The Feasibility of More Attenuated Dosage Schedules of ATO in Newly Diagnosed And Relapsed Acute Promyelocytic Leukaemia

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on behalf of the NCRI AML Working Group

Aims

- The NCRI AML17 Trial compared AIDA vs the combination of ATRA with ATO in both low and high risk patients
- We present extended follow up for the 235 randomized patients previously reported (Burnett et al Lancet Oncology 2015)
- To present the outcome for the 29 patients who received the same schedule of ATO after relapse from the AIDA .

Patients

- 235 patients with molecularly confirmed APL recruited into the randomisation question from May 2009-Oct 2013
- A further 70 patients were treated in AML17 with AIDA after closure of the randomization and were available for the study of ATO at relapse
- Results based upon follow-up to July 2017 with a median of 6 years for randomised patients

Arsenic Trioxide Schedule

Induction: ATO 0.3mg/kg days 1-5 in week 1
(8 weeks) then: 0.25mg/kg X 2/ week for 7 weeks

Consolidation: ATO 0.3mg/kg d 1-5 in week 1.
(4 cycles) 0.25mg/kg x 2 per week for 3 weeks

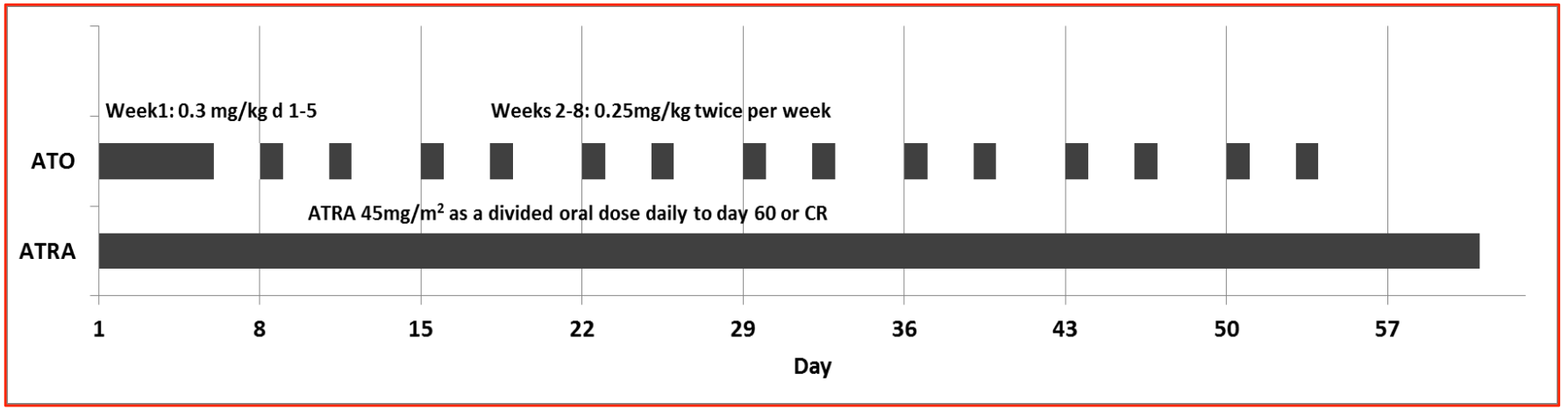
Total of 63 days of ATO

High risk patients received Mylotarg within the first 4 days of induction (6mg/m^2)

