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Differential impact of drugs on the outcome of ETV6-RUNX1 positive childhood B-cell precursor acute lymphoblastic leukemia: Results of the EORTC CLG 58881 and 58951 trials

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AUTHORS: Caroline Piette[1], Stefan Suciu[2], Emmanuelle Clappier[3,4], Yves Bertrand[5], Séverine Drunat[3], Sandrine Girard[6], Karima Yakouben[7], Geneviève Plat[8], Nicole Dastugue[8], Françoise Mazingue[9], Nathalie Grardel[9], Nadine van Roy[10], Anne Uyttebroeck[11], Vitor Costa[12], Odile Minckes[13], Nicolas Sirvent[14], Pauline Simon[15], Patrick Lutz[16], Alina Ferster[17], Claire Pluchart[18], Marilyne Poirée[19], Claire Freycon[20], Marie-Françoise Dresse[1], Frédéric Millot[21], Christophe Chantrain[22], Jutte van der Werff[23], Koen Norga[24], Caroline Gilotay[2], Pierre Simon Rohrlich[19], Yves Benoit[25] and Hélène Cavé[3,4]

[1]University dept. of Pediatrics, Pediatric Onco-Hematology, CHR Citadelle, Liège, Belgium;

[2] EORTC Headquarters, Brussels, Belgium;

[3] Département de Génétique, Hôpital Robert Debré, Assistance Publique des Hôpitaux de Paris (AP-HP), Paris, France;

[4] Institut Universitaire d'Hématologie, Université Paris Diderot, Paris-Sorbonne-Cité, Paris, France;

[5] Dept. of Pediatric Hematology, IHOP, Hospices Civils de Lyon and Claude Bernard Lyon University, Lyon, France;

[6] Laboratory of Hematology, East Lyon University Hospital, Hospices Civils de Lyon, Lyon, France

[7] Assistance Publique des Hôpitaux de Paris (AP-HP), Hôpital Robert Debré, Service d'Immuno-Hématologie pédiatrique, Paris, France;

[8] Dept. of Pediatric Onco-Hematology, Purpan University Hospital, Toulouse, France;

[9] Dept. of Pediatric Hematology-Oncology, Lille University Hospital, Lille, France;

[10] Center for Medical Genetics, Ghent University, Belgium;

[11] Dept. of Pediatrics, University Hospital Gasthuisberg, Leuven, Belgium;

[12] Dept. of Pediatrics, Portuguese Oncology Institute, Porto, Portugal;

[13] Dept. of Pediatric Onco-Hematology, Caen University Hospital, Caen, France;

[14] Dept. of Pediatric Onco-Hematology, Montpellier University Hospital, Montpellier, France;

[15] Dept. of Pediatric Onco-Hematology, Besançon University Hospital, Besançon, France;

[16] Dept. of Hematology, Hautepierre University Hospital, Strasbourg, France;

[17] Dept. of Pediatric Onco-Hematology, Hôpital Universitaire des Enfants Reine Fabiola (ULB), Brussels, Belgium;

[18] Dept. of Pediatric Onco-Hematology, Reims University Hospital, Reims, France;

[19] Dept. of Pediatric Onco-Hematology, Nice University Hospital, France;

[20] Dept. of Pediatric Onco-Hematology, Grenoble University Hospital, France;

[21] Dept. of Pediatric Onco-Hematology, Poitiers University Hospital, France;

[22] Dept. of Pediatrics, Clinique de l'Espérance, CHC, Liège, Belgium;

[23] Dept. of Pediatric Onco-Hematology, Universitair Ziekenhuis Brussel, Brussels, Belgium;

[24] Pediatric Onco-Hematology Unit, Antwerp University Hospital, Antwerp, Belgium

[25] Dept. of Pediatric Hematology-Oncology, Ghent University Hospital, Ghent, Belgium;

CORRESPONDING AUTHOR:

