A sequential approach with imatinib, chemotherapy and transplant for adult Ph+ acute lymphoblastic leukemia: final results of the GIMEMA LAL 0904 study

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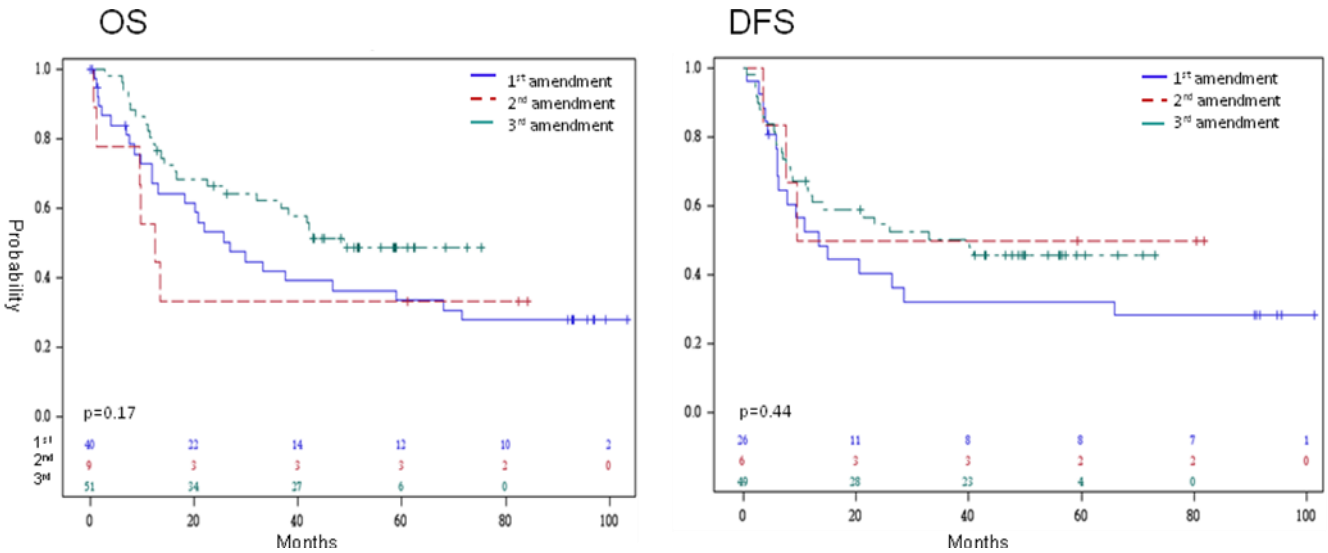
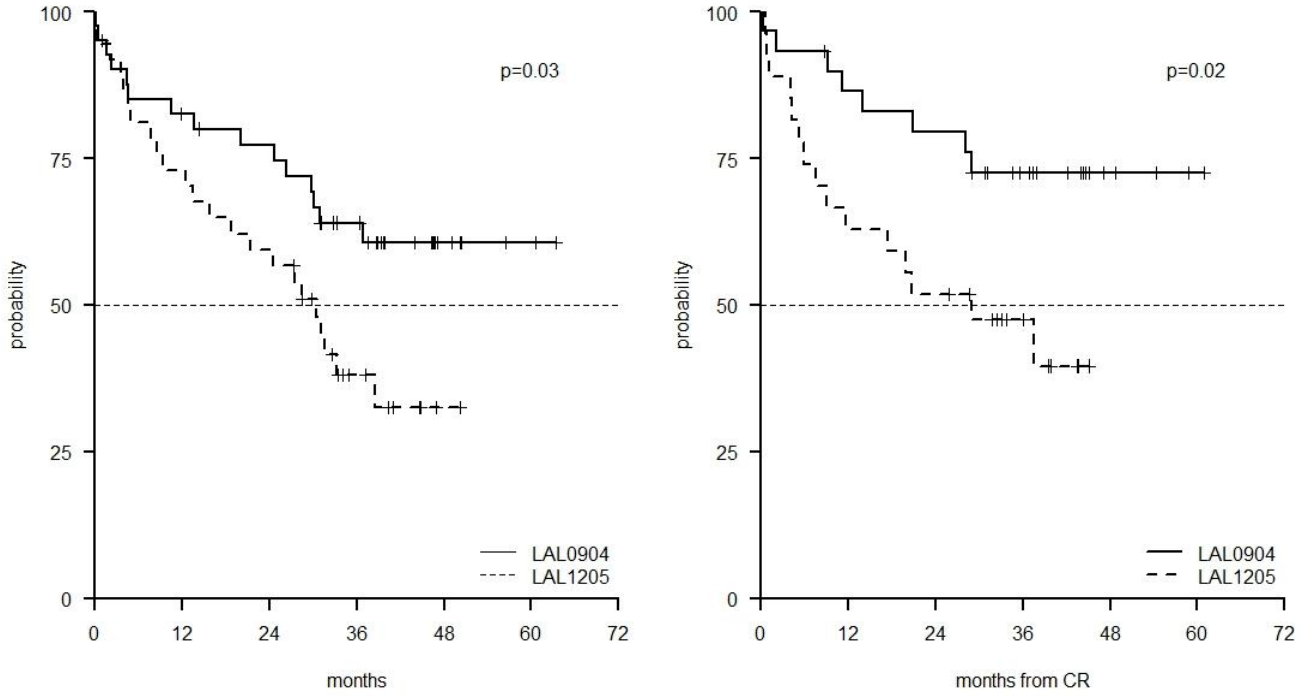
Supplementary Table 1. Distribution of Ph+ ALL cases enrolled in the GIMEMA 0904 protocol within the three amended versions.

