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MRD at the End of Induction and EFS in T-cell Lymphoblastic Lymphoma: Children's Oncology Group Trial AALL1231

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Abstract:
Defining prognostic variables in T-lymphoblastic lymphoma (T-LL) remains a challenge. AALL1231 was a COG phase 3 clinical trial for newly diagnosed with T Acute Lymphoblastic leukemia or T-LL patients randomizing children and young adults to a modified augmented BFM backbone to receive standard therapy (Arm A) or with addition of bortezomib (Arm B). Optional bone marrow (BM) samples to assess minimal residual disease (MRD) at the end of induction (EOI) were collected in T-LL analyzed to assess the correlation of MRD at the EOI to event-free survival (EFS). Eighty-six (41%) of the 209 T-LL patients accrued to this trial submitted samples for MRD assessment. Patients with MRD <0.1% (n= 75) at EOI had a superior 4-year EFS versus those with MRD >0.1% (n= 11), (89.0{plus minus}4.4% versus 63.6{plus minus}17.2%, p= 0.025). Overall survival did not significantly differ between the two groups. Cox regression for EFS using Arm A as a reference demonstrated that MRD EOI {greater than or equal to}0.1% was associated with a greater risk of inferior outcome (Hazard Ratio, HR= 3.73 (1.12-12.40, p= 0.032), which was independent of treatment arm assignment. Consideration to incorporate MRD at EOI into future trials will help establish its value in defining risk groups. CT# NCT02112916

Conflict of interest: COI declared - see note

COI notes: SPH has received honoraria from Amgen, consulting fees from Novartis and owns common stock in Amgen. MLL has received consulting fees from MediSix Therapeutics. MLH has served on advisory boards for Novartis and Sobi. DTT serves on advisory boards for Amgen, La Roche, Janssen, and Sobi. CEA serves on advisory boards for Sobi and OPNA and receives research support from Genentech.

Preprint server: No;

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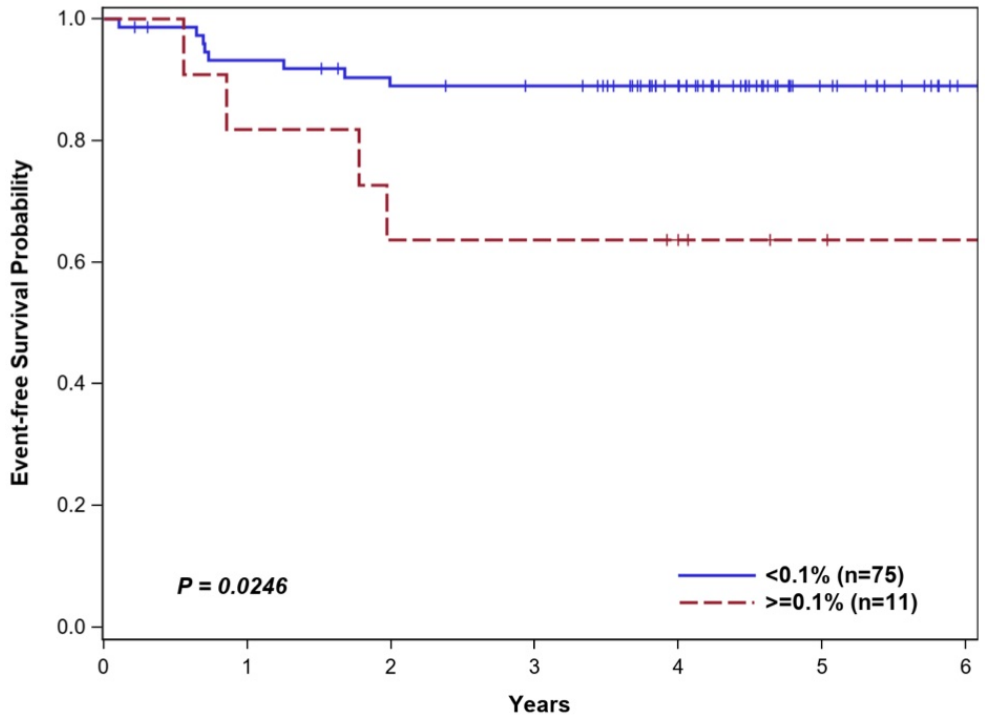
Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: The Children's Oncology Group Data Sharing policy describes the release and use of COG individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) Guidelines. Only data expressly released from the oversight of the relevant COG Data and Safety Monitoring Committee (DSMC) are available to be shared. Data sharing will ordinarily be considered only after the primary study manuscript is accepted for publication. For phase 3 studies, individual-level de-identified datasets that would be sufficient to reproduce results provided in a publication containing the primary study analysis can be requested from the NCTN/NCORP Data Archive at https://nctn-data-archive.nci.nih.gov/. Data are available to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. For non-phase 3 studies, data are available following the primary publication. An individual-level de-identified dataset containing the variables analyzed in the primary results paper can be expected to be available upon request. Requests for access to COG protocol research data should be sent to: datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use. For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests. In addition to above, release of data collected in a clinical trial conducted under a binding collaborative agreement between COG or the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical/biotechnology company must comply with the data sharing terms of the binding collaborative/contractual agreement and must receive the proper approvals.

