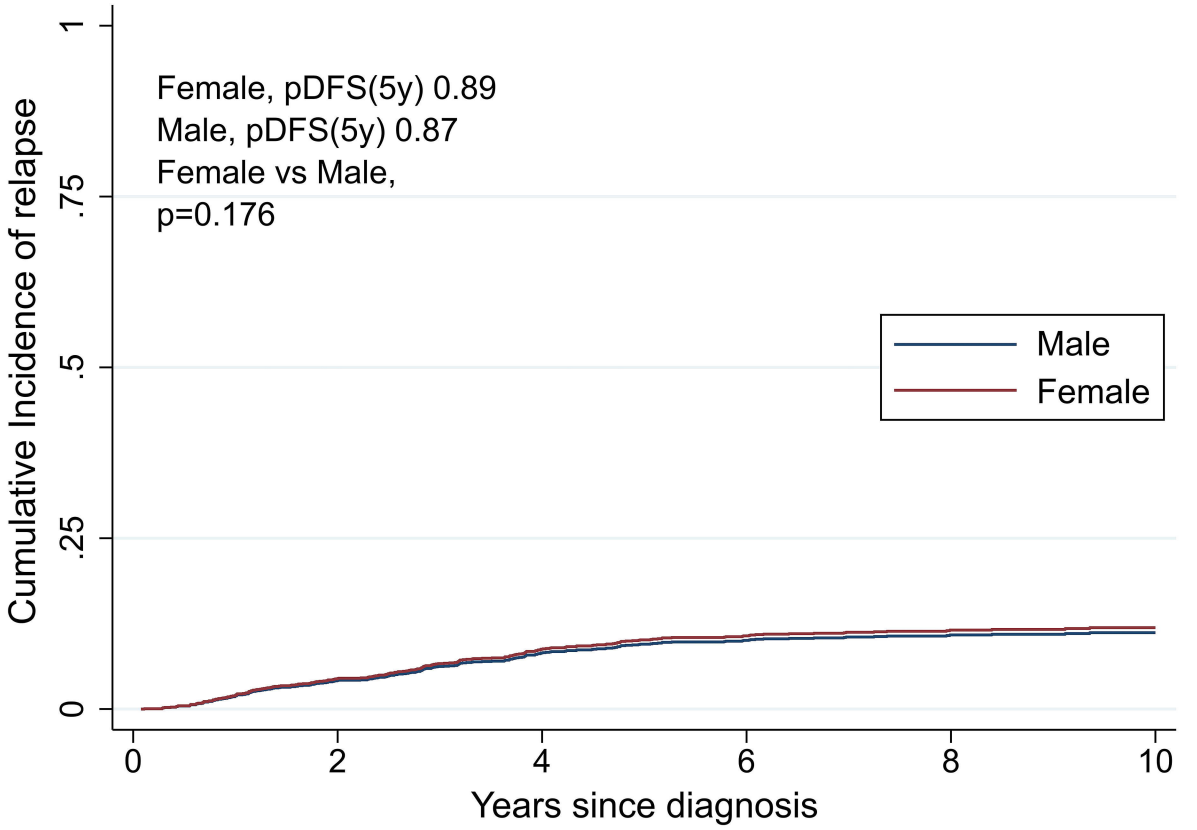
Figure 2. Cumulative incidence of relapse in the NOPHO ALL2008 trial. In panel a, the cumulative incidence of relapse is presented by sex. In panel b, the cumulative incidence of relapse is presented by age group. The panels also illustrate the timing of the relapses. (DFS = disease-free survival.)

Figure 3. Toxicities. The adjusted (by sex and final treatment group) log odds ratios with 95% confidence intervals for the eleven most common toxicities of the NOPHO ALL2008 trial presented by age groups. (Anaphylaxis = anaphylactic reaction to asparaginase; CTC = common terminology criteria for adverse events; PRES = posterior reversible encephalopathy syndrome; OR = odds ratio.)

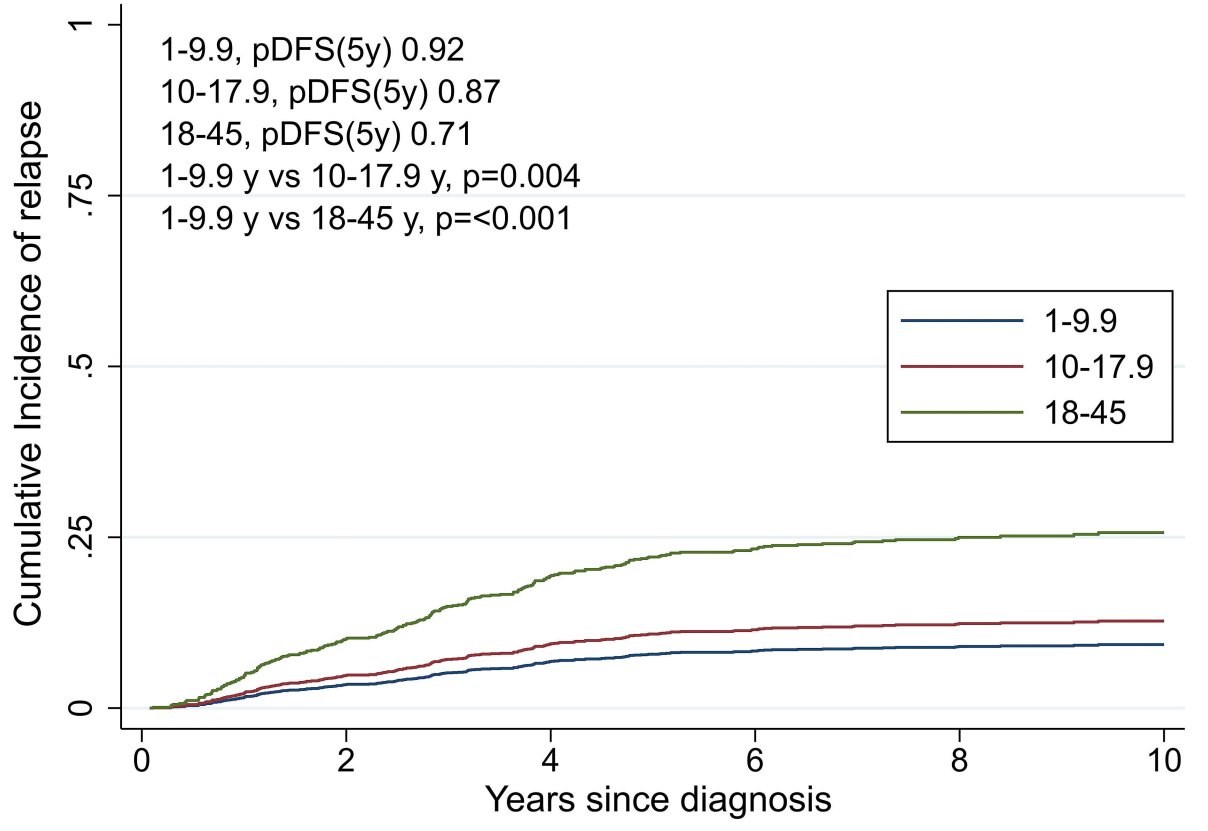
Figure 4. **Event-free survival (pEFS) at 5 years in the NOPHO ALL2008 trial presented by age group.** In panel a, the overall pEFS of the NOPHO ALL2008 trial at 5 years is presented by age group. In panel b, the pEFS of the standard-risk group at 5 years is presented by age group. In panel c, the pEFS of the intermediate-risk group at 5 years is presented by age group. In panel d, the pEFS of the high-risk group at 5 years is presented by age group. In panel e, the pEFS at 5 years of the high-risk group treated with HSCT in CR1 is presented by age group. In panel f, the pEFS at 5 years of the high-risk group treated with chemotherapy only is presented by age group. (y = years; HSCT = hematopoietic stem-cell transplantation; CR1 = first complete remission.)