Amendments	**Enrollment period**	**N patients**
1st amendment	October 2004-June 2009	40
2nd amendment	October 2006-October 2008	9
3rd amendment	July 2007-April 2010	51

Supplemental Figure 1. OS and DFS of the patients enrolled in the 3 different versions of the GIMEMA 0904 protocol. First amendment (blue line); second amendment (red dotted line); third amendment (green line).



Supplementary Figure 2. OS and DFS comparison between the GIMEMA 0904 and 1205 protocols. A landmark analysis was performed comparing GIMEMA 0904 (continuous lines) and 1205 (dotted lines; only patients with age ≤60 years included) and survival was calculated from the 12th month onwards. The cut-point at 12 months was chosen because the goal of this analysis was to evaluate the effects of a uniform post-consolidation treatment on outcome.



Supplementary Materials and Methods

Study design and therapy

Patients received a 7-day steroid pre-phase of oral prednisone at increasing doses (10-60 mg/m^2/day) and subsequently received induction therapy with oral imatinib 600 mg daily for 50 days. Prednisone (60 mg/m^2/day) was administered until day +24, then tapered and stopped at day +32. A consolidation treatment with the HAM regimen [cytarabine (3 gr/m^2/12 hrs for 4 days), mitoxantrone (10 mg/m^2/day for 3 days) and granulocyte colony-stimulating factor (G-CSF: 5 μg/Kg/day until PMN >1500 μL for 2 consecutive days)] associated with imatinib (600 mg/die), was performed; this regimen was followed, if possible, by a hematopoietic SCT, either allogeneic (allo-SCT) or autologous (au-SCT), if no donor was available.

Patients who did not achieve a CHR after the induction phase, underwent a cycle of HAM, followed by a consolidation cycle with high-dose (HD) cytosine-arabinoside (ARA-C 3 gr/m^2/day for 5 days), idarubicin (40 mg/m^2/day on day 3) and G-CSF (5 μg/Kg/day until PMN >1500 μL) for 2 consecutive days, associated with imatinib (600 mg/die).

CNS prophylaxis was performed with intrathecal methotrexate (15 mg) during induction on days +21 and +35, and during maintenance, for a total of 14 rachicenteses.

