Arsenic Trioxide Consolidation Results in Excellent Survival in Young Children as well as Older Children and Adolescents with Newly Diagnosed Acute Promyelocytic Leukemia (APL): A Report from the Children's Oncology Group Study AAML0631

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Young age as Risk Factor in APL?

- European APL Group (APL 93 and APL 2000) identified age <5 years as group with increased risk of relapse

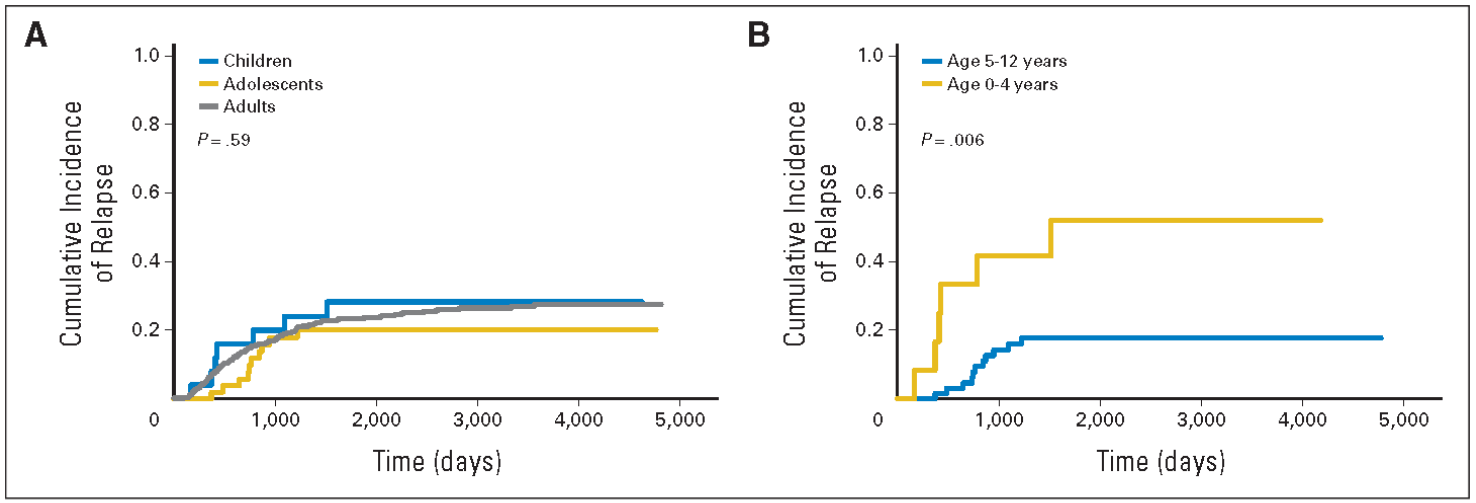

Fig 2. Cumulative incidence of relapse (A) according to age and (B) in patients ≤ 12 years.

Age in years	Number
<5	12
5 - <13	14
13 - 18	58

Bally, et al, JCO 2012

COG AAML0631 Study Design

- Phase III, non-randomized cooperative group trial
  - Historical control: AIDA0493 pediatric patients
- Eligibility
  - Age $\geq$ 2 to < 22 years
  - De novo APL confirmed by PML-RARA PCR
  - No prior therapy
  - No exclusions based on organ function or performance score
- Risk Group based on diagnostic WBC count
  - Standard risk (SR) for WBC < 10,000
  - High risk (HR) for WBC $\geq$ 10,000.