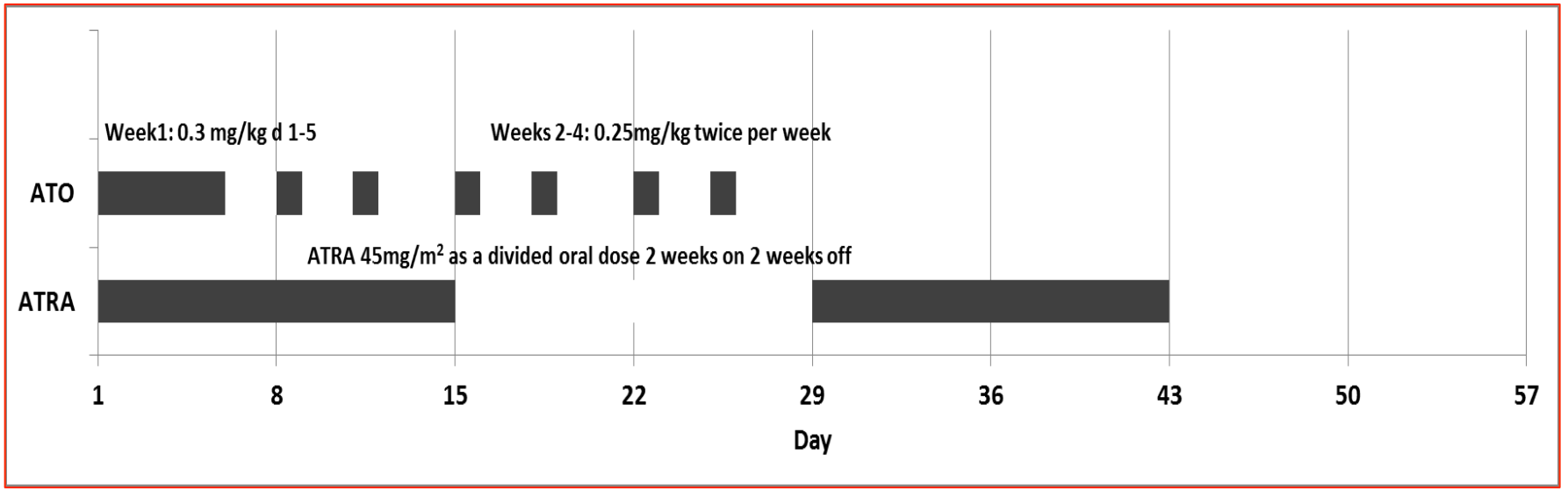
Provision was made for relapse post AIDA to receive the same schedule of ATO