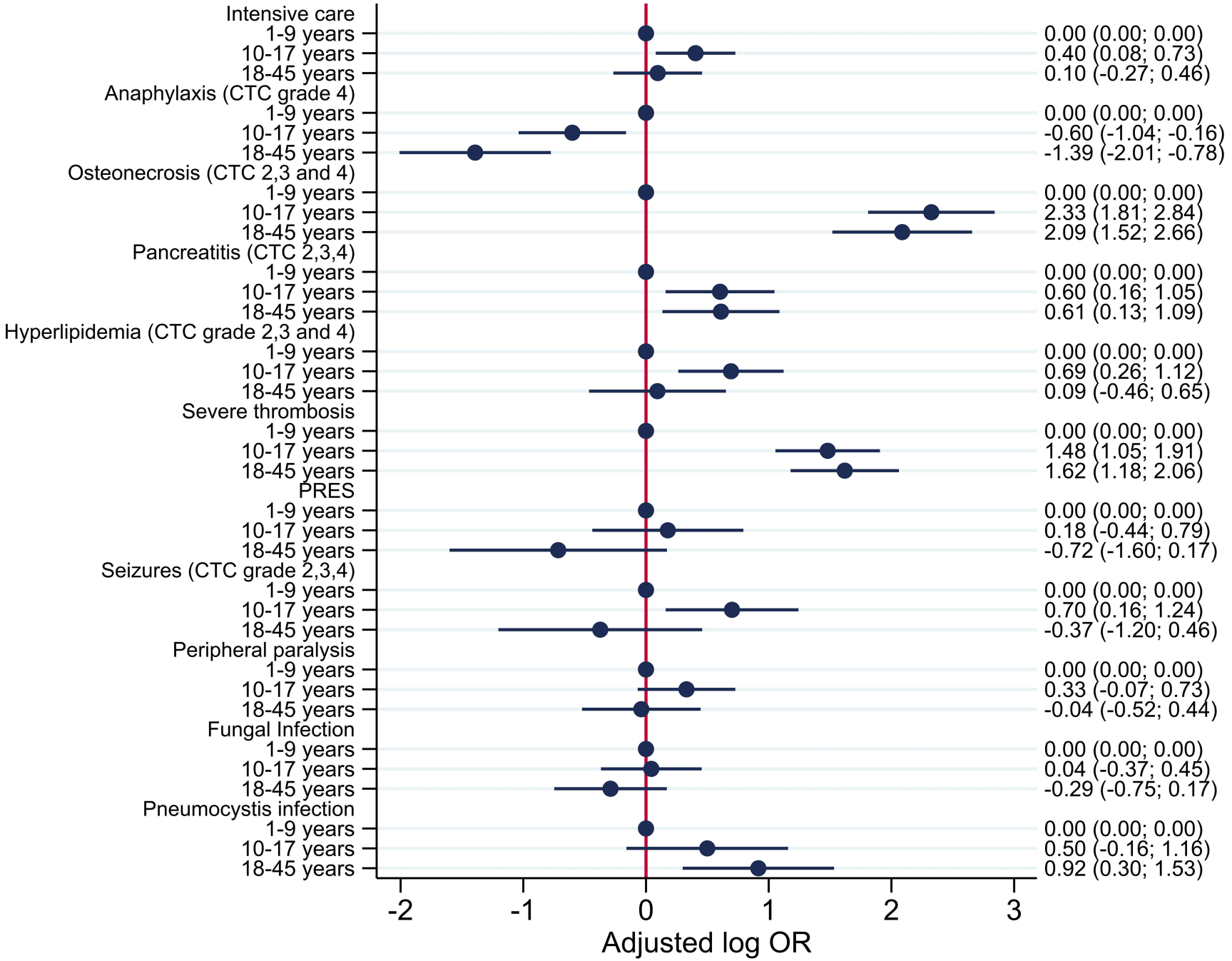

Patients 1-45 years old with Ph-negative BCP-ALL or T-ALL diagnosed 1.7.2008-1.3.2016 n=1871
Predisposition e.g. Down syndrome n=54
Diagnosis abroad n=20
Intolerance n=2
Pre-treatment n=15
Previous cancer n=4
Other treatment n=5
Included n=1771
Children n=1494
Adults n=277
No risk group n=21
SR n=792
IR n=628
HR n=330

A

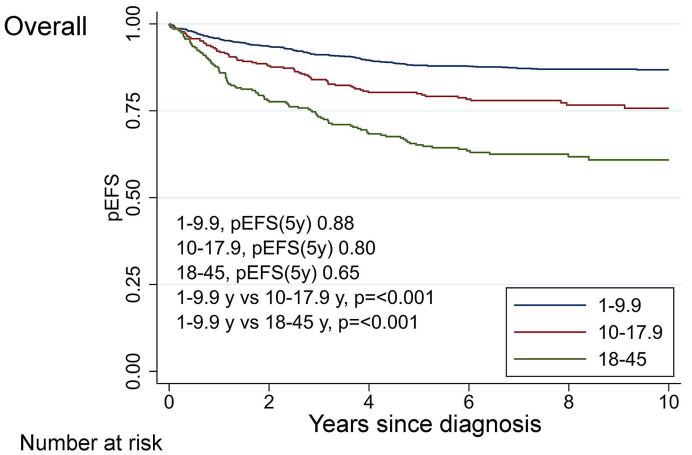

Female, pDFS(5y) 0.89
Male, pDFS(5y) 0.87
Female vs Male,
p=0.176
Male
Female
Cumulative Incidence of relapse
0
.25
.5
.75
1
0
2
4
6
8
10
Years since diagnosis

B


1-9.9, pDFS(5y) 0.92
10-17.9, pDFS(5y) 0.87
18-45, pDFS(5y) 0.71
1-9.9 y vs 10-17.9 y, p=0.004
1-9.9 y vs 18-45 y, p=<0.001
1-9.9
10-17.9
18-45
Cumulative Incidence of relapse
0
.25
.5
.75
1
0
2
4
6
8
10
Years since diagnosis


Intensive care
1-9 years
10-17 years
18-45 years
Anaphylaxis (CTC grade 4)
1-9 years
10-17 years
18-45 years
Osteonecrosis (CTC 2,3 and 4)
1-9 years
10-17 years
18-45 years
Pancreatitis (CTC 2,3,4)
1-9 years
10-17 years
18-45 years
Hyperlipidemia (CTC grade 2,3 and 4)
1-9 years
10-17 years
18-45 years
Severe thrombosis
1-9 years
10-17 years
18-45 years
PRES
1-9 years
10-17 years
18-45 years
Seizures (CTC grade 2,3,4)
1-9 years
10-17 years
18-45 years
Peripheral paralysis
1-9 years
10-17 years
18-45 years
Fungal Infection
1-9 years
10-17 years
18-45 years
Pneumocystis infection
1-9 years
10-17 years
18-45 years
0.00 (0.00; 0.00)
0.40 (0.08; 0.73)
0.10 (-0.27; 0.46)
0.00 (0.00; 0.00)
-0.60 (-1.04; -0.16)
-1.39 (-2.01; -0.78)
0.00 (0.00; 0.00)
2.33 (1.81; 2.84)
2.09 (1.52; 2.66)
0.00 (0.00; 0.00)
0.60 (0.16; 1.05)
0.61 (0.13; 1.09)
0.00 (0.00; 0.00)
0.69 (0.26; 1.12)
0.09 (-0.46; 0.65)
0.00 (0.00; 0.00)
1.48 (1.05; 1.91)
1.62 (1.18; 2.06)
0.00 (0.00; 0.00)
0.18 (-0.44; 0.79)
-0.72 (-1.60; 0.17)
0.00 (0.00; 0.00)
0.70 (0.16; 1.24)
-0.37 (-1.20; 0.46)
0.00 (0.00; 0.00)
0.33 (-0.07; 0.73)
-0.04 (-0.52; 0.44)
0.00 (0.00; 0.00)
0.04 (-0.37; 0.45)
-0.29 (-0.75; 0.17)
0.00 (0.00; 0.00)
0.50 (-0.16; 1.16)
0.92 (0.30; 1.53)
-2
-1
0
1
2
3
Adjusted log OR

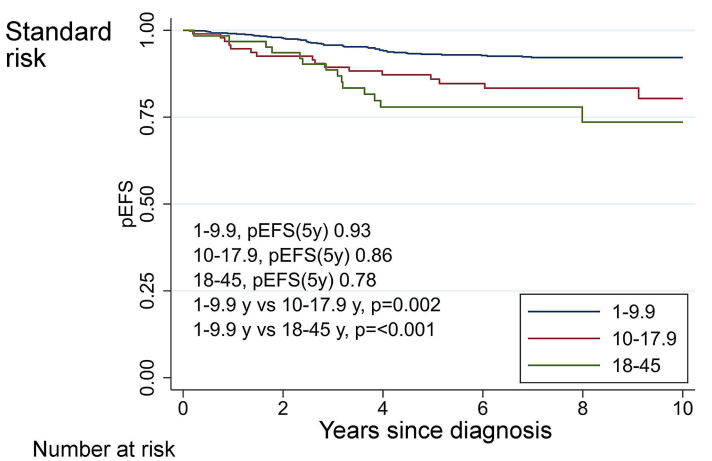
A



Number at risk

1-9.9	1188	1108	1028	914	701	421
10-17.9	306	269	236	193	116	65
18-45	277	215	179	140	84	37