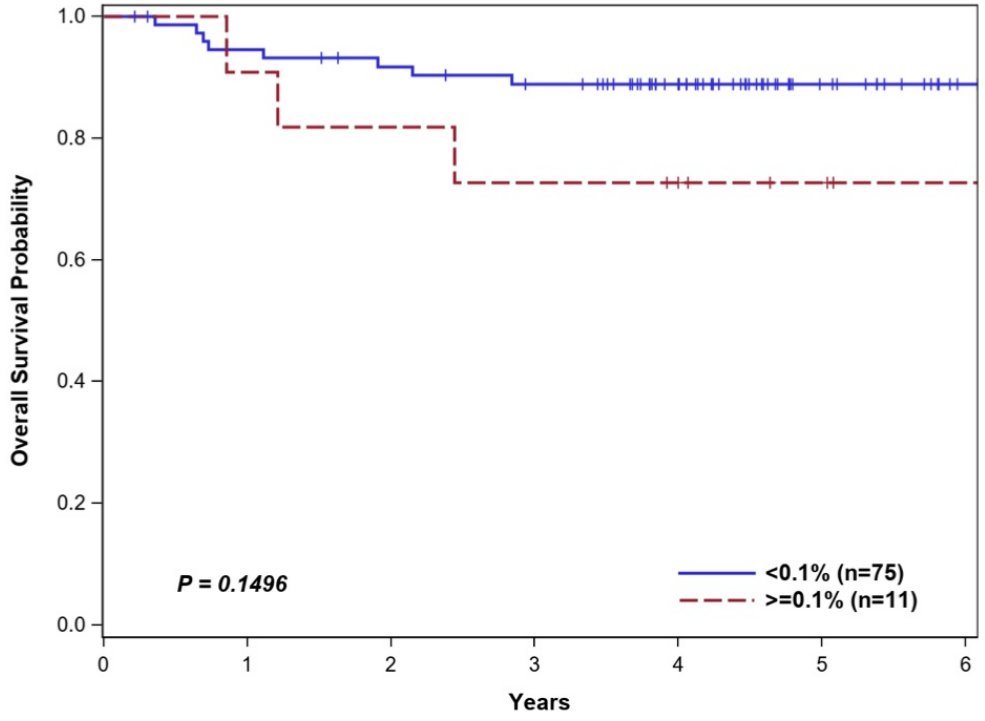
Clinical trial registration information (if any): NCT02112916

Figure 1

A.



B.