AML17: ATRA + ATO Schedule

Induction

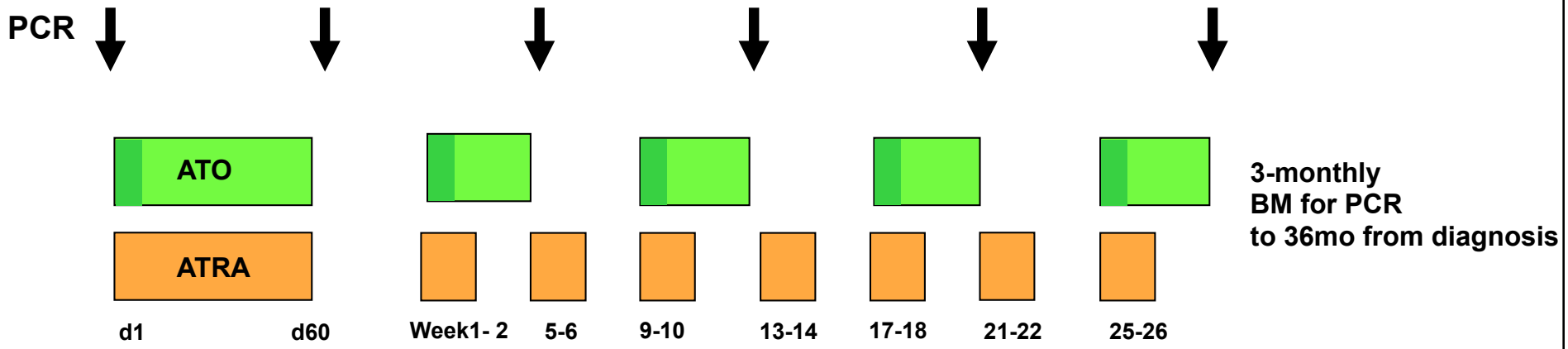


Consolidation

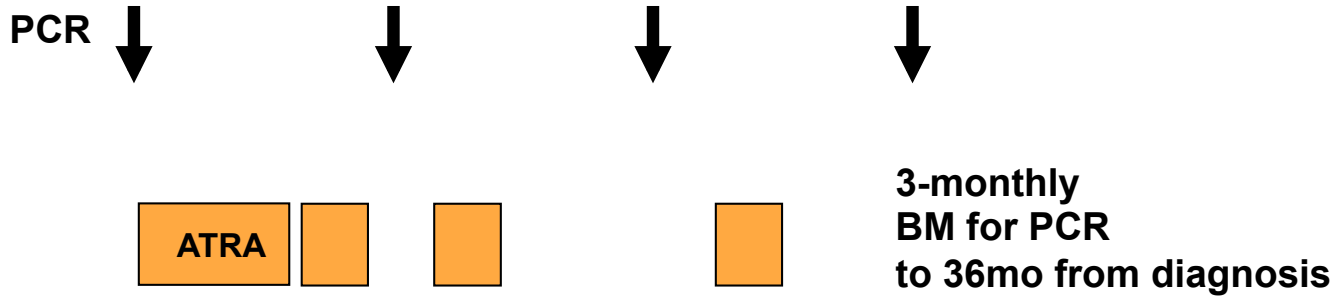


Strict Centralised MRD monitoring to guide treatment in NCRI AML17 trial

ATO-ATRA



AIDA

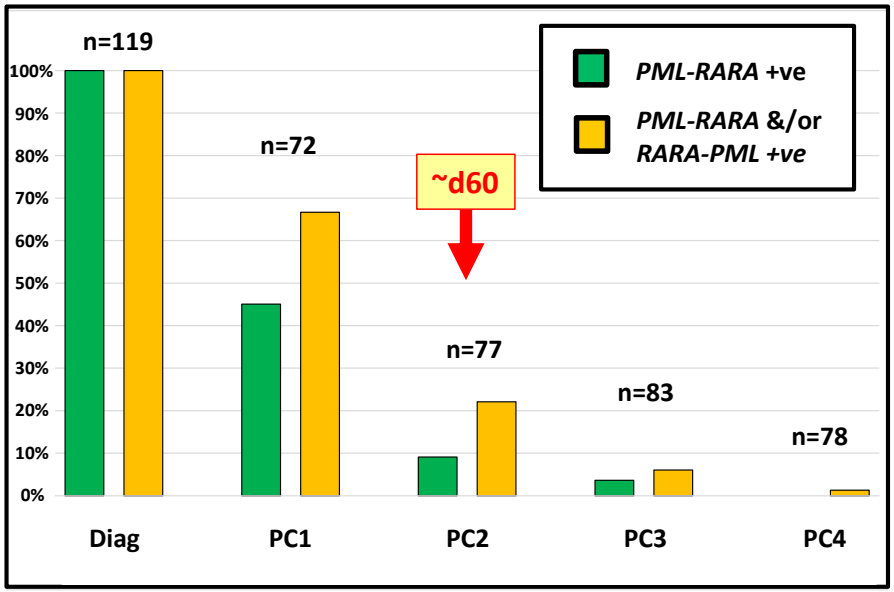


NCRI AML17: Kinetics of molecular response to AIDA and ATRA/ATO protocols

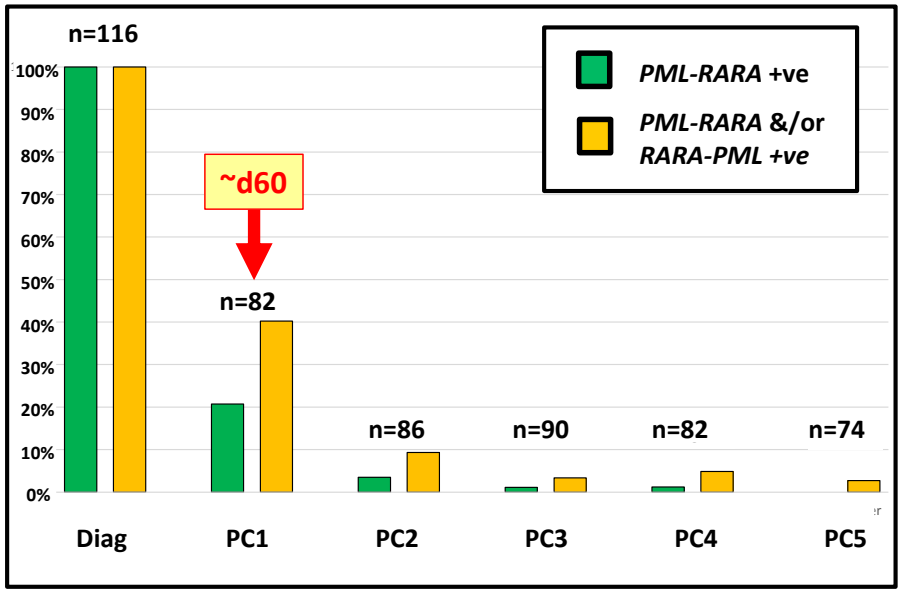
Median time to molecular remission: AIDA 83 days, ATO+ATRA 111days (p=0.06)

60-day PCR negativity: AIDA 73%, ATO+ATRA 56% (p=0.03).

