# Excellent prognosis of late relapses of *ETV6/RUNX1*-positive childhood acute lymphoblastic leukemia: lessons from the FRALLE 93 protocol

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## Online Supplementary Appendix

### *Summary of the FRALLE 93 stratification*

The FRALLE 93 study population was stratified into three groups [low-risk (LR), intermediate-risk (IR), and high-risk (HR)] based on the following risk factors: age, white-cell count at diagnosis, hemoglobin level, immunophenotype, karyotype, and response to steroids.

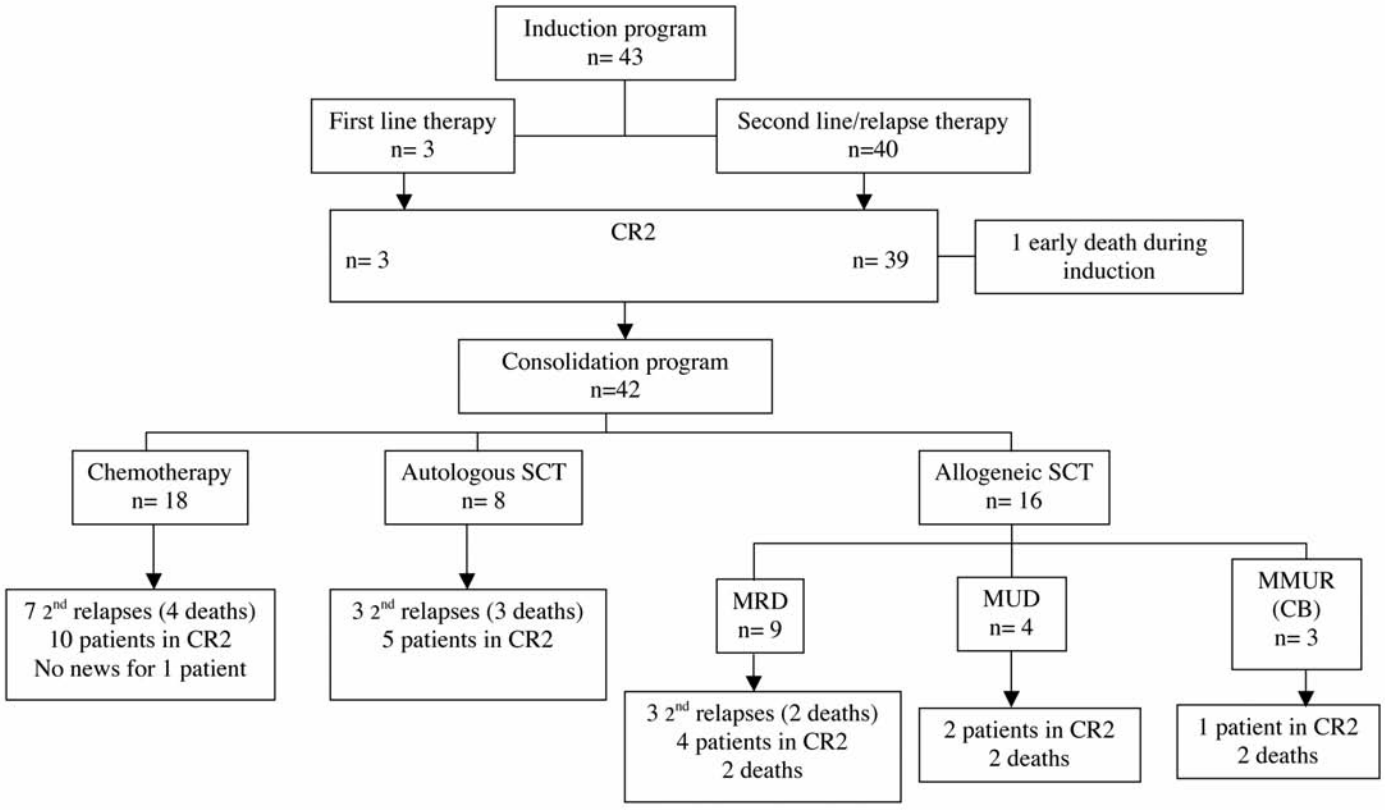
- LR was defined by age between 1 and 7 years, white-cell count <10x10$^9$/L, CD10-positive B lineage c-ALL, and no adverse cytogenetic findings.
- HR was defined by at least one major criterion: age below 1 year or >15 years, white-cell count >100x10$^9$/L, t(9;22) or t(4;11) or hypoploid or tetraploid karyotype, T-cell lineage, or at least two minor criteria: age >10 years, tumor syndrome, hemoglobin >10 g/dL, white-cell count >50x10$^9$/L, expression of two myeloid antigens such as CD13, CD33, or CD14.
- IR was defined by exclusion of LR and HR.