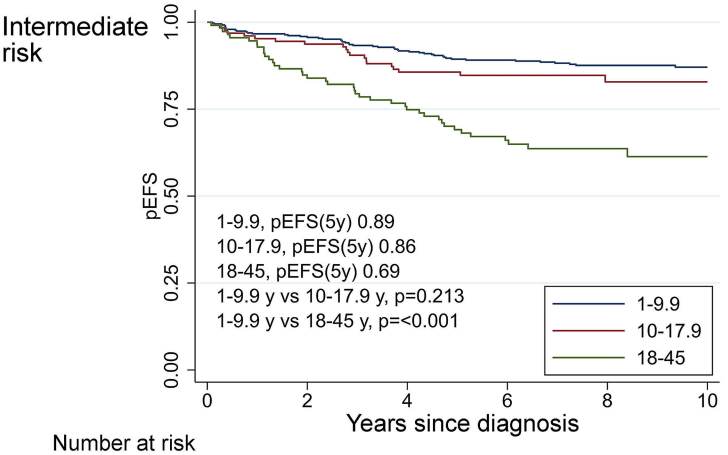
B



Number at risk

1-9.9	636	620	573	500	392	256
10-17.9	94	87	79	65	44	21
18-45	62	58	42	36	17	9

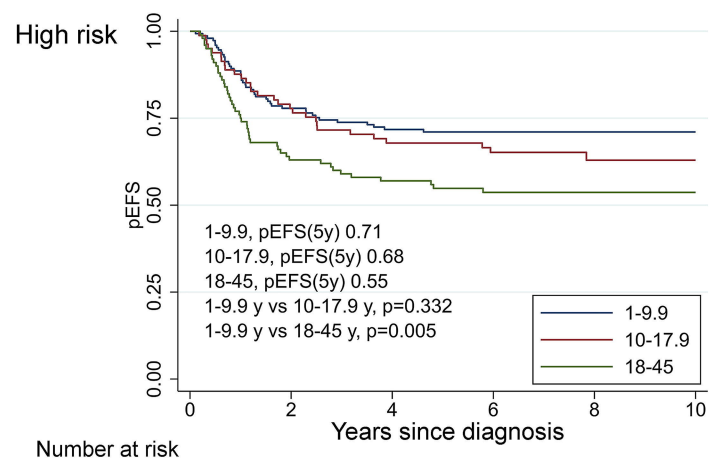
C



Number at risk

1-9.9	389	372	353	316	237	130
10-17.9	127	119	104	80	44	27
18-45	112	94	81	61	36	12

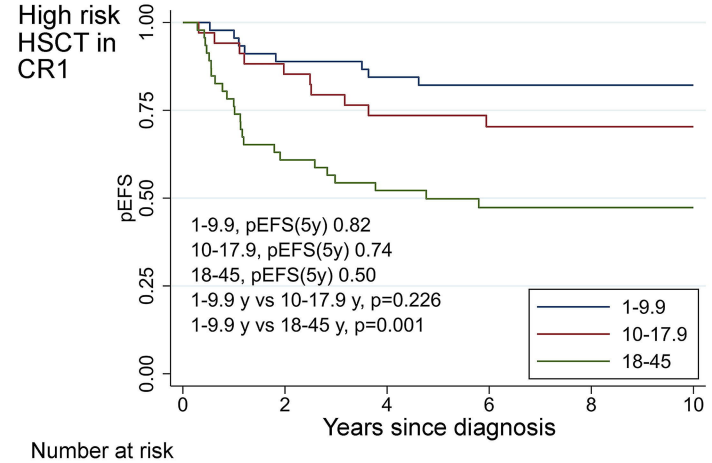
D



Number at risk

1-9.9	149	116	102	98	72	35
10-17.9	81	63	53	48	28	17
18-45	100	63	56	43	31	16

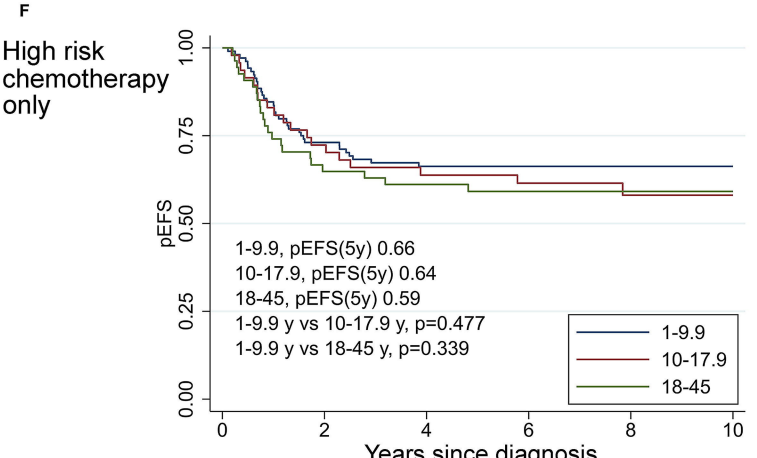
E



Number at risk

1-9.9	45	40	37	36	25	13
10-17.9	34	29	24	22	11	7
18-45	46	28	24	19	13	7

F



Number at risk

1-9.9	104	76	65	62	47	22
10-17.9	47	34	29	26	17	10
18-45	54	35	32	24	18	9

Supplementary data on methods

Minimal residual disease (MRD) was assessed by flow cytometry for patients with BCP-ALL and with PCR of clonal immune gene rearrangements for patients with T-ALL. If either method failed the alternative was used. With these combined methods only 0.14% of BCP [1] and 0.7% of T-ALL patients [2] had no MRD marker.

Statistical analyzes

Effect modification of risk group on age and sex was evaluated by conducting separate Cox regression analyzes for EFS and OS and competing-risks regression for relapse and death in CR1, for each risk group and by conducting Wald tests to identify any statistically significant interactions between risk group and age and sex, respectively. The robust sandwich estimator was used to calculate standard errors. The proportional hazard assumption was tested based on Schoenfeld residuals. Cumulative incidences were estimated based on Kaplan-Meier estimates and cause-specific hazard functions [3].

We analyzed treatment-related toxicity by describing frequencies of induction deaths (induction failure) and deaths in first complete remission (DCR1), as well as the 19 predefined toxicities registered in the trial database. The frequencies were compared separately by Chi-squared test between sexes, age groups, and risk groups. Logistic regression models, including age and sex, were performed for each of the treatment-related toxicities stratified by risk group. The results are presented as odds ratios (OR) with a 95% confidence interval. The 19 toxicities were separately analyzed by age using logistic regression adjusted for sex and the administered treatment arm. The OR were illustrated with a forest plot including only the predefined toxicities (11 of 19) with ≥50 observations to facilitate comparison with previous publication from the NOPHO ALL2008 trial [4].

References

1. Modvig S, Hallböök H, Madsen HO, et al. Value of flow cytometry for MRD-based relapse prediction in B-cell precursor ALL in a multicenter setting. Leukemia 2021;35(7):1894–1906.
2. Modvig S, Madsen HO, Siitonen SM, et al. Minimal residual disease quantification by flow cytometry provides reliable risk stratification in T-cell acute lymphoblastic leukemia. Leukemia 2019;33(6):1324–1336.
3. Marubini E, Valsecchi MG. Analysing survival data from clinical trials and observational studies. Chichester ; New York: J. Wiley; 1995. 414 p.

4. Toft N, Birgens H, Abrahamsson J, et al. Results of NOPHO ALL2008 treatment for patients aged 1–45 years with acute lymphoblastic leukemia. Leukemia 2018;32(3):606–615.

Supplementary Table S1 Frequencies of treatment-related toxicities by sex and age at diagnosis.