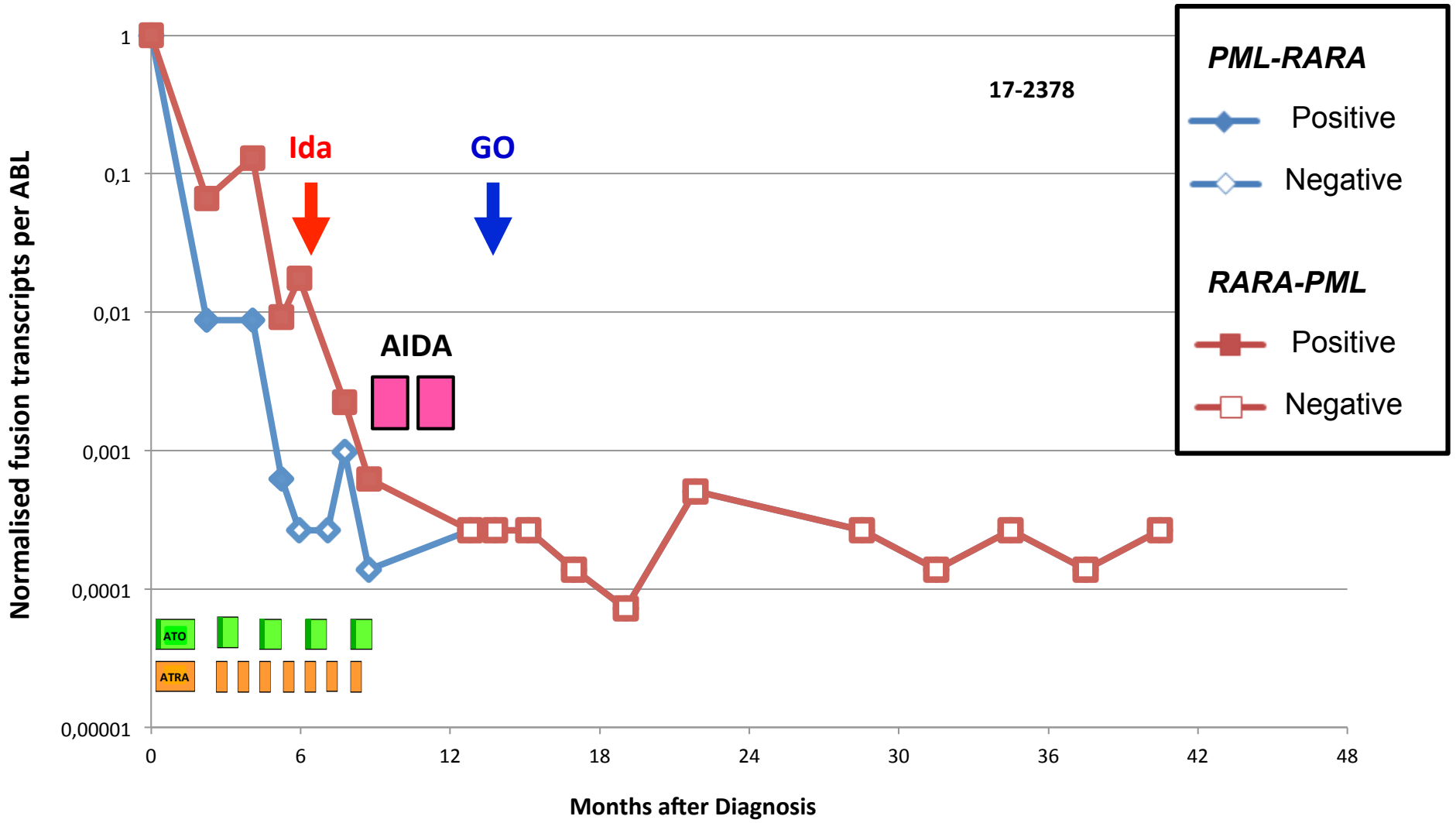
AIDA



ATRA + ATO



AML17: Monitoring of MRD in serial bone marrow samples by standardized RT-qPCR assay to guide management in APL