Hélène Cavé, UF de Génétique Moléculaire, Hôpital Robert Debré, 48, Boulevard Sérurier, 75019 Paris, France. Tel: 33 (0)1 40 03 57 11 ; Fax: 33 (0)1 40 03 22 77; e-mail: helene.cave@aphp.fr

or

Caroline Piette, University Department of Pediatric Oncology, CHR Citadelle, Boulevard du Douzième de Ligne, 1 – 4000 Liège, Belgium, tel. +32 4 225 60 97, fax. +32 4 225 82 96, e-mail: caroline.piette@chrcitadelle.be

RUNING HEAD: Drug impacts on ETV6-RUNX1 leukemias outcome: an EORTC study

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In childhood B-cell precursor acute lymphoblastic leukemias (BCP-ALL), the presence of an *ETV6-RUNX1* fusion transcript defines one of the most prevalent genetic subgroups, together with the High hyperdiploidy (HeH) ALL. Although *ETV6-RUNX1*$^{\boldsymbol{pos}}$ ALLs are associated with favourable outcome, their proper treatment strategies remain debatable, some groups suggesting crucial impact of upfront intensive treatment[1] while others favour low intensity antimetabolite-based therapy.[2]

To address this question, we evaluated the long-term prognostic and predictive value of *ETV6-RUNX1* in *BCR-ABL1* negative *de novo* BCP-ALL children (1 to 17 years old) treated in the European Organisation for Research and Treatment of Cancer (EORTC) studies 58881, opened between January 1989 and November 1998[3] (n=1692) and 58951 opened between December 1998 and August 2008[4,5] (n=1602). Particular attention was given to the effects of the randomized treatments (Supplementary Figures 1 and 2) in the *ETV6-RUNX1*$^{\boldsymbol{pos}}$ subgroup as compared to those observed in the HeH and “Others” BCP-ALL subgroups, in order to reveal specific drug response profiles related to distinct oncogenic process.

In total, 1887 BCP-ALL were screened for the presence of *ETV6-RUNX1*: 394 in study 58881 and 1493 in study 58951. In both studies, clinical features and outcome were similar to those of patients not screened (Supplementary Tables 1 and 2).

ETV6-RUNX1 was evidenced in 488/1887 patients (25.9%) and HeH in 595/1887 patients (31.5%). The 804 (42.6%) remaining patients ("Others") had others or unknown genetic abnormalities (Supplementary Figure 3). Clinical and biological features of patients according to the *ETV6-RUNX1* status and by genetic subgroups are presented in Supplementary Tables 3-4.

The median follow-up was 11.7 years and 6.7 years for study 58881 and 58951, respectively.

The 10-yr EFS rate was globally improved in study 58951 as compared with study 58881 (82.7% vs 73.1%). In both studies, the 10-yr EFS was significantly higher in the *ETV6-RUNX1^{pos}* group than in the *ETV6-RUNX1^{neg}* group (Table 1, Supplementary Figure 4). *ETV6-RUNX1^{pos}* patients had also a significantly higher 10-yr OS rate (93.3% vs 82.0% in 58881, 95.3% vs 87.8% in 58951, Supplementary Figures 5-6).

The 10-yr EFS of the *ETV6-RUNX1^{pos}* group was similar to that of the HeH group, but drastically superior to the one of the "Others" subgroup (Figure 1).

Noteworthy, in the *ETV6-RUNX1^{pos}* group, EFS events mostly occurred after the end of the maintenance therapy, with very few events before, and virtually no event after 6 years from diagnosis.

In both studies, the higher EFS of the *ETV6-RUNX1^{pos}* group was mainly due to lower rates of induction failures and relapses and to treatment related mortality rates below 1.5% (Supplementary Tables 3-4).

Erwinia-ASNase versus E. Coli-asparaginase (ASNase) for all risk-groups in study 58881[6]*, and prolonged versus classical number of ASNase administrations for non-very high risk (VHR) patients in study 58951.*[7]

In *ETV6-RUNX1****pos*** patients, the exact role of ASNase *in vivo* remains unclear. *In vitro* analyses have revealed that *ETV6-RUNX1****pos*** cells are exquisitely sensitive to asparaginase but similar outcomes have been described with[8] or without[9] intensive ASNase administration.