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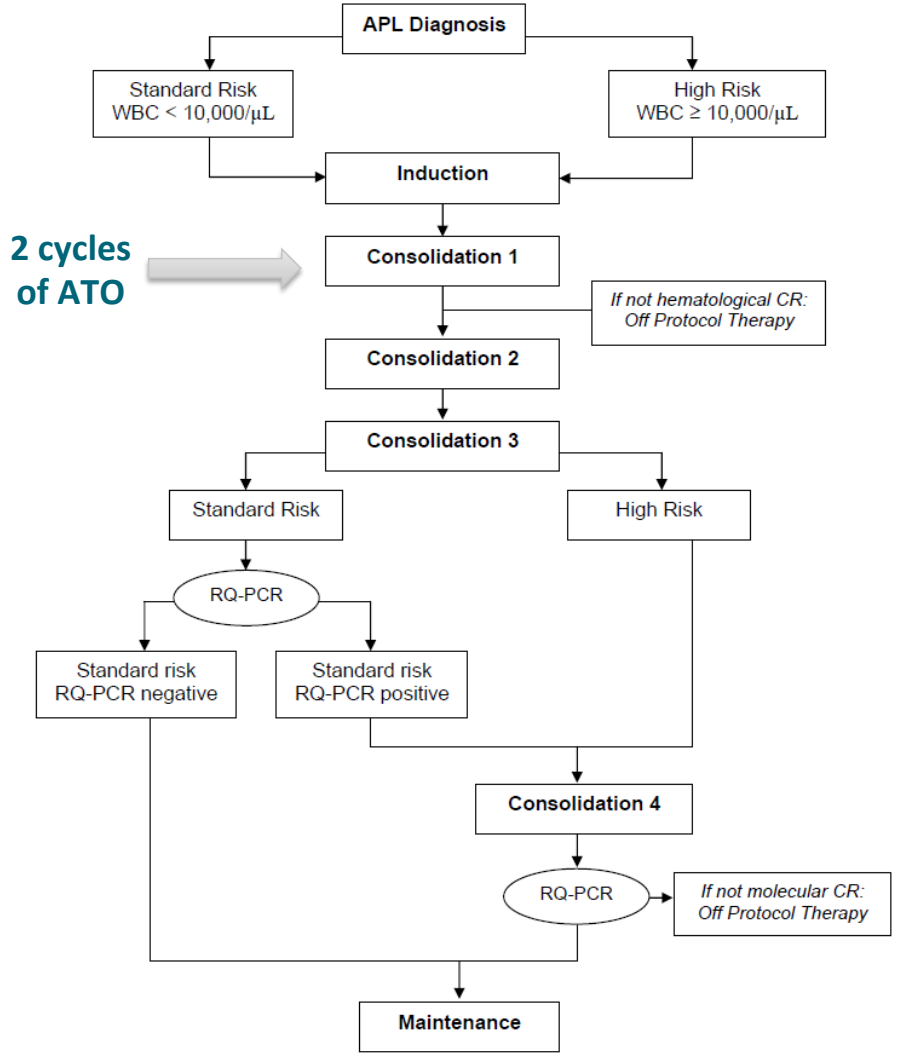
Treatment Schema



AAML0631 Treatment

- Induction
  - Idarubicin 12 mg/m2 x3 doses (SR D3,5,7; HR D1,3,5); ATRA D1-30
- Consolidation 1 (2 cycles, each 5 weeks)
  - ATO 0.15mg/kg 5days/week x 5 weeks; ATRA D1-14
- Consolidation 2
  - Ara-C 1000mg/m2 q12h D1-3; Mitoxantrone 10 mg/m2 D3,4; ATRA D1-14; Intrathecal Ara-C D1
- Consolidation 3
  - Idarubicin 5 mg/m2 D1,3,5; ATRA D1-14; IT Ara-C D1

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ATRA pediatric dosing of 25mg/m2/day divided BID

AAML0631 Treatment

- Consolidation 4 (HR APL and PCR+ SR APL)
  - Ara-C 1000mg/m2 q12h D1-3; Idarubicin 10 mg/m2 on day 4; ATRA D1-14
- Maintenance
  - Mercaptopurine 50mg/m2 oral daily; Methotrexate 25mg/m2 oral weekly; ATRA D1-14 every 12 weeks for 9 cycles; Intrathecal Ara-C D1 of Cycle 1 only

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ATRA pediatric dosing of 25mg/m2/day divided BID