Patients received an initial treatment consisting of a prednisone prophase and a triple-drug intrathecal injection. Induction treatment then included prednisone, vincristine, L-asparaginase, daunorubicin (except for patients in the LR group), and one or two more triple-drug intrathecal injections (TIT). The main treatment features of the SR and IR protocol were induction, consolidation, delayed intensification, and maintenance (total treatment time of 26 and 38 months for girls and boys, respectively). Treatment of the HR patients consisted of induction, consolidation, two delayed intensifications, and maintenance with a total treatment time of 2 years. LR patients received 16 TIT and IR patients received 18 TIT. HR children over 4 years old received 12 TIT before central nervous system radiotherapy, whereas younger children received 18 TIT, without radiotherapy. Very HR patients (steroid-resistant on day 8 or poor bone marrow early response to chemotherapy on day 21) received intensification with six cycles of chemotherapy alternating with methotrexate and high-dose cytarabine, followed by autografting. Allogeneic stem-cell transplantation was recommended for very HR patients with related matched donors and for all patients with t(9;22) or t(4;11) or hypoploid karyotype.

**Online Supplementary Table S1.** Details of the characteristics of the 43 patients with *ETV6/RUNX1*-positive ALL who relapsed.

| Patient | Years at dx | Gender | WBC x10$^9$/L | D8 PGR | D21 M status | End of induction | FRALLE 93 treatment risk group | Time of relapse (months) | Site of relapse | REZ-BFM | Salvage therapy | Post CR treatment | 2$^{nd}$ relapse | Status |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3.7 | male | 15.5 | yes | M1 | CR | IR | 74 | testis | S1-S2 | COOPRALL | CT | | alive |
| 2 | 4.8 | male | 11 | yes | M1 | CR | IR | 32 | BM | S3-S4 | NFL | autoSCT | BM | dead |
| 3 | 4.5 | female | 4.7 | yes | M1 | CR | LR | 51 | BM | S1-S2 | COOPRALL | CT | | alive |
| 4 | 5.5 | female | 27.2 | yes | M2 | CR | IR | 49 | BM | S1-S2 | COOPRALL | CT | | alive |
| 5 | 2.8 | female | 35.6 | yes | M1 | CR | IR | 34 | BM | S1-S2 | COOPRALL | autoSCT | | alive- |
| 6 | 7.3 | male | 10.4 | yes | M1 | CR | IR | 70 | BM | S1-S2 | COOPRALL | CT | BM+CNS | dead |
| 7 | 5.3 | male | 2.3 | yes | M1 | CR | IR | 43 | BM+testis | S1-S2 | COOPRALL | CT | CNS | alive |
| 8 | 5.8 | male | 12.4 | yes | M1 | CR | IR | 55 | BM+testis | S1-S2 | COOPRALL | CT | | alive |
| 9 | 2.6 | male | 229 | yes | M1 | CR | HR | 28 | BM+CNS | S1-S2 | Capizzi | no CR2 | | dead |
| 10 | 7.1 | female | 16.1 | yes | M2 | CR | IR | 60 | BM | S1-S2 | COOPRALL | alloSCT | | dead |
| 11 | 5.4 | male | 24.6 | yes | M1 | CR | IR | 47 | BM+testis | S1-S2 | COOPRALL | autoSCT | | alive |
| 12 | 11.4 | male | 10.3 | yes | M2 | CR | HR | 35 | BM | S3-S4 | COOPRALL | alloSCT | | alive |
| 13 | 2.6 | female | 6.4 | yes | M2 | CR | LR | 64 | BM | S1-S2 | COOPRALL | alloSCT | | dead |
| 14 | 1.7 | female | 50 | yes | M1 | CR | IR | 58 | BM | S1-S2 | COOPRALL | alloSCT | | alive |
| 15 | 4.7 | male | 80 | yes | M3 | CR | HR | 19 | BM | S3-S4 | COOPRALL | alloSCT | | Alive |
| 16 | 2.3 | female | 28.9 | yes | M1 | CR | IR | 32 | BM | S1-S2 | COOPRALL | alloSCT | | dead |
| 17 | 1.9 | male | 5.1 | yes | M1 | CR | HR | 28 | testis | S1-S2 | COOPRALL | CT | BM | dead |
| 18 | 7.7 | male | 9.1 | yes | M1 | CR | IR | 51 | BM | S1-S2 | COOPRALL | CT | BM | dead |
| 19 | 8.6 | male | 4.2 | yes | M2 | CR | HR | 62 | BM | S1-S2 | COOPRALL | alloSCT | | alive |
| 20 | 4.1 | female | 8.2 | yes | M1 | CR | IR | 57 | BM | S1-S2 | COOPRALL | CT | | alive |
| 21 | 3.9 | female | 8 | yes | M1 | CR | IR | 20 | CNS | S1-S2 | COOPRALL | autoSCT | CNS | dead |
| 22 | 3.1 | female | 36.8 | yes | M1 | CR | IR | 32 | BM | S1-S2 | COOPRALL | alloSCT | BM | dead |
| 23 | 4.2 | male | 19.3 | yes | M1 | CR | IR | 44 | BM+testis | S1-S2 | COOPRALL | alloSCT | testis | alive |
| 24 | 12.3 | female | 27.8 | no | M2 | CR | IR | 68 | other | S1-S2 | NFL | CT | | alive |
| 25 | 4.5 | female | 11.7 | yes | M2 | CR | IR | 32 | BM | S1-S2 | COOPRALL | CT | BM | dead |
| 26 | 4.0 | male | 6.3 | yes | M1 | CR | IR | 39 | CNS | S1-S2 | NFL | alloSCT | | alive |
| 27 | 3.4 | male | 6.1 | yes | M2 | CR | LR | 27 | BM | S3-S4 | COOPRALL | alloSCT | BM | dead |
| 28 | 3.7 | male | 5.2 | yes | M1 | CR | LR | 40 | BM+testis | S1-S2 | COOPRALL | CT | | alive |
| 29 | 2.0 | male | 51.3 | yes | M1 | CR | HR | 40 | BM+testis | S1-S2 | COOPRALL | autoSCT | | alive |
| 30 | 2.2 | male | 26.7 | yes | M1 | CR | IR | 66 | BM | S1-S2 | COOPRALL | CT | testis | alive |
| 31 | 2.7 | male | 61.3 | yes | M1 | CR | HR | 47 | BM | S1-S2 | COOPRALL | autoSCT | | alive |
| 32 | 5.3 | female | 223 | yes | M1 | CR | HR | 22 | BM | S3-S4 | COOPRALL | autoSCT | BM | dead |
| 33 | 3.8 | male | 19.8 | yes | M1 | CR | IR | 50 | BM | S1-S2 | COOPRALL | CT | BM | alive |
| 34 | 1.7 | male | 106 | yes | M1 | CR | HR | 33 | BM | S3-S4 | COOPRALL | alloSCT | | alive |
| 35 | 3.4 | male | 7 | yes | M2 | CR | IR | 56 | testis | S1-S2 | COOPRALL | CT | | alive |
| 36 | 2.6 | female | 24 | yes | M1 | CR | IR | 7 | BM | S3-S4 | COOPRALL | alloSCT | | dead |
| 37 | 3.5 | female | 22.2 | yes | M2 | CR | IR | 20 | BM | S3-S4 | COOPRALL | alloSCT | | dead |
| 38 | 5.0 | female | 6.1 | yes | M1 | CR | LR | 38 | BM | S1-S2 | COOPRALL | alloSCT | | dead |
| 39 | 5.8 | male | 8 | yes | M1 | CR | IR | 52 | testis | S1-S2 | COOPRALL | CT | | alive |
| 40 | 5.8 | male | 7 | yes | M1 | CR | IR | 70 | BM+CNS | S1-S2 | COOPRALL | CT | | alive |
| 41 | 3.3 | male | 181 | yes | M1 | CR | HR | 50 | BM | S1-S2 | UKALLR2 | CT | | ? |
| 42 | 2.1 | female | 3.8 | yes | M1 | CR | LR | 35 | BM | S1-S2 | COOPRALL | autoSCT | | alive |
| 43 | 4.8 | male | 63 | yes | M1 | CR | IR | 43 | BM+testis | S1-S2 | Capizzi | alloSCT | | alive |