In study 58881, 94 patients were randomized for *E. Coli*-ASNase (n=46) or Erwinia-ASNase (n=48), and 300 additional patients received *E. Coli*-ASNase (Table 1, Supplementary Table 5). The overall improvement of the 10-yr EFS with *E. Coli*-ASNase as compared to *Erwinia*-ASNase was approximately 10%, as in the main publication,[6] and around 33% in the HeH group. In contrast, in the *ETV6-RUNX1****pos*** group, the 10-yr EFS improvement was limited (3.7%). This is in line with results of the DFCI 95-01 study, showing no significant difference regarding EFS in 77 *ETV6-RUNX1****pos*** patients treated with either *E. Coli*- or *Erwinia*-ASNase.[8]

In study 58951, 1229 non-VHR patients were randomized for prolonged (“long-ASNase”) vs classical (“short-ASNase”) courses of asparaginase during consolidation/late intensification[7] (Table 1, Supplementary Table 5). Overall, the 10-yr DFS was 87.0% in the “long-ASNase” arm and 83.6% in the “short-ASNase” arm. In the *ETV6-RUNX1****pos*** subgroup (n=333), the impact of “long-ASNase” was weak with a 10-yr DFS rate of 94.8% in the “long-ASNase” vs 91.2% in the “short-ASNase” arm. In the HeH subgroup, “long-ASNase” did not prolong the DFS as compared to “short-ASNase”. St Jude obtained outstanding results (5-yr EFS of 96.8%) in *ETV6-RUNX1****pos*** patients treated with the Total XV regimen through intensified use of ASNase, vincristine and dexamethasone[10]. However, our results, while limited by the relatively low number of patients suggest that the benefit of ASNase intensification is low in *ETV6-RUNX1****pos*** patients and that similar results can be reached without ASNase intensification.

Prednisone (PRED) (60 mg/m²/day) versus dexamethasone (DEX) (6 mg/m²/day) during induction in study 58951.[5]

In the present analysis, the overall difference between DEX and PRED regarding EFS was not significant, as in the whole cohort analysis.[5] Similarly, no difference regarding EFS was observed in *ETV6-RUNX1****neg*** patients, or in the HeH and “Others” subgroups considered separately (Table 1, Supplementary Figures 7A,8).

By contrast, *ETV6-RUNX1* status had a significant impact (test of heterogeneity: *P*=0.05) on the treatment difference (Table 1, Supplementary Figures 7A,8). In the *ETV6-RUNX1****pos*** subgroup, the 10-yr EFS was higher in the DEX group as compared to PRED (95% vs 87.2%). This difference remained practically unchanged when adjusting by sex, NCI risk group and EORTC risk group (VHR vs non-VHR) by using a Cox model (HR=0.47, 99%CI=0.17-1.30; 2-sided Wald test: *P*=0.055). The 10-yr OS was comparable in both arms (96.3% vs 94.5%, HR=0.84, 99%CI=0.21-3.37; 2-sided logrank test: *P*=0.74).

A possible role for DEX in *ETV6-RUNX1****pos*** patients had already been suggested by the St Jude group, who obtained outstanding results with DEX pulses during maintenance therapy.[10] In the randomized trial AIEOP-BFM ALL 2000[11], higher 5-yr EFS rates were observed in the *ETV6-RUNX1****pos*** subgroup treated with DEX 10 mg/m² in induction when compared to PRED 60 mg/m², but this advantage did not translate into higher 5-yr OS. In study 58951, the improvement in *ETV6-RUNX1****pos*** patients regarding EFS did not either lead to an improvement in OS, since the majority of relapses occurred after the end of the maintenance therapy, and could then be salvaged with second line therapies. However, toxicities of salvage therapies have to be balanced with those of first line treatments and DEX at 6 mg/m² did not increase the incidence of infections and osteonecrosis in study 58951.[5] Furthermore, the majority of *ETV6-RUNX1**pos*** patients, being less than 10 year old, are at low risk of osteonecrosis.

