# Clinical Implications of Detection and Clearance of Post Induction Residual Disease in 2119 Children and Young Adults with AML: Children's Oncology Group Studies AAML0531 and AAML1031

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## Background

Measuring residual disease (RD) by difference from normal (DFN) flow cytometry predicts patient outcome following the first induction cycle and is a prognostic indicator in AML, particularly for those patients lacking prognostic genetic lesions (i.e. standard risk; SR).

## Objective

To assess prevalence of RD by DFN flow cytometry after induction 1 (EOI1) and induction 2 (EOI2), and to assess clearance of RD after initial induction and correlate with clinical outcomes in a large cohort of pediatric AML patients.

## Patients/Methods

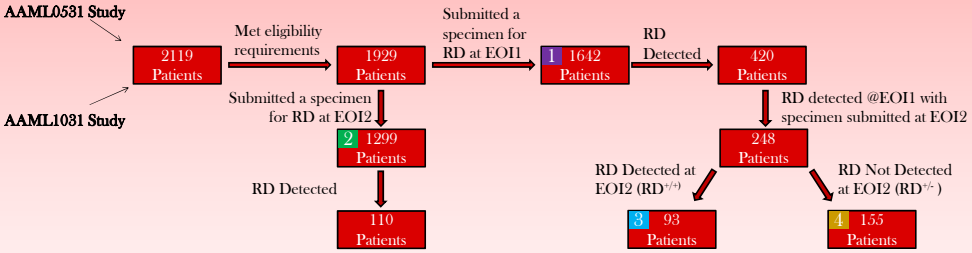
COG AML studies AAML0531 and AAML1031 collectively enrolled 2119 patients of whom 1929 met eligibility requirements (AAML0531, N=844, AAML1031, N=1085) and 1642 submitted a specimen for RD at the end of initial induction therapy (EOI1) and continued to subsequent therapy, while 1299 patients submitted a specimen at the end of second induction (EOI2) and continued on therapy. COG AAML0531 and AAML1031 both utilized an MRC backbone but differed in total number of chemotherapy courses, SCT allocation and preparative regimen. In addition, AAML1031 patients that were determined RD positive by DFN flow cytometry after EOI1 received intensified therapy. Since AAML1031 includes a sorafenib treatment arm that is ongoing, all patients with FLT3/ITD-High allelic ratio were excluded from this analysis.

- Detection of RD by DFN flow cytometry was determined with a standard panel of reagents applying a "difference from normal" algorithm in order to identify aberrant phenotypes vs normal regenerating marrow (Table 1).
- Clinical cutoff of the assay was 0.1% of total non-erythroid cells.
- Lower level of detection of the assay was 0.02% of non-erythroid cells.

| Tube # | FITC | PE | PerCP | APC |
|---|---|---|---|---|
| 1 | HLA-DR | CD11b | CD45 | CD34 |
| 2 | CD36 | CD38 | CD45 | CD34 |
| 3 | CD16 | CD13 | CD45 | CD34 |
| 4 | CD14 | CD33 | CD45 | CD34 |
| 5 | CD7 | CD56 | CD45 | CD34 |
| 6 | CD38 | CD117 | CD45 | CD34 |
| 7* | CD36 | CD64 | CD45 | CD34 |
| 8* | CD19 | CD123 | CD45 | CD34 |

Table 1: Standard panel of reagents used for RD detection by DFN flow cytometry. *Used only in AAML1031

## Results




**•Patients that are RD negative after EOI1 or EOI2 have significantly better overall survival (OS).**

| RD Status | | Overall Survival (%) | Significance |
|---|---|---|---|
| End of EOI1 1 | RD+ | 47.8 ± 5.2 | P <0 .001 |
| | RD- | 75.1 ± 2.6 | |
| End of EOI2 2 | RD- | 53.5 ± 10.6 | P <0.001 |
| | RD- | 74.3 ± 2.7 | |

Table 2: Actuarial 3 year OS based on RD from EOI1 and EOI2.

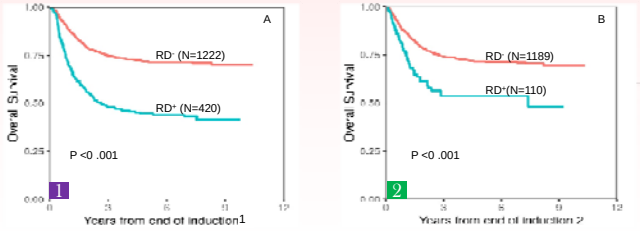



Figure 1. Kaplan-meyer (KM) curves of OS for patients who submitted a sample at A) EOI1 or B) EOI2 with and without detection of RD

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## Results

**•Clearance of RD from EOI1 to EOI2 does not increase OS.**

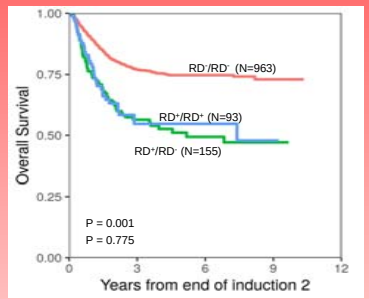


Figure 2. KM curve of OS for patients who submitted a sample at both EOI1 and EOI2 based on RD status.

| RD status of those EOI1+ N=248 | Overall Survival (%) | Significance |
|---|---|---|
| RD+/+ N= 93 37.5% 3 | 56.4 ± 8.4 | P=0.775 |
| RD+/- N=155 62.5% 4 | 54.7 ± 11.8 | |

Table 3: 3 year OS for the combined cohort of the RD+ patients at EOI1 with and without RD clearance at EOI2 (RD+/- and RD+/+)

- 248 patients were RD+ that had specimens submitted at both EOI1 and EOI2
- Patients with RD at EOI1 had similar outcomes regardless of resolution of RD at EOI2
- AAML0531 and AAML1031 (which differ in second induction course of therapy) had similar rate of conversion (RD+/-) and resultant clinical outcome (Table 5).

**•Standard Risk Patients: Clearance of RD from EOI1 to EOI2 does not increase OS.**

| Standard Risk Patients | RD status | Overall Survival (%) | Significance |
|---|---|---|---|
| AML0531 N=65 | RD+/+ N=33 | 42.4 ± 17.2 | P = 0.485 |
| | RD+/- N=32 | 46.9 ± 17.6 | |
| AML1031 N=97 | RD+/+ N=30 | 45.6 ± 17.2 | P = 0.144 |
| | RD+/- N=67 | 41.5 ± 13.4 | |

Table 4: Rate of RD clearance for AML0531 and AML1031 among standard risk patients.

| Standard Risk Patients | Conversion Rate (RD+/-) | Significance |
|---|---|---|
| AML0531 | 13.3% | P=.262 |
| AML1031 | 17.2% | |

Table 5: Conversion rates (RD+ to RD-) in similarly matched standard risk patients for AML0531 and AML1031.

## Summary

- Patients that are RD negative after EOI1 or EOI2 have significantly better overall survival.
- Persistence of RD detected by MDF after one course of therapy is highly associated with adverse outcome in AML.
- ***Clearance of RD from EOI1 to EOI2 is not associated with improved outcome on two sequential COG trials with similar but not identical therapy.***
- ***Reducing leukemia burden after EOI1 may not translate into better survival.***

References

1) Loken MR et. al. Residual disease detected by multidimensional flow cytometry signifies high relapse risk in patients with de novo acute myeloid leukemia: a report from Children's Oncology Group. Blood. 2012 Aug 23;120(8):1581-8.

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