	Sex, N (%)			**Age at diagnosis in years, N (%)**			
	Male	**Female**	***p*-value**	**Age 1-9.9**	**Age 10-17.9**	**Age 18-45**	***p*-value**
Heart failure	8 (0.8)	5 (0.6)	0.783	8 (0.7)	4 (1.3)	1 (0.4)	0.374
Anaphylaxis	110 (11.2)	96 (12.2)	0.517	167 (14.1)	27 (8.8)	12 (4.3)	**<0.001**
Osteonecrosis	42 (4.3)	62 (7.9)	**0.001**	26 (2.2)	47 (15.4)	31 (11.2)	**<0.001**
Pancreatitis	73 (7.4)	63 (8.0)	0.655	76 (6.4)	32 (10.5)	28 (10.1)	**0.015**
Severe hyperlipidemia	75 (7.6)	59 (7.5)	0.910	82 (6.9)	35 (11.4)	17 (6.1)	**0.017**
Abdominal catastrophe	15 (1.5)	13 (1.6)	0.836	14 (1.2)	6 (2.0)	8 (2.9)	0.102
Liver dysfunction with encephalopathy	25 (2.5)	29 (3.7)	0.167	35 (2.9)	14 (4.6)	5 (1.8)	0.142
Veno-occlusive disease (VOD)	15 (1.5)	27 (3.4)	**0.009**	31 (2.6)	8 (2.6)	3 (1.1)	0.308
Dialysis/severe kidney dysfunction	26 (2.6)	14 (1.8)	0.261	14 (1.2)	16 (5.2)	10 (3.6)	**<0.001**
Hypertension (crisis)	6 (0.6)	12 (1.5)	0.092	14 (1.2)	4 (1.3)	0	0.182
CNS/catastrophic bleeding	20 (2.0)	15 (1.9)	0.844	16 (1.3)	7 (2.3)	12 (4.3)	**0.005**
Thrombosis	93 (9.5)	56 (7.1)	0.076	51 (4.3)	49 (16.0)	49 (17.7)	**<0.001**
PRES	28 (2.8)	37 (4.7)	**0.040**	44 (3.7)	15 (4.9)	6 (2.2)	0.213
Coma	12 (1.2)	11 (1.4)	0.746	14 (1.2)	6 (2.0)	3 (1.1)	0.527
Seizure	39 (4.0)	35 (4.4)	0.620	45 (3.8)	22 (7.2)	7 (2.5)	**0.010**
Peripheral paralysis	95 (9.7)	89 (11.3)	0.264	123 (10.4)	38 (12.4)	23 (8.3	0.266
PJP pneumonia	39 (4.0)	25 (3.2)	0.373	31 (2.6)	14 (4.6)	19 (6.9)	**0.002**
Invasive fungal infection	103 (10.5)	76 (9.6)	0.563	112 (9.4)	38 (12.4)	29 (10.5)	0.295
Intensive care	167 (17.0)	128 (16.2)	0.676	174 (14.6)	69 (22.5)	52 (18.8)	**0.002**

Supplementary Table S2. Frequencies of treatment-related toxicities by final treatment group. (1750 patients included in the analyzes since 21 patients could not be assigned a risk group.)

	Standard Risk **N (%)**	**Intermediate Risk** **N (%)**	**High Risk** **N (%)**	***p*-value**
Heart failure	4 (0.5)	5 (0.8)	4 (1.2)	0.43
Anaphylaxis	91 (11.5)	70 (11.0)	45 (13.9)	0.41
Osteonecrosis	43 (5.5)	47 (7.4)	14 (4.3)	0.12
Pancreatitis	60 (7.6)	54 (8.5)	21 (6.5)	0.54
Severe hyperlipidemia	63 (8.0)	64 (10.1)	7 (2.2)	**<0.001**
Abdominal catastrophe	9 (1.1)	8 (1.3)	8 (2.5)	0.21
Liver dysfunction with encephalopathy	25 (3.2)	19 (3.0)	8 (2.5)	0.82
Veno-occlusive disease (VOD)	24 (3.0)	16 (2.5)	2 (0.6)	0.054
Dialysis/severe kidney dysfunction	8 (1.0)	10 (1.6)	20 (6.2)	**<0.001**
Hypertension (crisis)	6 (0.8)	7 (1.1)	4 (1.2)	0.70
CNS/catastrophic bleeding	9 (1.1)	16 (2.5)	6 (1.9)	0.15
Thrombosis	57 (7.2)	59 (9.3)	32 (9.9)	0.23
PRES	19 (2.4)	32 (5.0)	14 (4.3)	**0.028**
Coma	6 (0.8)	9 (1.4)	6 (1.9)	0.26
Seizure	33 (4.2)	27 (4.2)	14 (4.3)	0.99
Peripheral paralysis	90 (11.4)	78 (12.3)	16 (4.9)	**0.001**
PJP pneumonia	19 (2.4)	26 (4.1)	19 (5.9)	**0.016**
Invasive fungal infection	48 (6.1)	56 (8.8)	71 (21.9)	**<0.001**
Intensive care	98 (12.4)	101 (15.9)	88 (27.2)	**<0.001**

Supplementary Table S3. Odds ratios (OR) for treatment-related toxicities stratified by risk group.

Risk group		Intensive care	Anaphylaxis	Osteonecrosis	Pancreatitis	Severe hyper-lipidemia	Thrombosis	PRES
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Standard	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	1.63 (0.92-2.91)	0.46 (0.19-1.08)	**8.91 (4.29-18.52)**	1.95 (0.96-3.94)	1.75 (0.87-3.52)	**4.39 (2.31-8.32)**	0.92 (0.21-4.09)
	Age 18-45 yrs	0.89 (0.37-2.14)	0.38 (0.12-1.24)	**8.63 (3.54-21.07)**	**2.77 (1.26-6.06)**	1.93 (0.83-4.53)	**4.24 (1.95-9.24)**	1.67 (0.37-7.58)
	Male	1	1	1	1	1	1	1
	Female	1.07 (0.70-1.64)	1.04 (0.67-1.62)	**3.84 (1.91-7.73)**	0.93 (0.54-1.59)	1.46 (0.87-2.45)	0.90 (0.51-1.58)	2.22 (0.86-5.72)
Inter-mediate	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	**1.78 (1.08-2.95)**	0.34 (0.15-0.78)	**8.06 (3.53-18.41)**	1.97 (0.98-3.95)	**1.89 (1.05-3.43)**	**3.12 (1.49-6.52)**	1.47 (0.65-3.33)
	Age 18-45 yrs	0.93 (0.51-1.70)	0.26 (0.10-0.66)	**8.71 (3.81-19.94)**	**2.48 (1.26-4.85)**	0.83 (0.38-1.78)	**7.24 (3.75-13.99)**	0.50 (0.15-1.71)
	Male	1	1	1	1	1	1	1
	Female	0.75 (0.49-1.16)	1.05 (0.63-1.73)	1.65 (0.89-3.07)	1.18 (0.67-2.07)	0.65 (0.38-1.11)	0.63 (0.35-1.13)	1.19 (0.58-2.43)
High	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	0.85 (0.46-1.59)	0.90 (0.44-1.84)	**4.82 (1.29-17.99**)	0.90 (0.32-2.51)	3.68 (0.66-20.65)	**9.28 (3.00-28.74)**	0.82 (0.24-2.79)
	Age 18-45 yrs	1.06 (0.60-1.89)	0.19 (0.06-0.55)	NA	0.37 (0.10-1.34)	0.75 (0.07-8.39)	**4.51 (1.39-14.68)**	0.17 (0.02-1.38)
	Male	1	1	1	1	1	1	1
	Female	1.21 (0.74-2.00)	1.14 (0.59-2.18)	1.84 (0.60-5.61)	1.62 (0.66-3.96)	1.17 (0.25-5.37)	1.18 (0.55-2.55)	2.61 (0.85-8.05)

Continued:

Risk group		Seizures	Peripheral paralysis	Invasive fungal infection	PJ pneumonia	Heart failure	Abdominal catastrophe	Liver DF with encephalopathy
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Standard	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	**2.48 (1.08-5.73)**	1.59 (0.86-2.91)	0.49 (0.15-1.61)	1.14 (0.25-5.17)	2.18 (0.22-21.21)	1.14 (0.14-9.59)	1.37 (0.46-4.10)
	Age 18-45 yrs	1.01 (0.23-4.41)	1.22 (0.53-2.80)	1.44 (0.54-3.83)	**5.31 (1.78-15.82)**	NA	4.10 (0.80-21.05)	0.57 (0.08-4.35)
	Male	1	1	1	1	1	1	1
	Female	1.36 (0.68-2.75)	1.37 (0.88-2.12)	1.07 (0.59-1.92)	1.57 (0.62-3.93)	0.41 (0.04-3.92)	1.70 (0.45-6.46)	1.35 (0.61-3.00)
Inter-mediate	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	1.88 (0.80-4.43)	1.55 (0.89-2.73)	1.55 (0.82-2.92)	2.42 (0.99-5.90)	0.77 (0.08-6.96)	3.14 (0.62-15.80)	**3.99 (1.41-11.28)**
	Age 18-45 yrs	0.64 (0.18-2.25)	0.80 (0.40-1.60)	0.57 (0.23-1.39)	1.39 (0.48-4.04)	NA	2.22 (0.37-13.49)	2.05 (0.59-7.17)
	Male	1	1	1	1	1	1	1
	Female	0.59 (0.26-1.33)	1.22 (0.76-1.97)	0.95 (0.55-1.65)	0.76 (0.34-1.72)	0.74 (0.12-4.47)	0.76 (0.18-3.23)	1.81 (0.71-4.61)
High	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	1.38 (0.42-4.53)	0.35 (0.07-1.69)	0.84 (0.44-1.59)	0.71 (0.18-2.84)	3.71 (0.33-41.79)	0.58 (0.06-5.67)	0.59 (0.12-2.99)
	Age 18-45 yrs	0.46 (0.09-2.27)	0.74 (0.24-2.31)	0.62 (0.32-1.18)	1.86 (0.66-5.21)	1.56 (0.10-25.52)	1.99 (0.43-9.18)	NA
	Male	1	1	1	1	1	1	1
	Female	2.76 (0.90-8.50)	0.47 (0.15-1.49)	0.87 (0.51-1.51)	0.55 (0.19-1.57)	1.61 (0.22-11.71)	0.96 (0.22-4.13)	1.32 (0.32-5.46)