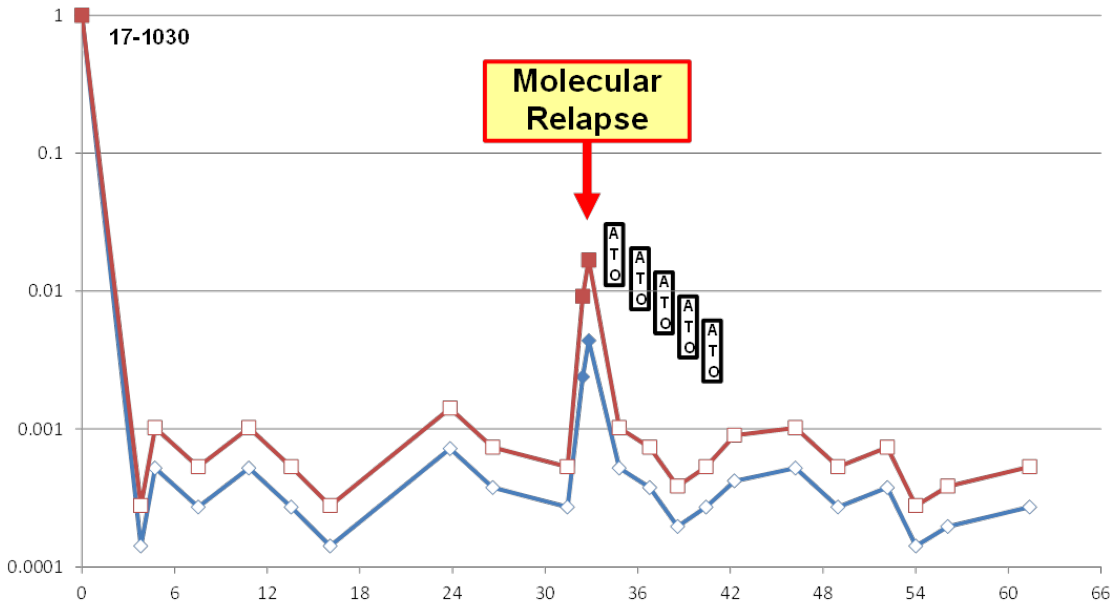


Centralised Molecular Monitoring in AML17

MRD based intervention with ATO in patient 17-1030 with molecular relapse post AIDA

Over 5800 PCRs performed as part of AML17 APL trial

Monitoring of MRD in serial bone marrow samples by standardized RT-qPCR assay to guide management in APL



AML17 APL: Demographics (n=235)

Characteristic	AIDA (n=119)	ATRA+ATO (n=116)
Age:		
16-29	22	22
30-39	18	17
40-49	28	27
50-59	27	25
60+	24	25
Median	47	47
Range	16-77	16-75
Sex:		
Male	60	60
Female	59	56
WBC:		
0-9.9	92	86
10-49.9	20	21
50-99.9	7	8
100+	0	1
Median	2.2	3.0
Range	0.4-78.2	0.4-100.9
Diagnosis:		
De Novo	117	113
Secondary	2	3

Characteristic	AIDA (n=119)	ATRA+ATO (n=116)
WHO PS:		
0	80	82
1	32	29
2	5	4
3	1	1
4	1	0
RARA-PML:		
Positive	82	89
Negative	37	27
Breakpoint:		
Intron 4	4	4
BCR1	64	63
BCR2	6	7
BCR3	45	42