Monthly intravenous (i.v.) 6-mercaptopurine (6-MP) (1 g/m²) vs no i.v. 6-MP during maintenance therapy for non-high risk patients in study 58881.[12]

A total of 200 patients were randomized for the i.v. 6-MP question (Supplementary Table 5).[12] The addition of i.v. 6-MP was associated with a significantly lower 10-yr DFS (2-sided logrank test: *P*=0.03) (Table 1).

Strikingly, in *ETV6-RUNX1**pos*** patients, the 10-yr DFS was 71.4% in the i.v. 6-MP group vs 100% in the classic maintenance group, whereas the treatment difference was less marked in the HeH and "Others" subgroups (Table 1, Supplementary Figure 7B,9). *ETV6-RUNX1**pos*** patients treated with classic maintenance outside the randomisation (n=47) had a 10-yr DFS from CR of 82.7%.

The addition of i.v. 6-MP was previously shown to lead to significantly worse outcome in study 58881.[12] The present analysis further showed that the deleterious effect of i.v. 6-MP was mainly observed in the *ETV6-RUNX1**pos*** subgroup. *ETV6-RUNX1**pos*** relapses have been suggested to arise from quiescent pre-leukemic clones persisting after eradication of the overt leukemia cells, and prolonged exposure to 6-MP/methotrexate during maintenance therapy increases the risk of second cancers[13]. Thus, i.v. 6-MP might have fostered the oncogenic process, leading to "secondary leukemia" relapses in *ETV6-RUNX1**pos*** patients.

Alternatively, the deleterious effect of i.v. 6-MP could be related to a specific susceptibility of *ETV6-RUNX1**pos*** cells to antileukemic agents that inhibit *de novo* purine synthesis. High-doses of 6-MP result in a preferential increase in methylated metabolites via thio-purine methyl-transferase as compared to cytotoxic thioguanine nucleotides via hypoxanthine-guanine phosphoribosyltransferase (HGPRT). *ETV6-RUNX1*^{pos} cells express low levels of HGPRT as compared to other ALL subgroups.[14] High-dose 6-MP could thus result in a higher production of methylated metabolites, especially in *ETV6-RUNX1*^{pos} cells. Because methylated metabolites inactivate *de novo* purine synthesis[15], critical for cell progression, they could induce cell dormancy, protecting *ETV6-RUNX1*^{pos} cells from maintenance therapy. At completion of maintenance therapy, quiescent leukemia cells could re-enter cell cycle and lead to relapse, which is consistent with the high rate of relapses occurring after the end of maintenance in *ETV6-RUNX1*^{pos} patients randomized in the i.v. 6-MP arm.

Vincristine-corticosteroid pulses vs no pulses during maintenance therapy for average risk (AR) patients in study 58951.[4]

A total of 301 patients were randomly assigned for this question (Supplementary Table 5).

Overall, the 10-yr DFS was higher in the pulse arm, as previously reported,[4] but the difference was not significant in this sub-analysis (Table 1).

In the HeH subgroup, the 10-yr DFS was approximately 90% in both arms. In the “Others” subgroup, the pulses improved the 10-yr DFS by approximately 11%, while *ETV6-RUNX1*^{pos} patients had similar outstanding outcomes in both arms (Table 1).

Noteworthy, these latter AR patients treated with *E. Coli*-ASNase had already outstanding outcome with 10-yr DFS rate of 96.1%. If these data are confirmed, vincristine-corticosteroid pulses could be avoided in this specific subgroup.

In conclusion, our observations identified *in vivo* treatment sensitivities, which were specific to the *ETV6-RUNX1*^{pos} subgroup: the benefit of dexamethasone instead of prednisone in induction, the limited role of asparginase intensification, and the importance of low intensity maintenance therapy. These results stress the benefit of analysing homogeneous oncogenetic subgroups when comparing different therapeutic schemes.

Of course, interpretation of such retrospective subgroup analyses needs to be done with caution as they were unplanned in the study design, so they were underpowered. Such findings are exploratory in nature, and require confirmation in other studies.