Continued:

Risk group		Veno-occlusive disease OR (95%CI)	Dialysis/severe kidney DF OR (95%CI)	Hypertensive crisis OR (95%CI)	CNS/catastrophic bleeding OR (95%CI)	Coma OR (95%CI)
Standard	Age 1-9.9 yrs	1	1	1	1	1
	Age 10-17.9 yrs	1.10 (0.32-3.80)	3.95 (0.92-16.93)	NA	2.59 (0.49-13.65)	3.34 (0.60-18.53)
	Age 18-45 yrs	1.34 (0.30-5.96)	NA	NA	3.95 (0.74-21.03)	NA
	Male	1	1	1	1	1
	Female	**2.59 (1.09-6.15)**	0.17 (0.02-1.43)	2.38 (0.43-13.06)	0.17 (0.02-1.34)	0.62 (0.11-3.40)
Inter-mediate	Age 1-9.9 yrs	1	1	1	1	1
	Age 10-17.9 yrs	1.14 (0.36-3.61)	**7.84 (1.50-41.03)**	1.31 (0.25-6.88)	0.80 (0.17-3.82)	1.09 (0.22-5.47)
	Age 18-45 yrs	NA	4.95 (0.81-30.08)	NA	2.65 (0.90-7.83)	0.57 (0.07-4.84)
	Male	1	1	1	1	1
	Female	2.57 (0.88-7.52)	0.57 (0.14-2.25)	1.54 (0.34-6.97)	1.23 (0.45-3.35)	1.46 (0.39-5.52)
High	Age 1-9.9 yrs	1	1	1	1	1
	Age 10-17.9 yrs	1.28 (0.08-20.97)	3.02 (0.95-9.60)	1.98 (0.27-14.55)	1.94 (0.27-14.19)	1.28 (0.21-7.87)
	Age 18-45 yrs	NA	2.16 (0.66-7.05)	NA	1.70 (0.23-12.48)	0.55 (0.06-5.42)
	Male	1	1	1	1	1
	Female	NA	1.09 (0.43-2.76)	4.39 (0.45-43.20)	3.26 (0.58-18.22)	3.00 (0.54-16.75)

CI=Confidence interval, yrs=years, PRES=Posterior reversible encephalopathy syndrome, PJP=Pneumocystis jiroveci pneumonia, DF=dysfunction, CNS=Central nervous system, NA=Not applicable.

Supplementary Table S4. Odds ratios (OR, 95% confidence interval) for all 19 predefined toxicities by age groups (adjusted for sex and treatment group).

Toxicity	**N (%)**	**OR (95% CI)**
Intensive care +/- assisted ventilation		
Age 1-9.9	174/1188 (14.6)	1
Age 10-17.9	69/306 (22.5)	**1.50 (1.08-2.07)**
Age 18-45	52/277 (18.8)	1.10 (0.77-1.58)
Anaphylaxis (CTCAE grade 4)		
Age 1-9.9	167/1188 (14.1)	1
Age 10-17.9	27/306 (8.8)	0.55 (0.35-0.85)
Age 18-45	12/277 (4.3)	0.25 (0.13-0.46)
Osteonecrosis (CTCAE grade 2-4)		
Age 1-9.9	26/1188 (2.2)	1
Age 10-17.9	47/306 (15.4)	**10.23 (6.11-17.13)**
Age 18-45	31/277 (11.2)	**8.07 (4.56-14.26)**
Pancreatitis (CTCAE grade 2-4)		
Age 1-9.9	76/1188 (6.4)	1
Age 10-17.9	32/306 (10.5)	**1.83 (1.17-2.85)**
Age 18-45	28/277 (10.1)	**1.84 (1.14-2.97)**
Severe hyperlipidemia (CTCAE grade 2-4)		
Age 1-9.9	82/1188 (6.9)	1
Age 10-17.9	35/306 (11.4)	**2.00 (1.30-3.07)**
Age 18-45	17/277 (6.1)	1.10 (0.63-1.92)
Thrombosis		
Age 1-9.9	51/1188 (4.3)	1
Age 10-17.9	49/306 (16.0)	**4.40 (2.87-6.73)**
Age 18-45	49/277 (17.7)	**5.05 (3.25-7.86)**
PRES (posterior reversible encephalopathy syndrome)		
Age 1-9.9	44/1188 (3.7)	1
Age 10-17.9	15/306 (4.9)	1.19 (0.65-2.21)
Age 18-45	6/277 (2.2)	0.49 (0.20-1.19)
Seizures (CTCAE grade 2-4)		
Age 1-9.9	45/1188 (3.8)	1
Age 10-17.9	22/306 (7.2)	**2.02 (1.17-3.46)**
Age 18-45	7/277 (2.5)	0.69 (0.30-1.58)
Peripheral paralysis		
Age 1-9.9	123/1188 (10.4)	1
Age 10-17.9	38/306 (12.4)	1.39 (0.93-2.07)
Age 18-45	23/277 (8.3)	0.96 (0.59-1.56)
Fungal infection		
Age 1-9.9	112/1188 (9.4)	1
Age 10-17.9	38/306 (12.4)	1.04 (0.69-1.57)
Age 18-45	29/277 (10.5)	0.75 (0.47-1.18)
Pneumocystis jirovecii pneumonia		
Age 1-9.9	31/1188 (2.6)	1

Age 10-17.9	14/306 (4.6)	1.65 (0.85-3.18)
Age 18-45	19/277 (6.9)	**2.50 (1.35-4.63)**
Heart failure		
Age 1-9.9	8/1188 (0.7)	1
Age 10-17.9	4/306 (1.3)	1.64 (0.47-5.70)
Age 18-45	1/277 (0.4)	0.42 (0.05-3.50)
Abdominal problems leading to laparotomy		
Age 1-9.9	14/1188 (1.2)	1
Age 10-17.9	6/306 (2.0)	1.55 (0.57-4.18)
Age 18-45	8/277 (2.9)	2.15 (0.84-5.49)
Liver dysfunction with encephalopathy		
Age 1-9.9	35/1188 (2.9)	1
Age 10-17.9	14/306 (4.6)	1.70 (0.89-3.24)
Age 18-45	5/277 (1.8)	0.67 (0.25-1.77)
Veno-occlusive disease (VOD)		
Age 1-9.9	31/1188 (2.6)	1
Age 10-17.9	8/306 (2.6)	1.24 (0.55-2.77)
Age 18-45	3/277 (1.1)	0.57 (0.17-1.94)
Dialysis/severe kidney dysfunction		
Age 1-9.9	14/1188 (1.2)	1
Age 10-17.9	16/306 (5.2)	**3.51 (1.65-7.48)**
Age 18-45	10/277 (3.6)	2.02 (0.85-4.80)
Hypertensive crisis		
Age 1-9.9	14/1188 (1.2)	1
Age 10-17.9	4/306 (1.3)	0.97 (0.31-3.08)
Age 18-45	0/277	
CNS/catastrophic bleeding		
Age 1-9.9	16/1188 (1.3)	1
Age 10-17.9	7/306 (2.3)	1.61 (0.64-4.04)
Age 18-45	12/277 (4.3)	**3.02 (1.35-6.74)**
Coma		
Age 1-9.9	14/1188 (1.2)	1
Age 10-17.9	6/306 (2.0)	1.43 (0.53-3.85)
Age 18-45	3/277 (1.1)	0.71 (0.20-2.59)

Supplementary Table S5. The hazard ratios (HR) or sub-distribution hazard ratios (SHR) and 95% confidence intervals (CI) for the studied outcomes in each risk group from Cox regression or competing-risks regression. Test results of interactions by age and sex for each outcome in risk groups are presented as well. (Patients without assigned risk group excluded, N=21).