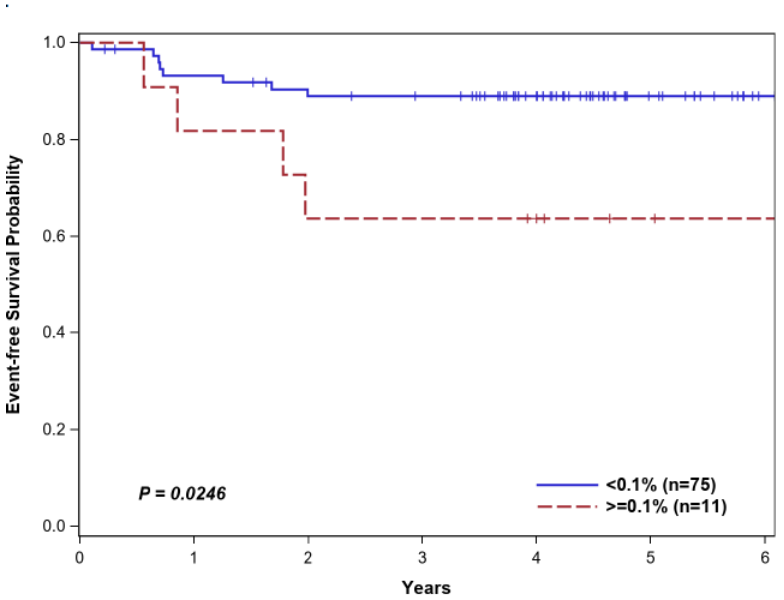


Minimal Residual Disease Measurements at the End of Induction Therapy and Event--Free Survival in Pediatric T-Cell Lymphoblastic Lymphoma (T-LL)

Context of Research

- **Modern therapy has improved the outcomes for pediatric patients with T cell lymphoblastic lymphoma (TLL)**
- **Many features of the disease and of the patients fail to identify those subjects who are less likely to achieve long term disease control**
- **Minimal Residual Disease (MRD) is a test using flow cytometry which can detect small amounts lymphoma cells in the bone marrow at different stages of therapy**
- **A group of patients participating in a Children's Oncology Group trial for newly diagnosed patients with TLL volunteered to submit MRD samples from the bone marrow after the first phase of therapy (induction)**
- **Those with MRD levels <0.1% of tumor did better than those with ≥0.1 %**

Main Findings



Event-free survival in T-LL patients comparing subjects with MRD <0.1% to those with MRD ≥1%

Conclusions: MRD measured at the end of induction therapy may identify patients who are at risk for treatment failure.

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Blood Visual Abstract

Title: MRD at the End of Induction and EFS in T-cell Lymphoblastic Lymphoma: Children's Oncology Group Trial AALL1231.

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Short Title: MRD and EFS in Pediatric T-Lymphoblastic Lymphoma

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Data Sharing: The Children's Oncology Group Data Sharing policy describes the release and use of COG individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) Guidelines. Only data expressly released from the oversight of the relevant COG Data and Safety Monitoring Committee (DSMC) are available to be shared. Data sharing will ordinarily be considered only after the primary study manuscript is accepted for publication. For phase 3 studies, individual-level de-identified datasets that would be sufficient to reproduce results provided in a publication containing the primary study analysis can be requested from the NCTN/NCORP Data Archive at https://nctn-data-archive.nci.nih.gov/. Data are available to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. For non-phase 3 studies, data are available following the primary publication. An individual-level de-identified dataset containing the variables analyzed in the primary results paper can be expected to be available upon request. Requests for access to COG protocol research data should be sent to: datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use.

For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests. In addition to above, release of data collected in a clinical trial conducted under a binding collaborative agreement between COG or the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical/biotechnology company must comply with the data sharing terms of the binding collaborative/contractual agreement and must receive the proper approvals

Word Counts:
Title: 110/120 characters
Short Title: 49/50 characters
Abstract: 195/200
Manuscript: 1189/1500
Figure/Table: 1 Figure, 1 Table/2 total
Supplemental figure 1
References: 12/25

Key Point 1: The level of MRD in the bone marrow at the end of induction correlates with event free survival in T cell lymphoblastic lymphoma.