AAML0631 Treatment

- Total anthracycline:
  - SR (without Consolidation 4)
    - 355 mg/m2 Daunorubicin equivalents
    - 45% reduction compared to AIDA0493
  - HR & PCR+SR (with Consolidation 4):
    - 405 mg/m2 Daunorubicin equivalents
    - 38% reduction compared to AIDA0493

Assuming 5:1 conversion ratio for both
Idarubicin and Mitoxantrone to Daunorubicin

Trial Accrual

- Accrual open for 3 years, 8 months
  - 3/9/2009 to 11/9/2012
- 108 patients enrolled
- 101 patients evaluable for outcome
  - 66 SR APL patients
  - 35 HR APL patients
  - Exclusions: 4 PML-RARA PCR negative, 3 local consent issues

Characteristics by Age

Accrual by Age Group	Total Number	High Risk Group: N (%)
Young Children (2 - <5 years)	6	4 (67%)
Older Children (5 - <13 years)	27	6 (22%)
Adolescents (13 - <22 years)	68	25 (37%)

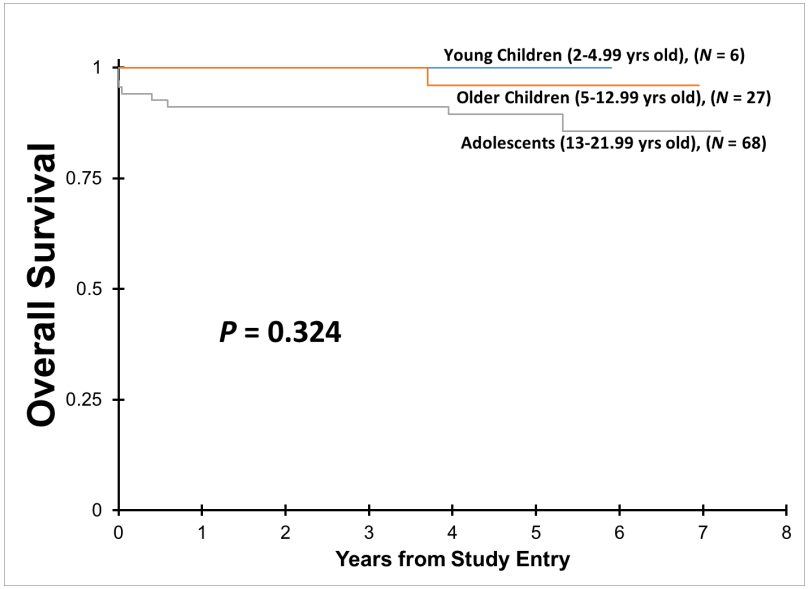
3-way comparison of High Risk proportion: P= 0.096

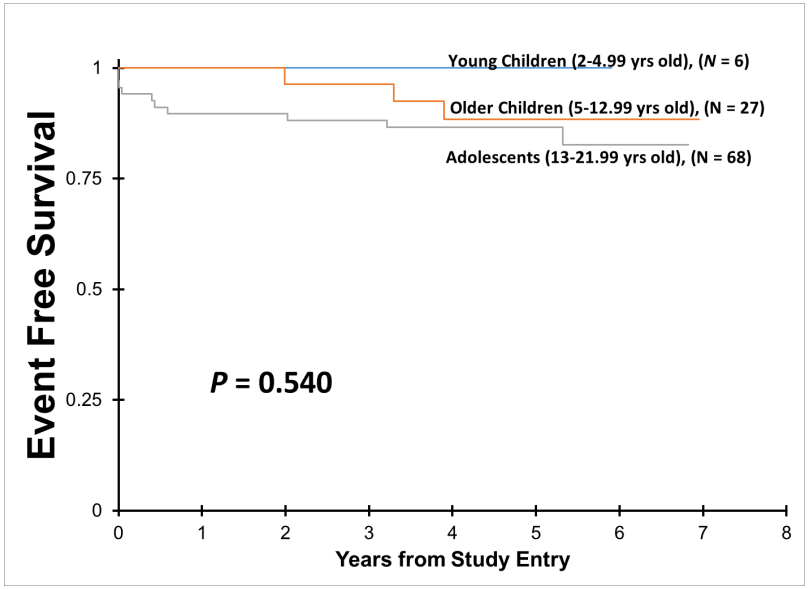
Cytogenetic Complexity	Classic t(15;17) N (%)	t(15;17) plus other abnormalities
Young Children (2 - <5 years)	5 (83%)	1 (17%)
Older Children (5 - <13 years)	11 (42%)	15 (58%)
Adolescents (13 - <22 years)	46 (70%)	20 (30%)