	EFS (HR, 95% CI)		**Relapse** (SHR, 95% CI)		**Death in CR1** (SHR, 95% CI)		**OS** (HR, 95% CI)	
Standard risk								
Age <10 y	1		1		1		1	
Age 10-17.9 y	**2.40**	**(1.36-4.25)**	**2.83**	**(1.48-5.40)**	2.29	(0.45-11.60)	**4.42**	**(1.92-10.16)**
Age 18-45 y	**3.40**	**(1.86-6.24)**	**4.76**	**(2.45-9.23)**	1.76	(0.22-14.37)	**6.42**	**(2.68-15.38)**
Female	1		1		1		1	
Male	1.12	(0.71-1.77)	1.04	(0.61-1.76)	0.98	(0.26-3.68)	0.84	(0.41-1.70)
Intermediate risk								
Age <10 y	1		1		1		1	
Age 10-17.9 y	1.37	(0.81-2.32)	1.30	(0.72-2.33)	1.84	(0.54-6.28)	**3.01**	**(1.42-6.41)**
Age 18-45 y	**3.43**	**(2.26-5.22)**	**3.28**	**(2.06-5.22)**	**3.65**	**(1.30-10.23)**	**7.84**	**(4.11-14.96)**
Female	1		1		1		1	
Male	1.18	(0.80-1.72)	1.39	(0.91-2.14)	0.63	(0.25-1.57)	1.05	(0.62-1.78)
High risk								
Age <10 y	1		1		1		1	
Age 10-17.9 y	1.28	(0.80-2.04)	0.82	(0.43-1.59)	1.74	(0.82-3.68)	1.19	(0.71-2.01)
Age 18-45 y	**1.86**	**(1.22-2.84)**	**1.99**	**(1.20-3.29)**	1.20	(0.55-2.61)	**1.95**	**(1.25-3.05)**
Female	1		1		1		1	
Male	0.85	(0.59-1.23)	0.82	(0.52-1.31)	0.98	(0.52-1.87)	0.86	(0.58-1.28)
Interactions:								
*Sex*risk group*		*p*=0.38		*p*=0.22		*p*=0.77		*p*=0.69
*Age*risk group*		*p*=0.14		*p*=0.06		*p*=0.51		*p*=0.002

Supplementary Table S6. A separate analysis for the patients in the intermediate-risk group: The hazard ratios (HR) or sub-distribution hazard ratios (SHR) and 95% confidence intervals (CI) for the studied outcomes in multivariate Cox and competing-risks regression analysis adjusted by sex, age group, immunophenotype, WBC at diagnosis, and MRD at the end of induction.

	EFS		**Relapse***		**Death in CR1***		**OS**	
	HR	**95% CI**	**SHR**	**95% CI**	**SHR**	**95% CI**	**HR**	**95% CI**
Age <10 y	1		1		1		1	
Age 10-17.9 y	1.44	(0.85-2.44)	1.44	(0.80-2.59)	1.62	(0.49-5.40)	**2.93**	**(1.38-6.25)**
Age 18-45 y	**3.79**	**(2.47-5.81)**	**3.89**	**(2.44-6.20)**	**2.94**	**(0.95-9.07)**	**7.88**	**(4.07-15.26)**
Female	1		1		1		1	
Male	1.30	(0.88-1.91)	**1.55**	**(1.02-2.35)**	0.59	(0.20-1.72)	1.09	(0.62-1.89)
BCP	1		1		1		1	
T-cell	0.79	(0.43-1.46)	0.59	(0.28-1.21)	1.94	(0.51-7.32)	1.33	(0.60-2.91)
EOI-MRD								
<0.1%	1		1		1		1	
0.1-4.9%	**1.81**	**(1.13-2.90)**	**1.92**	**(1.16-3.20)**	1.01	(0.27-3.74)	1.71	(0.87-3.36)
WBC								
<100	1		1		1		1	
≥100	1.70	(0.93-3.12)	1.60	(0.79-3.27)	1.76	(0.54-5.73)	1.81	(0.83-3.99)

*Competing risks (death in CR1, SMN, relapse) were considered in the analyzes.

Supplementary Table S7. Probability of survival at 5 years after first relapse in total and by risk groups of primary treatment.

		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (103)	0.65	±0.05	1	
	10-17.9 (43)	0.38	±0.08	1.81	1.09-2.98
	18-45 (77)	0.28	±0.05	2.67	1.74-4.11
Sex (N)	female (89)	0.47	±0.05	1	
	male (134)	0.47	±0.04	0.98	0.68-1.42
Time to relapse (N)	very early (58)	0.15	±0.05	1	
	early (48)	0.58	±0.07	0.34	0.20-0.59
	late (117)	0.58	±0.05	0.30	0.20-0.44

Survival at 5 years after relapse in standard risk group (pOS 0.70 ±0.06)

		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (33)	0.84	±0.07	1	
	10-17.9 (13)	0.53	±0.14	3.73	1.26-11.06
	18-45 (12)	0.50	±0.14	4.08	1.30-12.75
Sex (N)	female (24)	0.62	±0.10	1	
	male (34)	0.75	±0.08	0.63	0.25-1.55
Time to relapse (N)	very early (8)	0.13	±0.12	1	
	early (14)	0.79	±0.11	0.16	0.05-0.52
	late (36)	0.80	±0.07	0.12	0.05-0.30

Survival at 5 years after relapse in intermediate risk group (pOS 0.56 ±0.06)

		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (40)	0.82	±0.06	1	
	10-17.9 (16)	0.38	±0.13	3.47	1.30-9.26
	18-45 (33)	0.35	±0.09	4.89	1.95-12.26
Sex (N)	female (33)	0.60	±0.09	1	
	male (56)	0.53	±0.07	1.20	0.61-2.36
Time to relapse (N)	very early (14)	0.21	±0.11	1	
	early (22)	0.64	±0.10	0.35	0.14-0.86
	late (53)	0.61	±0.07	0.34	0.17-0.70

Survival at 5 years after relapse in high risk group (pOS 0.20 ±0.05)

		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (29)	0.24	±0.08	1	
	10-17.9 (13)	0.31	±0.13	0.78	0.34-1.80
	18-45 (32)	0.13	±0.06	1.21	0.70-2.11
Sex (N)	female (31)	0.23	±0.08	1	
	male (43)	0.18	±0.06	1.14	0.67-1.92
Time to relapse (N)	very early (34)	0.15	±0.06	1	
	early (12)	0.25	±0.13	0.85	0.37-1.95
	late (28)	0.25	±0.08	0.64	0.37-1.11

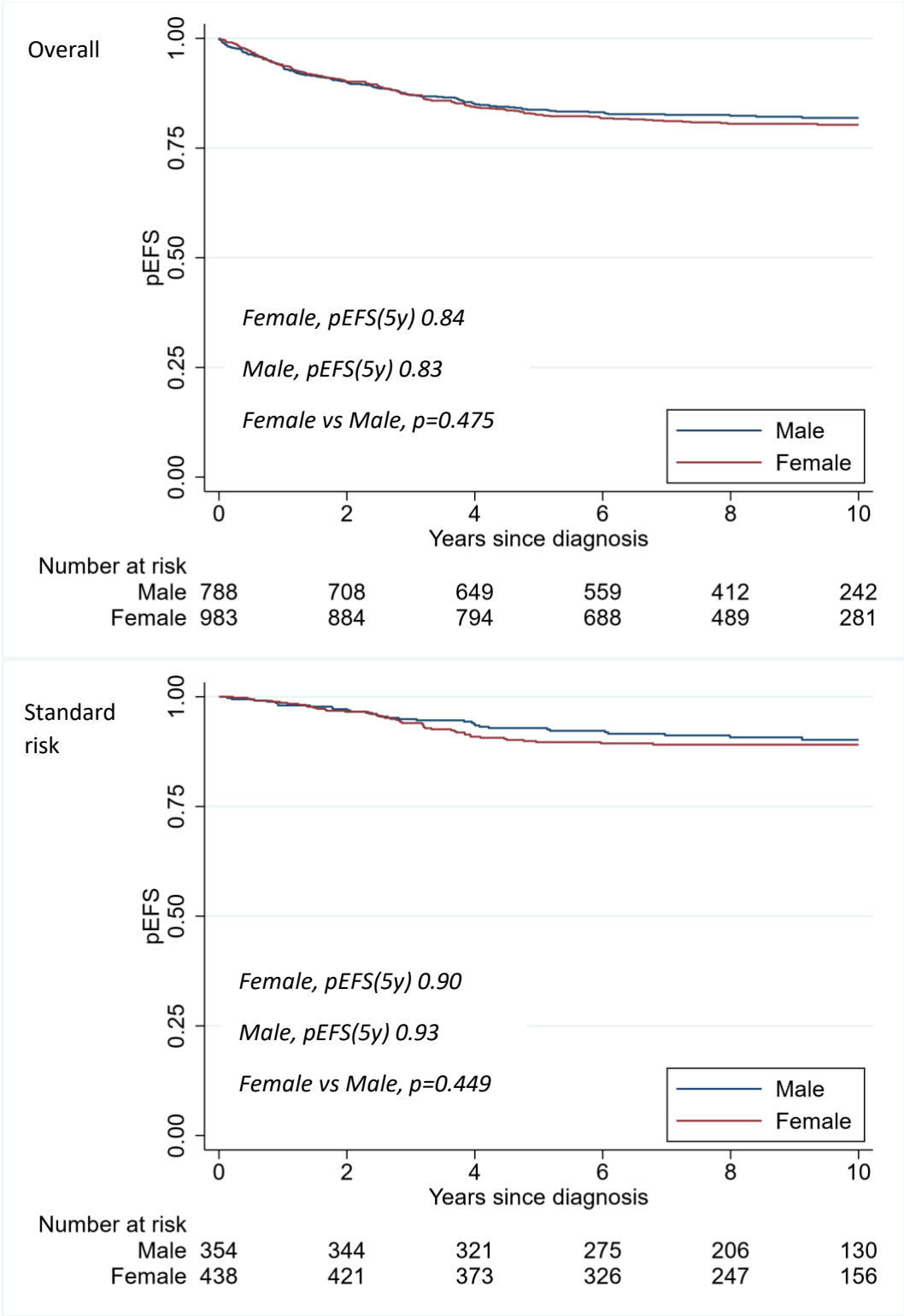
Survival at 5 years after relapse in high risk chemo group (pOS 0.20 ±0.06)