In future randomized studies one should aim not only to evaluate the overall treatment effect, but also the possible heterogeneity of treatment difference according to the ALL subgroups.

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Supplementary information is available at Leukemia's website.

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FIGURE LEGENDS

Table 1 - Outcome by genetic subgroup according to the randomized questions of EORTC studies 58881 and 58951

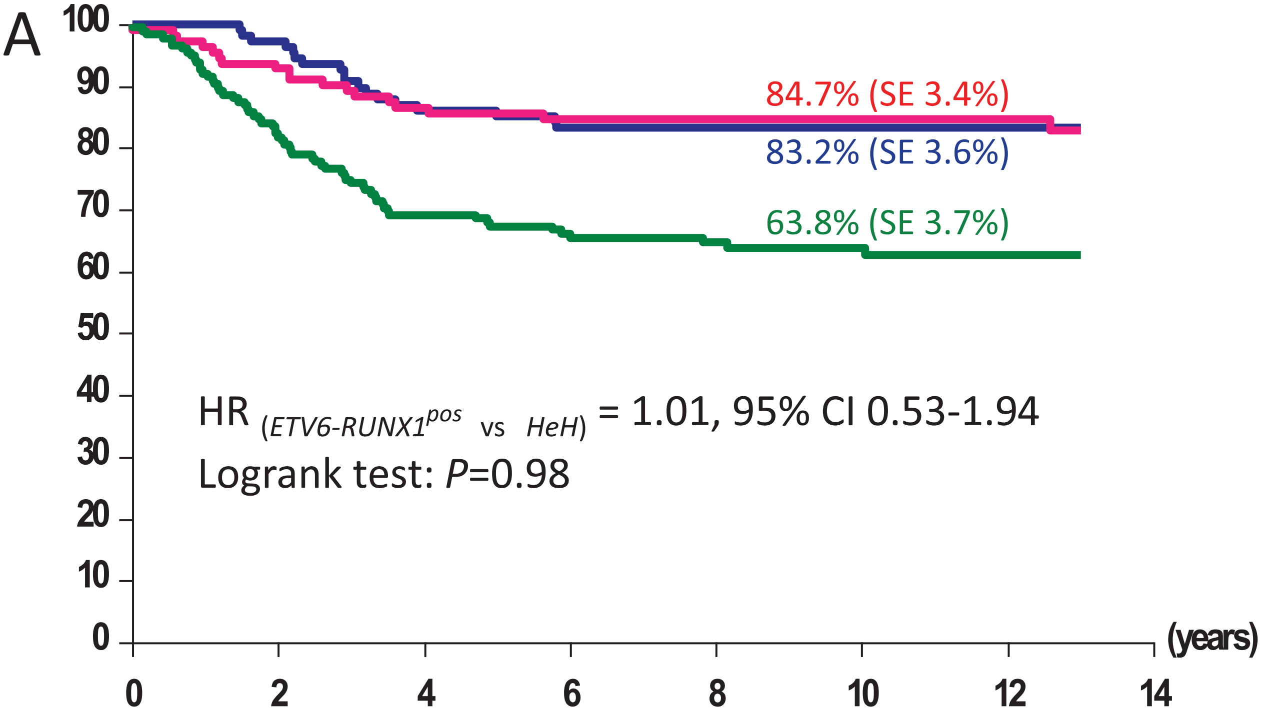
Figure 1 - Kaplan-Meier curves of event-free survival by genetic subgroup (*ETV6-RUNX1*^{pos}, HeH or “Others”) in EORTC study (A) 58881 and (B) 58951

Table 1 - Outcome by genetic subgroup according to the randomized questions of EORTC studies 58881 and 58951