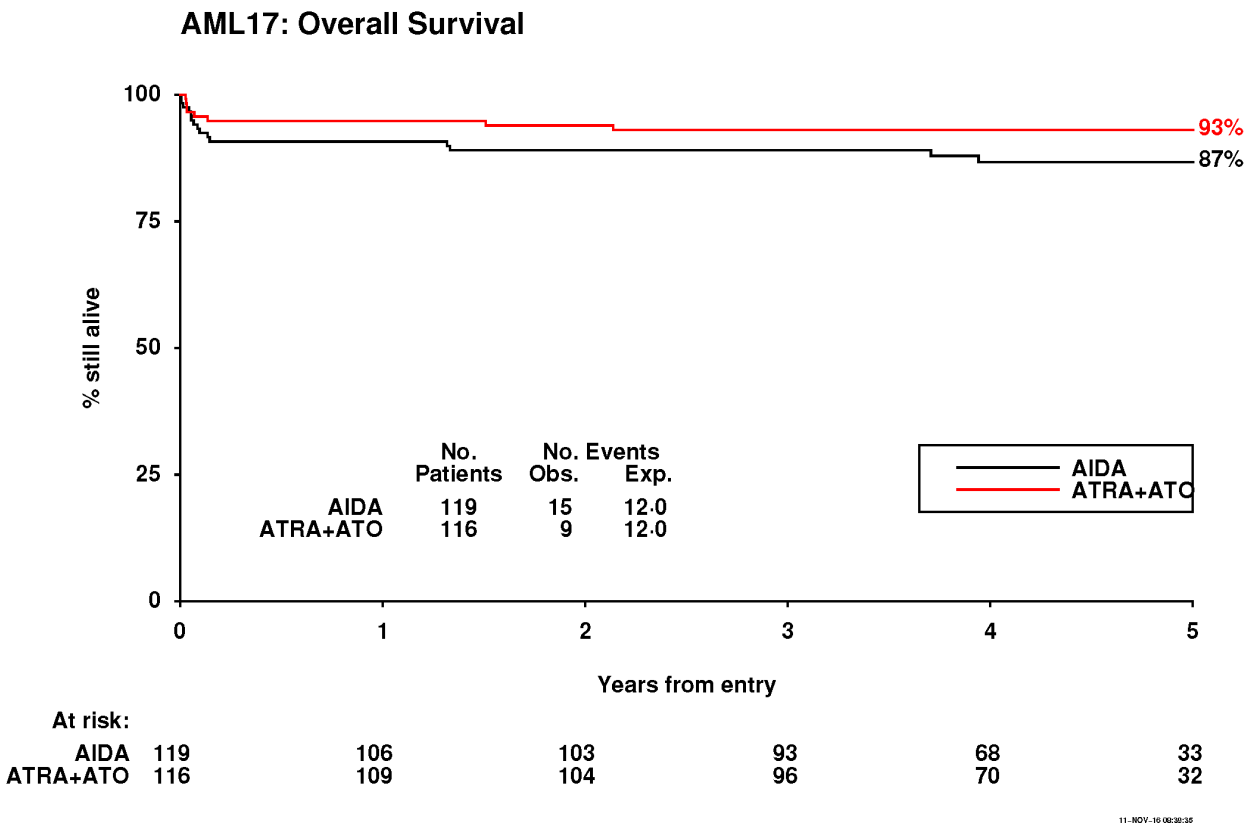
AML 17 APL Randomisation: Key Outcomes

Outcome	AIDA	ATRA+ATO	HR/OR & CI	p-value
CR	89%	94%	0.54 (0.21-1.34)	0.18
Molecular negativity	88%	91%	0.71 (0.31-1.65)	0.4
30-day mortality	6%	4%	0.72 (0.23-2.31)	0.6
Resistant disease	5%	2%	0.37 (0.09-1.50)	0.16
60-day mortality	9%	5%	0.55 (0.21-1.43)	0.2
4-year survival	89%	93%	0.60 (0.26-1.42)	0.2