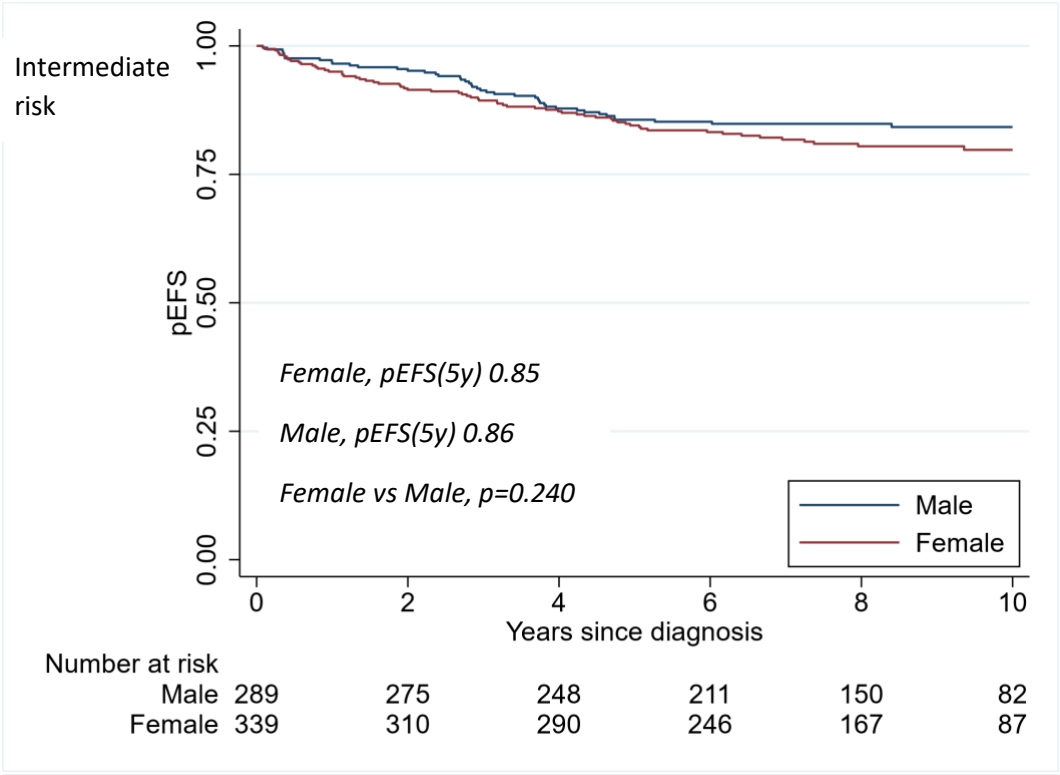
		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (23)	0.22	±0.09	1	
	10-17.9 (8)	0.38	±0.17	0.49	0.19-1.28
	18-45 (13)	.	.	1.32	0.65-2.69
Sex (N)	female (19)	0.21	±0.09	1	
	male (25)	0.20	±0.08	0.98	0.49-1.98
Time to relapse (N)	very early (24)	0.13	±0.07	1	
	early (10)	0.20	±0.13	0.89	0.39-2.07
	late (10)	0.40	±0.15	0.44	0.18-1.06

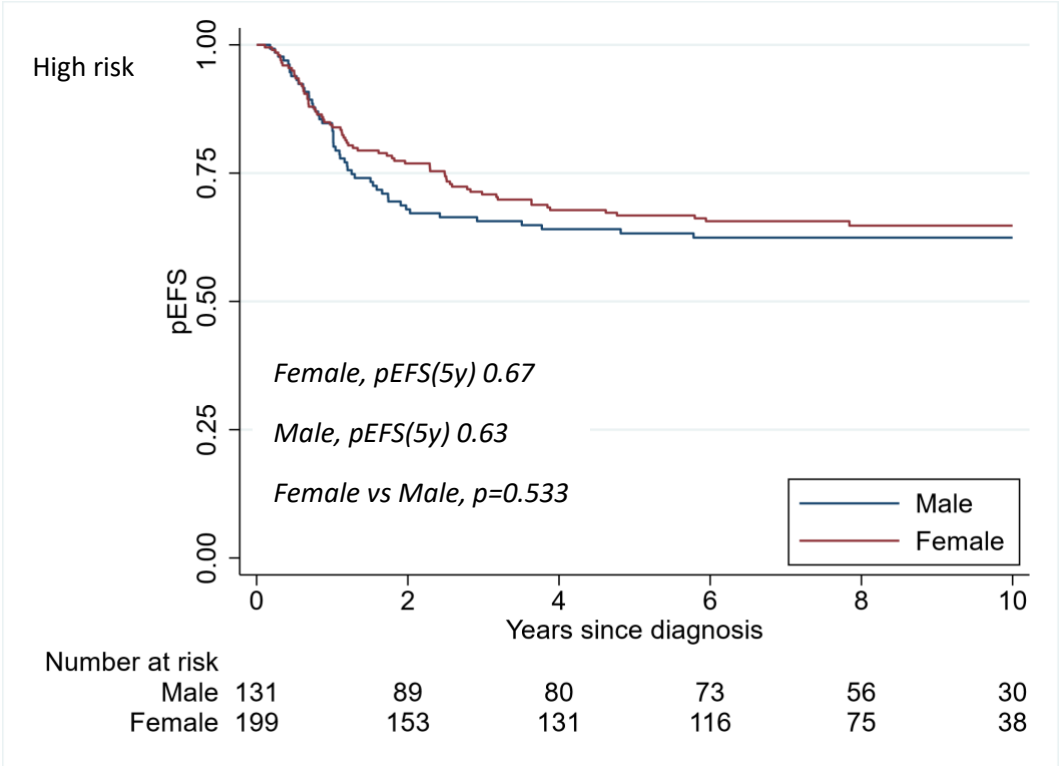
Survival at 5 years after relapse in high risk SCT-CR1 group (pOS 0.20 ±0.07)

		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (6)	0.33	±0.19	1	
	10-17.9 (5)	0.20	±0.18	1.90	0.40-9.10
	18-45 (19)	0.16	±0.08	1.82	0.66-5.00
Sex (N)	female (12)	0.25	±0.13	1	
	male (18)	0.17	±0.09	1.38	0.63-3.05
Time to relapse (N)	very early (10)	0.20	±0.13	1	
	early (2)	0.50	±0.35	0.50	0.04-5.87
	late (18)	0.17	±0.09	0.94	0.39-2.22