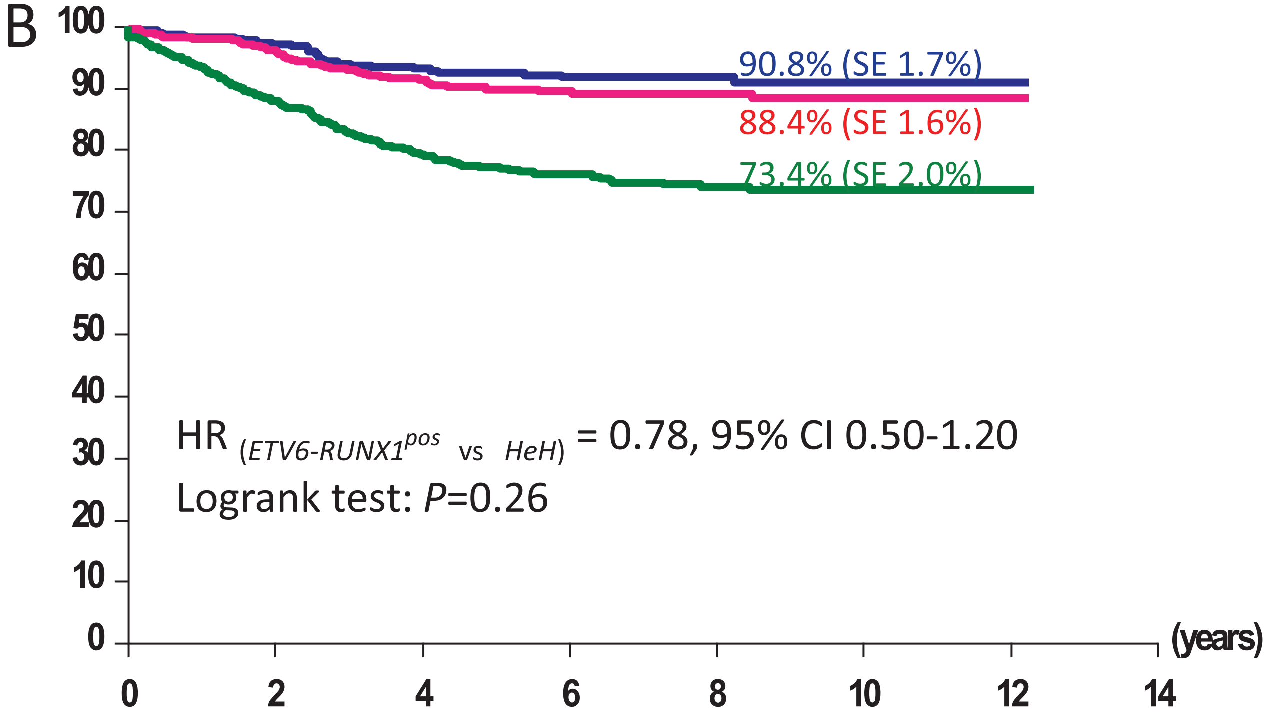
	All	***ETV6-RUNX1^{pos}***	***ETV6-RUNX1^{neg}***	**HeH**	**Others [1]**	**Heterogeneity test** ETV6-RUNX1^{pos} vs ETV6-RUNX1^{neg}	**Heterogeneity test** ETV6-RUNX1^{pos} vs HeH vs Others
***Erwinia*-ASNase versus *E. Coli*-ASNase for all risk-groups in study 58881**							
10-yr EFS rates [2]							
Erwinia-ASNase	66.7% (n=48)	80.0% (n=15)	60.6% (n=33)	56.3% (n=16)	64.7% (n=17)		
E. Coli-ASNase [3]	76.2% (n=346)	83.7% (n=93)	73.4% (n=253)	89.5% (n=95)	63.7% (n=158)		
HR [4] *95%* or 99%** CI*	*0.63* *0.34-1.18**	*0.78* *0.13-4.54***	*0.56* *0.22-1.42***	*0.09* *0.02-0.58***	*0.96* *0.31-2.95***	*P=0.67*	*P=0.02*
Long-ASNase versus Short-ASNase administrations during consolidation/late intensification for non-VHR patients in study 58951							
10-yr DFS rates [5]							
Short-ASNase	83.6% (n=607)	91.2% (n=177)	80.5% (n=430)	90.1% (n=188)	72.8% (n=242)		
Long-ASNase	87.0% (n=622)	94.8% (n=156)	84.5% (n=466)	88.2% (n=239)	80.7% (n=227)		
HR [4] *95%* or 99%** CI*	*0.85* *0.62-1.16**	*0.65* *0.22-1.97***	*0.85* *0.55-1.32***	*1.45* *0.65-3.23***	*0.71* *0.42-1.21***	*P=0.57*	*P=0.13*
DEXA (6 mg/m²/day) versus PRED (60 mg/m²/day) during induction in study 58951							
10-yr EFS rates [2]							
PRED	81.8% (n=745)	87.2% (n=197)	79.8% (n=548)	88.8% (n=233)	73.2% (n=315)		
DEXA	83.7% (n=748)	95.0% (n=183)	80.1% (n=565)	88.0% (n=251)	73.7% (n=314)		
HR [4] *95%* or 99%** CI*	*0.92* *0.71-1.19**	*0.46* *0.18-1.17***	*1.00* *0.69-1.44***	*1.19* *0.59-2.47***	*0.96* *0.63-1.46***	*P=0.05*	*P=0.11*
Monthly i.v. 6-MP (1 g/m²) vs no i.v. 6-MP during maintenance therapy for non-high risk patients in study 58881							
10-yr DFS rates [5]							
No 6-MP iv	84.6% (n=102)	100% (n=23)	80.0% (n=79)	91.7% (n=36)	70.3% (n=43)		
6-MP iv	72.4% (n=98)	71.4% (n=35)	73.0% (n=63)	79.3% (n=29)	67.7% (n=34)		
HR [4] *95%* or 99%** CI*	*1.91* *1.05-3.48**	*5.82* *1.12-30.22***	*1.47* *0.59-3.64***	*1.89* *0.37-9.80***	*1.32* *0.44-3.94***	*P=0.06*	*P=0.15*
Vincristine-corticosteroid pulses vs no pulses during maintenance therapy for AR patients in study 58951							
10-yr DFS rates [5]							
No Pulse	82.8% (n=153)	96.1% (n=53)	75.7% (n=100)	88.5% (n=26)	71.1% (n=74)		
Pulse	87.5% (n=148)	95.1% (n=44)	84.3% (n=104)	91.3% (n=23)	82.3% (n=81)		
HR [4] *95%* or 99%** CI*	*0.70* *0.39-1.27**	*1.18* *0.09-15.58***	*0.62* *0.27-1.40***	*0.76* *0.08-7.65***	*0.58* *0.24-1.38***	*P=0.54*	*P=0.78*