Statistical methods

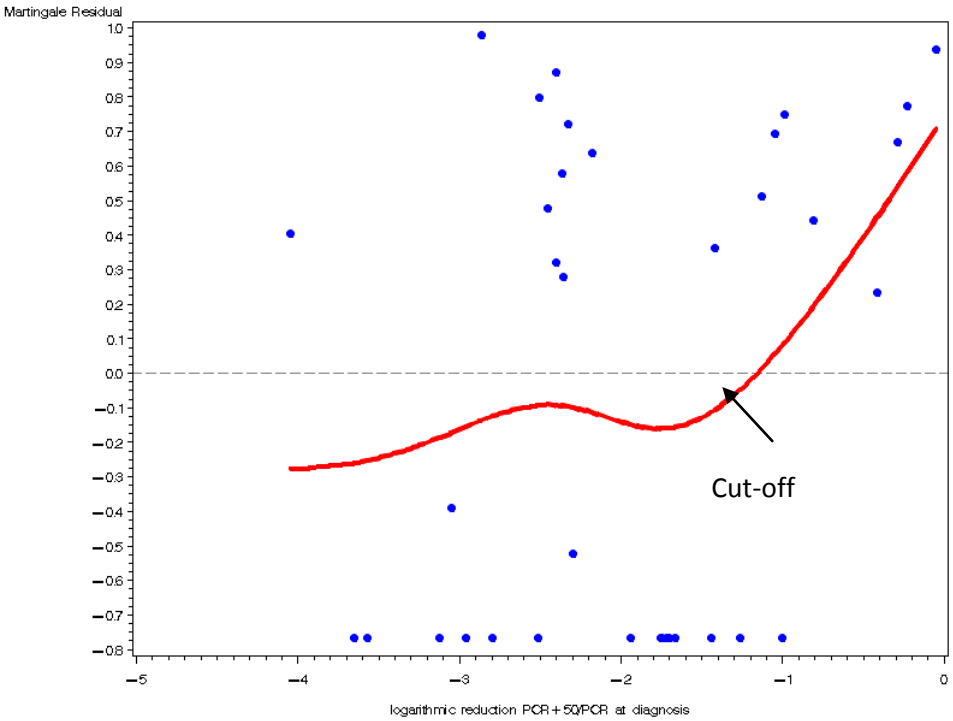
To evaluate the effects of this total therapy scheme, we performed the statistical analysis according to intention to treat (ITT) principle.

OS was defined as the time from diagnosis to death, DFS was defined as the time from CHR to relapse, death, or last follow-up for patients alive in first CHR - were estimated using the Kaplan-Meier method and cumulative incidence of relapse (CIR) was calculated from CHR to relapse or last follow-up for patients alive in first CHR, using the cumulative incidence method and considering death in CHR as a competing risk. The role of transplant was evaluated in a Cox model with a time-dependent covariate.

The distribution of missing values was evaluated, as a category, in survival analysis and no statistical significance was found. In the analysis for BCR-ABL1 levels reduction, only evaluable patients at each time point were considered and multiple imputation methods were not carried out.

The cut-off for log BCR-ABL1 reduction at d+50 for DFS was given by means a smother estimated by a spline method on the plot of the distribution of martingale residuals on the y axis and log reduction values on the x axis, as now shown in the Supplementary Figure 3. The optimal cut-off divides the underestimated with the overestimated residuals (martingale residual=0).

Supplementary Figure 3. Graphical plot of cut-off definition by martingale residual analysis. Y axis: distribution of martigale residuals, x axis: BCR-ABL1 log reduction values,


Martingale Residual
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
−0.1
−0.2
−0.3
−0.4
−0.5
−0.6
−0.7
−0.8
−5
−4
−3
−2
−1
0
logarithmic reduction PCR+5Q/PCR at diagnosis
Cut-off

Supplemental Appendix. List of investigators of the GIMEMA working group,

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