Key Point 2: MRD at the end of induction may be one of the few prognostic variables for event free survival in pediatric T cell lymphoblastic lymphoma

Abstract: Defining prognostic variables in T-lymphoblastic lymphoma (T-LL) remains a challenge. AALL1231 was a COG phase 3 clinical trial for newly diagnosed with T Acute Lymphoblastic leukemia or T-LL patients randomizing children and young adults to a modified augmented BFM backbone to receive standard therapy (Arm A) or with addition of bortezomib (Arm B). Optional bone marrow (BM) samples to assess minimal residual disease (MRD) at the end of induction (EOI) were collected in T-LL analyzed to assess the correlation of MRD at the EOI to event-free survival (EFS). Eighty-six (41%) of the 209 T-LL patients accrued to this trial submitted samples for MRD assessment. Patients with MRD <0.1% (n= 75) at EOI had a superior 4-year EFS versus those with MRD ≥0.1% (n= 11), (89.0±4.4% versus 63.6±17.2%, p= 0.025). Overall survival did not significantly differ between the two groups. Cox regression for EFS using Arm A as a reference demonstrated that MRD EOI ≥0.1% was associated with a greater risk of inferior outcome (Hazard Ratio, HR= 3.73 (1.12-12.40, p= 0.032), which was independent of treatment arm assignment. Consideration to incorporate MRD at EOI into future trials will help establish its value in defining risk groups. CT# NCT02112916

Introduction: Traditional variables such as stage or radiologic response to therapy have failed to correlate with event-free survival (EFS) in recent trials in T-Lymphoblastic Lymphoma (T LL)[1-5]. AALL1231 was a Children's Oncology Group (COG) phase 3 clinical trial for newly diagnosed patients with T-cell Acute Lymphoblastic Leukemia (T-ALL) or T-LL that randomized children and young adults (age 1-30 years) to a modified COG-augmented BFM (aBFM) backbone to receive standard therapy (Arm A) or with addition of bortezomib (Arm B) during induction and delayed intensification (DI) (1.3mg/m^2 x 4 doses per block)[6]. We previously reported the favorable results of T-LL patients receiving bortezomib[6]. We now report our analysis of a subgroup of T-LL participants who voluntarily submitted bone marrow samples at the end of induction (EOI) to assess the correlation of minimal residual disease (MRD) at EOI on event free survival EFS and overall survival (OS). Identification of variables that correlate with EFS are essential to develop risk-based therapies. MRD has shown to be a powerful prognostic tool for both B-ALL and T-ALL[7 8]. Despite these advances in ALL, the relationship of EOI MRD to clinical risks in patients with T-LL is not known.

Methods: Newly diagnosed T-LL, stages II-IV were eligible for enrollment on COG ALL1231 (NCT02112916)[6]. Prior steroid therapy was allowed if the administration was both less than 5 days within 7 days and less than 14 days in the 28 days prior to initiating induction therapy. T-LL patients were stratified as standard risk (SR) if they demonstrated <1% malignant cells in the bone marrow at diagnosis [minimally detectable disease (MDD)], had no CNS involvement, no steroid pretreatment and demonstrated at least a partial response (PR) at the EOI. Intermediate (IR) patients had any of the following: steroid pre-treatment, >1% MDD, disease detectible in the CNS or testes at diagnosis, and still achieved at least a partial response (PR) at the EOI. Very high risk (VHR) had any of the features of IR, but achieved no better than stable disease (SD) at the EOI. Bone marrow samples to assess MRD at the EOI were an optional submission for T-LL participants, and these specimens were analyzed by flow cytometry having previously demonstrated a validated sensitivity of 0.01% to assess its correlation to EFS[9 10].

Event-free survival (EFS) was the primary outcome and defined as time from study enrollment to first event: death in induction or remission, refractory disease, relapse, second malignant neoplasm, or last contact date for those who were event-free. Overall survival was defined as time from study enrollment to death or last contact date. Proportions were compared using a chi-square test or Fisher's exact test. Survival rates were estimated using the Kaplan-Meier method and standard errors[11 12]. Multivariable analyses used Cox regression included treatment arm and risk group. Per-protocol, subgroup analyses of overall outcomes, including by race, ethnicity, and sex, were performed. A $p < 0.05$ was considered statistically significant for comparisons. Analyses were performed using SAS version-9.4 (SAS Institute, Cary NC)[13].

This study was conducted by COG under a National Cancer Institute held Investigational New Drug (IND) application for bortezomib (NSC#68129;IND#58443). AALL1231 was approved by the Cancer Therapy and Evaluation Program, the Pediatric Central Institutional Review Board (IRB), and participating center IRBs. Written informed consent and assent (if applicable) were obtained before study entry.