[1] including patients with t(4;11) BCP-ALL; [2] Event-free survival (EFS) was calculated from the date of CR to the date of first relapse or death. Patients who failed to reach CR by the end of induction-consolidation were considered as having an event at time 0; [3] Patients randomized or not for ASNase; [4] The estimated hazard ratio (HR) and its confidence interval (CI) were derived from log-rank test computations. Heterogeneities between these HRs were tested for significance using the Cochran's Q test. All analyses were based on the intent-to-treat principle; [5] Disease-free survival (DFS) was computed from the date of randomization until first relapse or death in CR for patients who were randomized for a given question after the achievement of CR.

Abbreviations: AR: Average risk; ASNase: asparaginase; CI: confidence interval; DEX: dexamethasone; DFS: disease-free survival; EFS: event-free survival; HeH: High hyperdiploidy; HR: hazard ratio; i.v.: intravenous; PRED: prednisone; VHR: very high risk; 6-MP: 6-mercaptopurine



O	N	Number of patients at risk :						
18	108	105	92	81	63	55	41	🟦 ***ETV6-RUNX1*** ^{pos}
18	111	103	96	90	65	52	46	🟥 **HeH**
63	175	143	119	105	79	64	53	🟩 **Others**



O	N	Number of patients at risk :						
31	380	369	307	212	120	52	2	🟦 ***ETV6-RUNX1*** ^{pos}
50	484	464	371	244	143	58	8	🟥 **HeH**
150	629	552	410	266	174	71	4	🟩 **Others**