4-year EFS	74%	91%	0.36 (0.19-0.70)	0.003
4-year Frank RFS	83%	97%	0.24 (0.09-0.63)	0.004
4-year Molecular RFS*	70%	98%	0.17 (0.08-0.39)	<.0001
4-year CIDCR	1%	2%	1.72 (0.18-16.6)	0.6
4-year CIHR	13%	1%	0.16 (0.05-0.48)	0.001
4-year CIMR*	27%	0%	0.12 (0.05-0.30)	<.0001
4-year CITAML	3%	0%	0.15 (0.003-7.48)	0.3

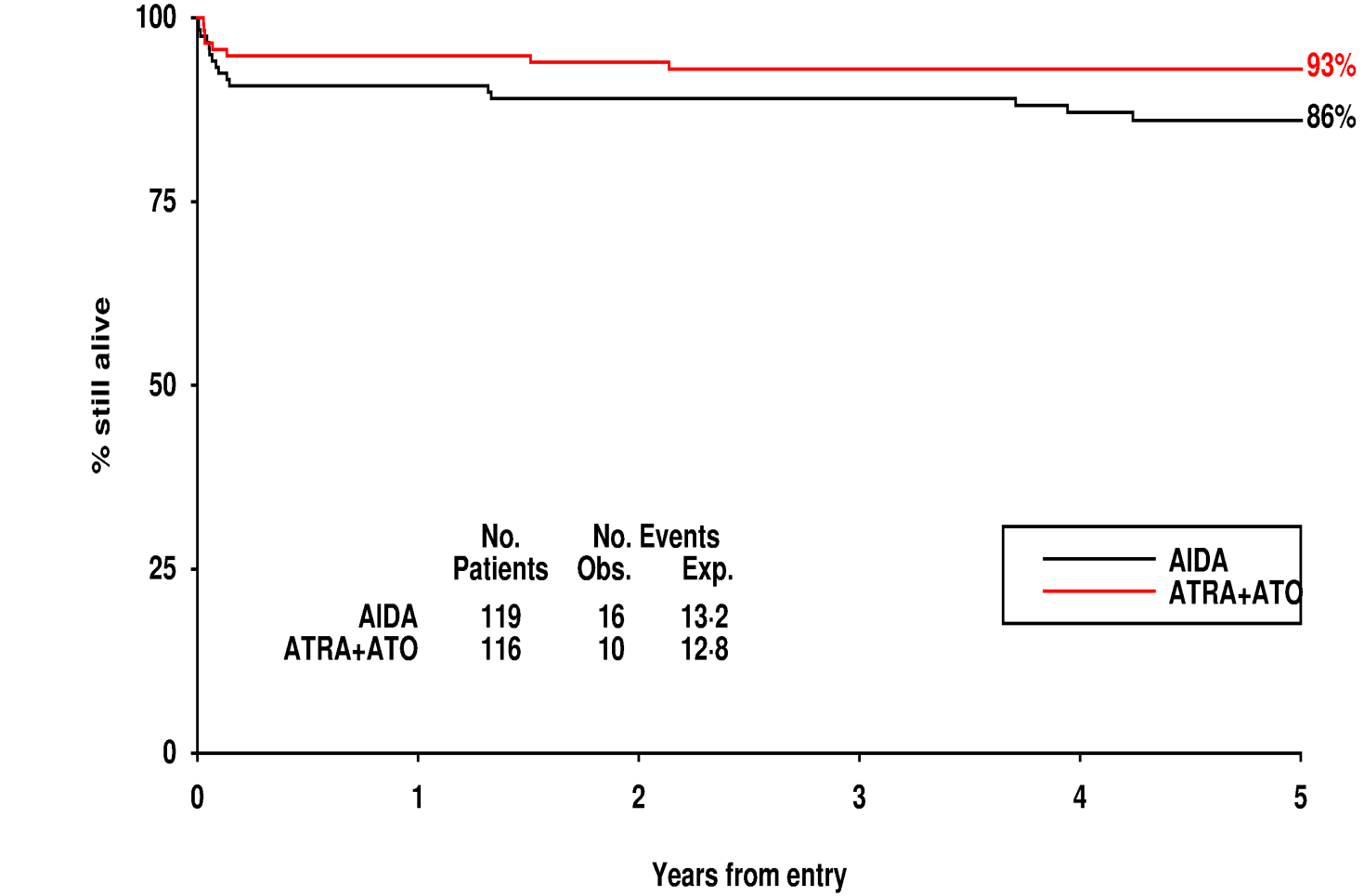
AML 17 APL Randomisation: Updated Outcomes