Results and Discussion: AALL1231 accrued 209 T-LL patients from 2014 to 2017 (Supplemental figure 1). At the EOI, 43.6% of patients were in radiologic remission, 55.4% had a PR and 1% had SD or no response. There were 86 (41%) patients for whom EOI samples for MRD assessment were submitted. Demographic characteristics in this subgroup did not significantly differ from the T-LL cohort (Table 1). There were differences observed in percent blasts observed in the bone marrow at diagnoses ($p<0.0001$) and stage ($p=0.0004$) although stage was unknown for 55.7% of the patients who submitted a sample for MRD assessment. There was a history of steroid pretreatment in 25.6% of patients; 62.2% had less than 1% of MDD in the bone marrow at diagnosis. resulting in 30.2%, and 67.5% of patients assigned SR and IR respectively. Those who participated in the MRD assessment had a higher representation of intermediate risk patients than those patients who did not (67.5% vs 38.2%, $p= 0.0003$). There were no VHR patients in this cohort and 2.3 % of patients could not be classified in a specific risk group. Complete response (CR) rate was 51.6%, 48.4% had a PR, and none had SD (Table 1).

There was a significant difference in the 4-year EFS comparing Arm A to Arm B (78 + 8.1% versus 91.2+ 4.9%, ($p=0.046$). In addition, a significant difference was also observed in 4-year OS with those patients not receiving bortezomib, (Arm A, 78.8 + 8.1%) compared to those receiving bortezomib Arm B 93.3+ 4.3%, ($p=0.023$), consistent with previously published results (Table 1). When examining MRD, there were 8 events in patients with MRD<0.1% (4 relapsed, 3 remission deaths, and one patient with progression) and 4 events in patients with MRD $\geq$ 0.1% (3 relapses, 1 remission death). Patients with MRD <0.1% (n=75) at EOI had a superior EFS versus MRD ≥0.1% (n= 11), (89.0±4.4% versus 63.6±17.2%, $p= 0.025$). Analysis of the cohort above and below 0.01% failed to distinguish significant differences possibly due to the small sample size (71 <0.01 vs 15 $\geq$0.01%). Furthermore, when examining the 4 patients with MRD <0.1 and >0.01, they are all free of disease. Overall survival did not significantly differ between the two groups (88.9 $\pm$ 4.4% versus 72.7±15.5% $p= 0.15$) (figure 1). Intermediate Risk and SR patients had similar EFS (Arm A 73.9±7.5% versus 80.4±6.7, Arm B 87.2±5.8 % versus 90.5±4.8%). Cox regression for EFS demonstrated inferior outcomes for those with MRD EOI ≥0.1%, (Hazard Ratio, HR = 3.73 (1.12-12.40, $p= 0.032$) which was independent of treatment

arm. Overall survival failed to reach statistical significance for patients MRD EOI ≥0.1%, HR = 2.714 (0.72-10.44, p=0.14). Of note, Cox regression did not demonstrate a significant impact on EFS comparing Arm A to Arm B [HR= 0.57 (0.289-1.073, p= 0.080], or increasing MDD at diagnosis comparing <1% to 1-5% [HR= 0.830 (0.255-2.699)] or >5%, HR=2.67 (0.336-21.145) p= 0.141. Furthermore, MRD EOI $\geq$ 0.1% compared to EOI< 0.1% did not differ in CR rates (55% versus 51%) or PR rates (45% versus 49%). In summary, MRD EOI was the only factor significantly associated with EFS.

Thus, in this phase 3 clinical trial, MRD <0.1% in the bone marrow at EOI for T-LL was associated with improved EFS, regardless of treatment arm for both univariate and multivariate analyses. These findings are consistent with a previous report examining MRD at the end of induction[14]. Race, age, gender, risk group, MDD, risk groups, and radiologic response to therapy were not prognostic. No chromosomal or molecular characterization of the disease was available. This is the first report demonstrating that MRD at EOI is an independent risk factor correlating with EFS using a uniform means of assessing MRD. The findings most likely reflect a greater and more rapid reduction of disease burden, perhaps reflecting greater sensitivity to therapy consistent with results from other pediatric lymphoma and leukemia trials. The study was limited as submission of EOI bone marrow specimens was voluntary and thus only 41% of the T-LL enrolled had specimens available for MRD analysis. Larger numbers of patients would have permitted better analysis of MRD levels (0.01-0.1%) and differences in treatment assignments due to disk stratification. Recent trials have failed to identify clear prognostic variables which would aid in risk stratifying patients for treatment[6 15]. Given the paucity of available prognostic factors in this disease, incorporation of MRD at the EOI in large clinical trials will establish its value in risk stratification for future therapeutic trials to clarify the significance of this variable.