*D8 PGR: a good prednisone response was defined as a blast count <1000/μL blood after the first 7 days on 60 mg/m$^2$/day of prednisone (i.e. on day 8) and one triple-drug intrathecal injection. D21 M status: a good early response to chemotherapy was defined by a blast count <5% in bone marrow smears on day 21 (M1) and a poor early chemotherapy response by a blast count ≥5% (with two categories: M2 = 5-25% and M3 = >25%). CR: complete remission was defined by no physical evidence of disease, no detectable leukemic blasts on blood smears and <5% blasts on bone marrow smears, active hematopoiesis and normal cerebrospinal fluid. WBC: white blood cell count; BM: bone marrow; CNS: central nervous system; LR: low risk group; IR: intermediate risk group; HR: high risk group; dx: diagnosis; CT: chemotherapy; auto/allo SCT: autologous/allogeneic stem-cell transplantation; NFL: new first line therapy. ALL REZ-BFM S1-S2 classification is defined as isolated bone marrow relapses ≥ 6 months after completion of primary therapy, isolated extramedullary relapses, and combined bone marrow relapses ≥ 18 months after completion of primary therapy). ALL REZ-BFM S3-S4 classification is defined as isolated bone marrow relapses <6 months and combined bone marrow relapses < 18 months after primary diagnosis.*




**Online Supplementary Figure S1.** Flowchart of salvage therapy after relapse. SCT: stem cell transplantation. CR: complete remission; MRD: matched related donor; MUD: matched unrelated donor; MMUR: mismatched unrelated donor; CB: cord blood.