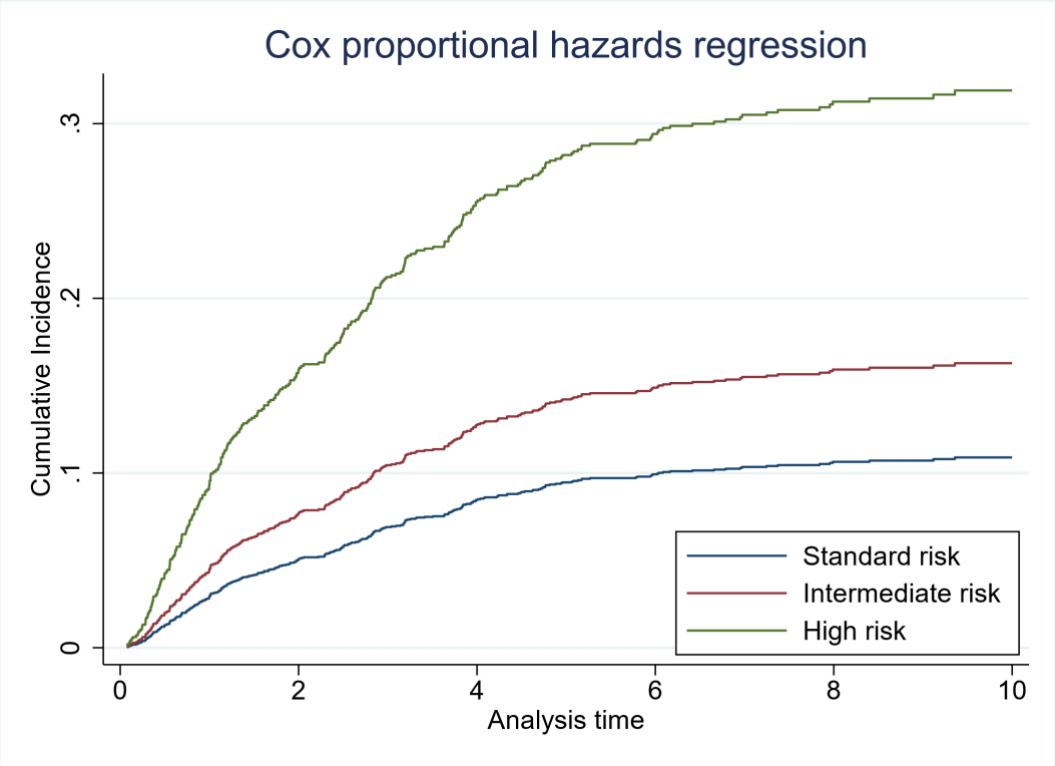
Supplementary Figure S1. Event-free survival (pEFS) at 5 years overall and in the final risk groups of the NOPHO ALL2008 trial by sex.



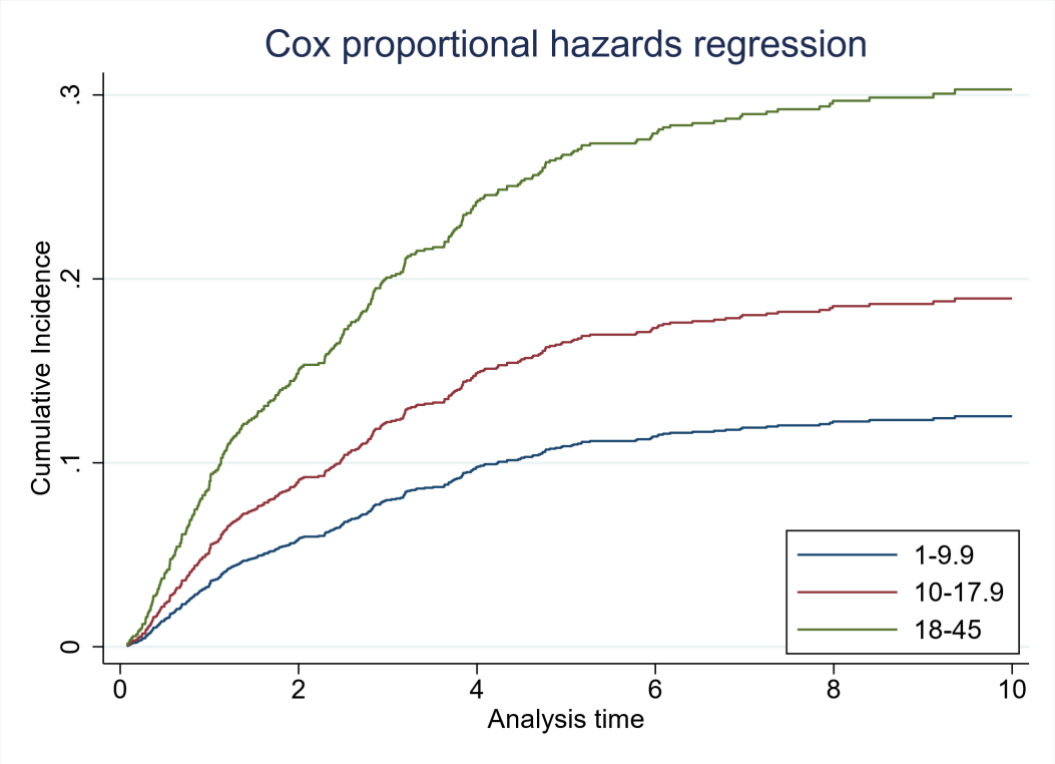

Intermediate risk
pEFS
1.00
0.75
0.50
0.25
0.00
Female, pEFS(5y) 0.85
Male, pEFS(5y) 0.86
Female vs Male, p=0.240
Male
Female
0
2
4
6
8
10
Years since diagnosis
Number at risk
Male 289 275 248 211 150 82
Female 339 310 290 246 167 87


High risk
pEFS
1.00
0.75
0.50
0.25
0.00
Female, pEFS(5y) 0.67
Male, pEFS(5y) 0.63
Female vs Male, p=0.533
Male
Female
0
2
4
6
8
10
Years since diagnosis
Number at risk
Male 131 89 80 73 56 30
Female 199 153 131 116 75 38

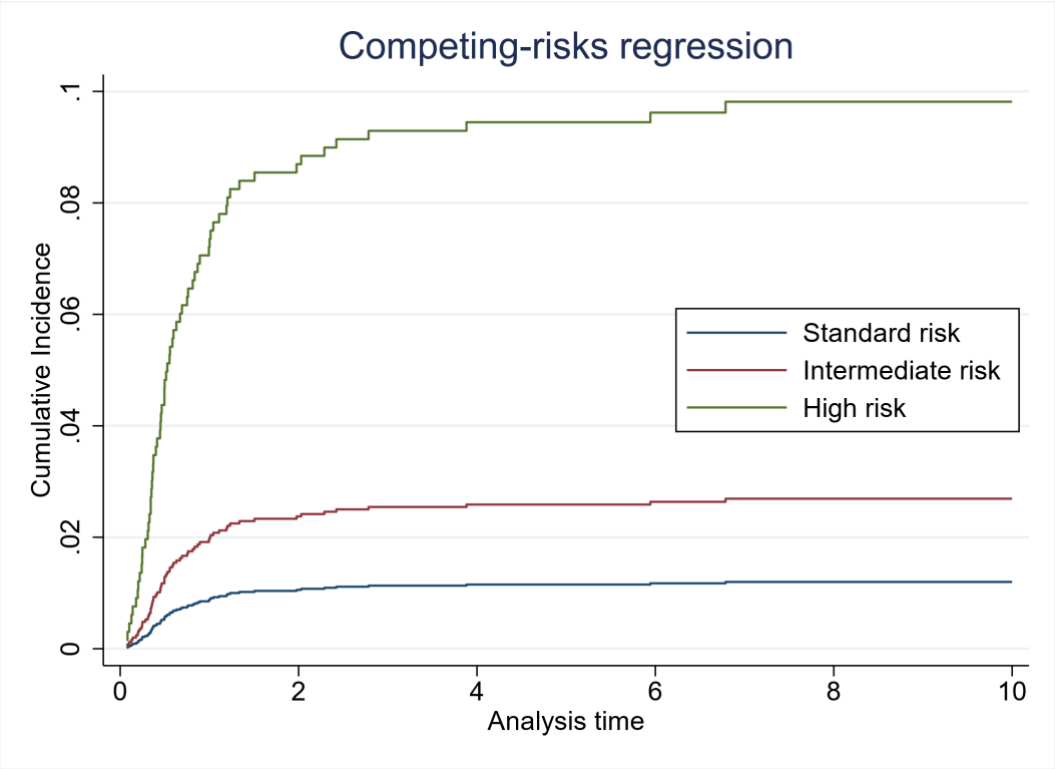
Supplementary Figure S2a. Predicted cumulative incidence of lower 5-year event-free survival in each risk group adjusted by sex and age group (patients without assigned risk group excluded, N=21).



Supplementary Figure S2b. Predicted cumulative incidence of lower 5-year event-free survival in each age group adjusted by sex and risk group (patients without assigned risk group excluded, N=21).



Supplementary Figure S2c. Predicted cumulative incidence of death in first complete remission (DCR1) in each risk group adjusted by sex and age group. Patients without assigned risk group excluded, N=21. Competing risks (relapse, second malignancy) taken into account.



Supplementary Figure S2d. Predicted cumulative incidence of relapse in each risk group adjusted by sex and age group. Patients without assigned risk group excluded, N=21. Competing risks (DCR1, second malignancy) taken into account.