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Conflicts of Interest

SPH has received honoraria from Amgen, consulting fees from Novartis and owns common stock in Amgen. MLL has received consulting fees from MediSix Therapeutics. MLH has served

on advisory boards for Novartis and Sobi. DTT serves on advisory boards for Amgen, La Roche, Janssen, and Sobi. CEA serves on advisory boards for Sobi and OPNA and receives research support from Genentech.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 1: Patient Characteristics of Those Submitting and Those Not Submitting MRD Samples

Characteristic	Patients Submitting MRD Samples, Total (%)	Patient without MRD Samples Total (%)	P-value
Age, years			
<10	31 (36.0%)	31 (25.2%)	
10-16	33 (38.4%)	59 (48.0%)	0.213
≥16	22 (25.6%)	33 (26.8%)	
Sex			
Male	67 (77.9%)	92 (74.8%)	0.604
Female	19 (22.1%)	31 (25.2%)	
CNS			
CNS1	78 (90.7%)	118 (96.7%)	0.171
CNS2	5 (5.8%)	3 (2.5%)	
CNS3	3 (3.5%)	1 (0.5%)	
Testicular disease			
Yes	2 (2.3%)	1 (0.8%)	
No	65 (75.6%)	91 (74.0%)	0.596
N/A female	19 (22.1%)	31 (25.2%)	
Pre steroid treatment			
Yes	22 (25.6%)	41 (33.3%)	0.229
No	64 (74.4%)	82 (66.7%)	
Race			
American Indian or	0	0	
Alaskan Native	2 (2.3%)	4 (3.2%)	
Asian	0	0	
Native Hawaiian or Other	1 (1.2%)	0 (0%)	
Pacific Islander	8 (9.3%)	28 (22.8%)	0.095
Multiple races	62 (72.1%)	76 (61.8%)	
Black or African American	13 (15.1%)	15 (12.2%)	
White			
Unknown			
Ethnicity			
Hispanic or Latino	14 (16.3%)	18 (14.6%)	0.870
Not Hispanic or Latino	66 (76.7%)	98 (79.7%)	
Unknown	6 (7.0%)	7 (5.7%)	

Bone Marrow Blast			
<1% blasts	51 (59.3%)	15(12.2%)	
1-5% blasts	29 (33.7%)	9 (7.3%)	<0.0001
≥5% blasts	2 (2.3%)	1 (0.8%)	
Unknown	4 (4.7%)	98 (79.7%)	
Bone Marrow MRD % Day 29			
<0.01	71 (82.6%)		
0.01 to < 0.1	4 (4.6%)		
0.1 to < 1	6 (7.0%)		
1 < 10	2 (2.3%)		
≥10	3 (3.5%)		
Day 29 Response			
Complete Response	44 (51.6%)	44 (37.9%)	
Partial Response	42 (48.4%)	40 (60.4%)	0.098
Stable Disease / No Response	0	2 (1.7%)	
Risk group			
Standard risk	26 (30.2%)	63 (51.2%)	
Intermediate risk	58 (67.5%)	47 (38.2%)	
Very high risk	0	2 (1.6%)	0.0003
No risk group	2 (2.3%)	11 (9.0%)	
Murphy Stage			
I	1 (1.2%)	1(0.8%)	
II	1 (1.2%)	1 (0.8%)	0.0004
III	17 (19.8%)	41 (33.3%)	
IV	19 (22.1%)	3 (2.5%)	
Unknown	48 (55.7%)	77 (62.6%)	

Figure Legend

Figure 1: MRD at EOI In T-LL: EFS and OS in T-LL patients comparing MRD of <0.1% to patients with MRD >1%.