(3 patients with missing cytogentic data)

3-way comparison of complex cytogenetics: P= 0.028

Survival by Age Group





Survival by Age Group	3 yr OS	3 yr EFS
Young Children (2 - <5 years)	100%	100%
Older Children (5 - <13 years)	100%	96%
Adolescents (13 - <22 years)	91%	88%
P-value	0.324	0.540

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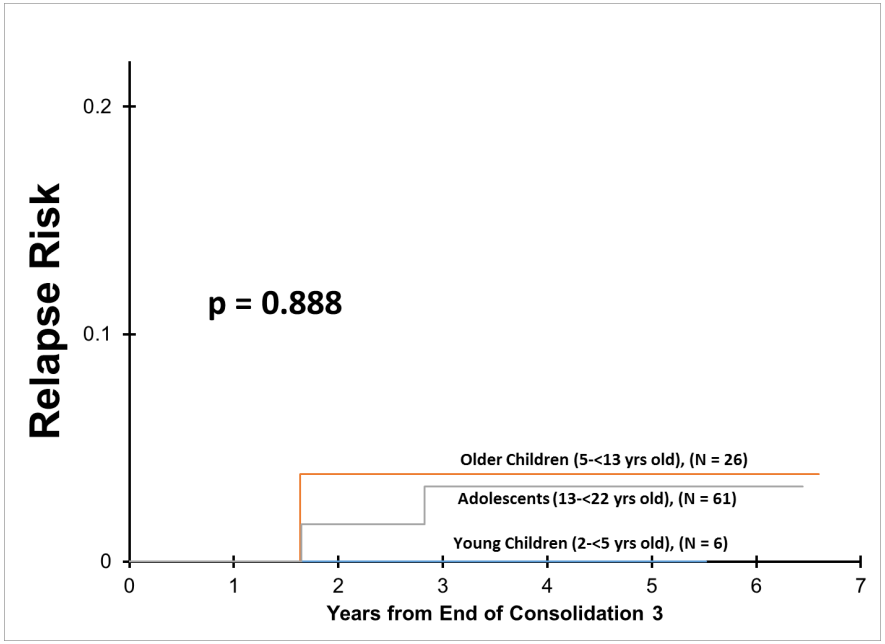
Relapse Risk by Age Group



Relapse by Age Group	3 yr RR
Young Children (2 - <5 years)	0%
Older Children (5 - <13 years)	4%
Adolescents (13 - <22 years)	3%
P-value	0.888

Conclusions

- Although limited by small numbers, our data suggests similar outcomes for young children, older children and adolescents treated on our study
  - Young age should not be used for risk stratification in APL when therapy includes ATO consolidation
- Incorporating ATO consolidation allows dose reduction of anthracyclines while maintaining excellent outcomes in pediatric APL
  - Current COG study AAML1331 is studying APL0406 ATO/ATRA regimen in pediatrics

Study Committee

- Todd Alonzo, PhD
- Laura Burden, CCRP
- Jim Feusner, MD
- Cecilia Fu, MD
- Tom Geller, MD
- Rob Gerbing, MS
- John Gregory, MD
- Betsy Hirsch, PhD
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Special thanks: Alan Gamis, Bob Arceci, Yaddanapudi Ravindranath, Malcolm Smith, Bill Woods

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