Outcome	AIDA	ATRA+ATO	HR/OR & CI	p-value
CR	91%	96%	0.46 (0.17-1.27)	0.13
Molecular negativity	90%	93%	0.67 (0.27-1.66)	0.4
30-day mortality	6%	4%	0.72 (0.23-2.31)	0.6
Resistant disease	3%	0%	0.14 (0.02-0.97)	0.05
60-day mortality	9%	5%	0.55 (0.21-1.43)	0.2
5-year survival	87%	93%	0.61 (0.27-1.35)	0.2
5-year EFS	79%	93%	0.38 (0.19-0.77)	0.007
5-year Frank RFS	87%	97%	0.33 (0.13-0.85)	0.02
5-year Molecular RFS*	77%	98%	0.19 (0.09-0.41)	<.0001
5-year CIDCR	2%	2%	1.72 (0.18-16.6)	0.6
5-year CIHR	10%	1%	0.16 (0.05-0.48)	0.001
5-year CIMR*	21%	0%	0.12 (0.05-0.30)	<.0001
5-year CITAML	1%	0%	0.15 (0.003-7.48)	0.3

Overall Survival



AML17: Overall Survival



At risk:

AIDA	119	106	104	98	89	66
ATRA+ATO	116	109	104	97	85	66

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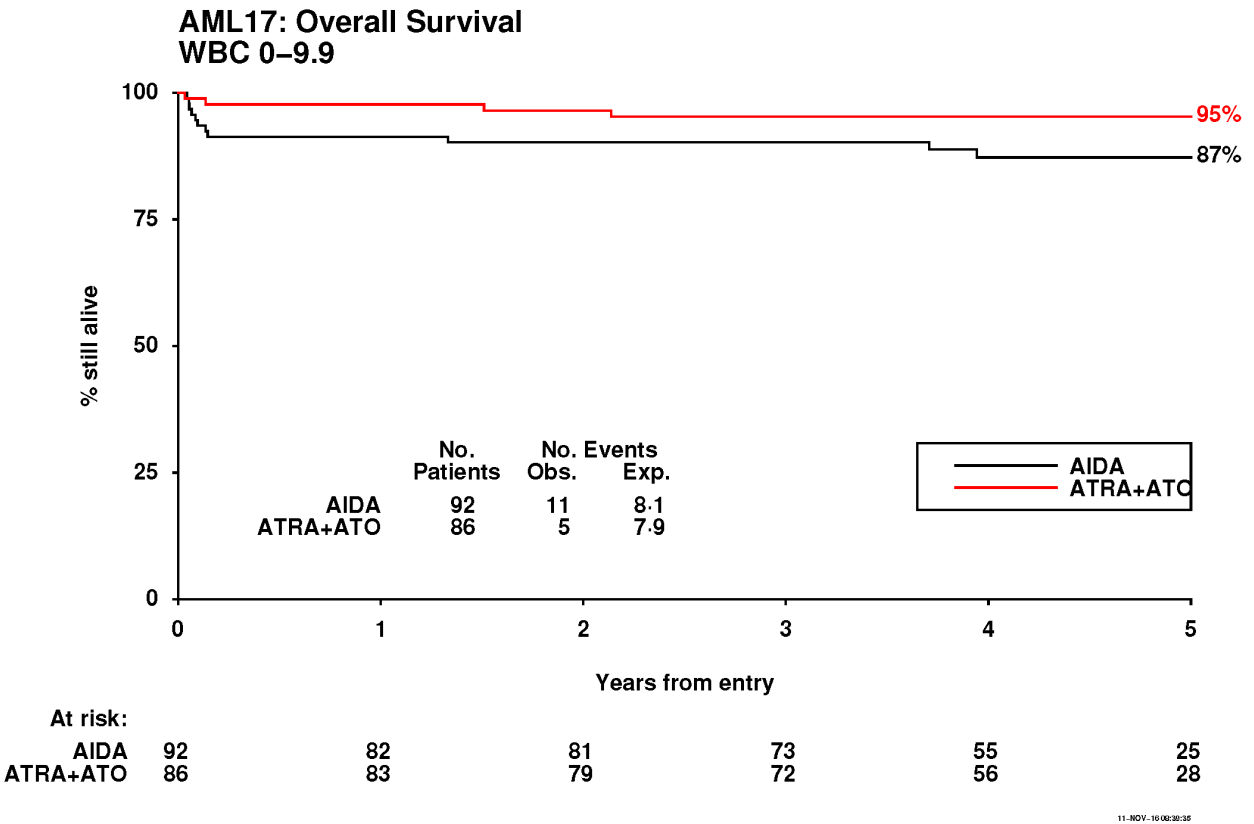
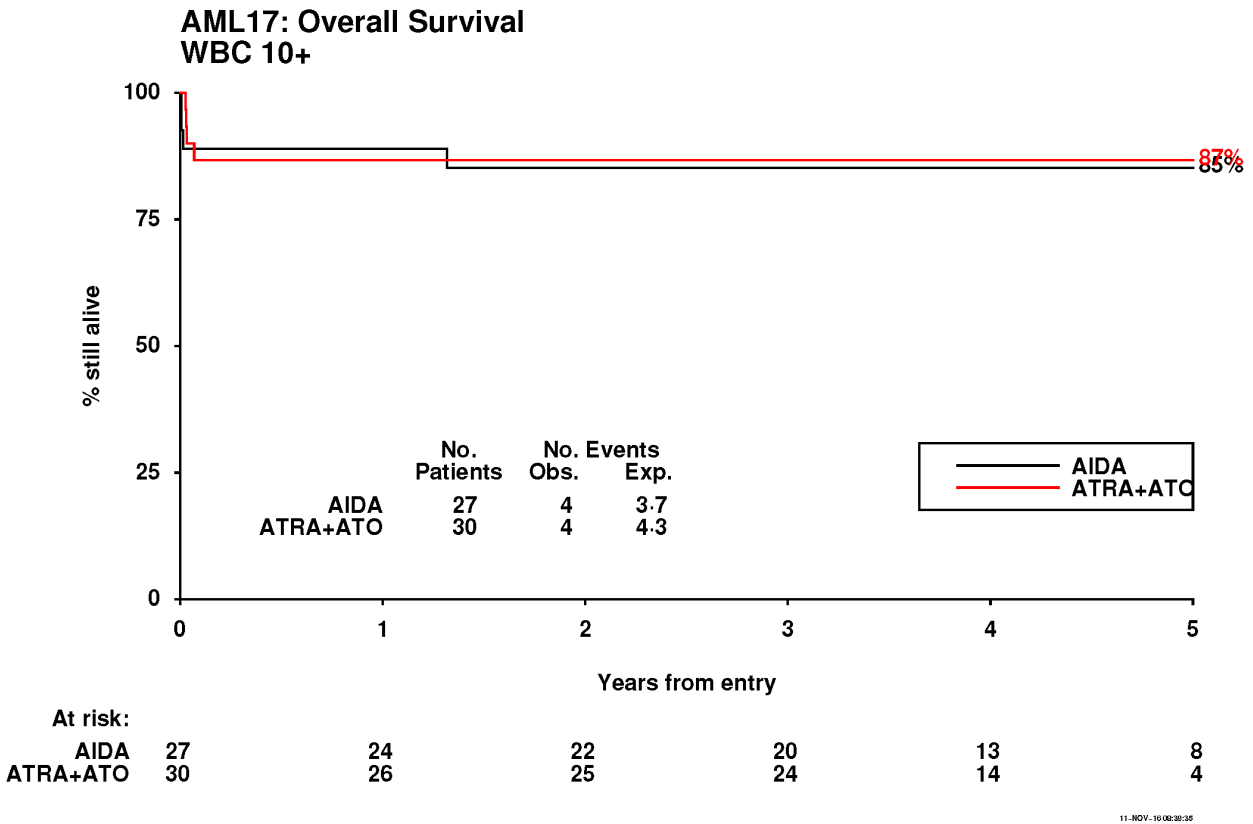
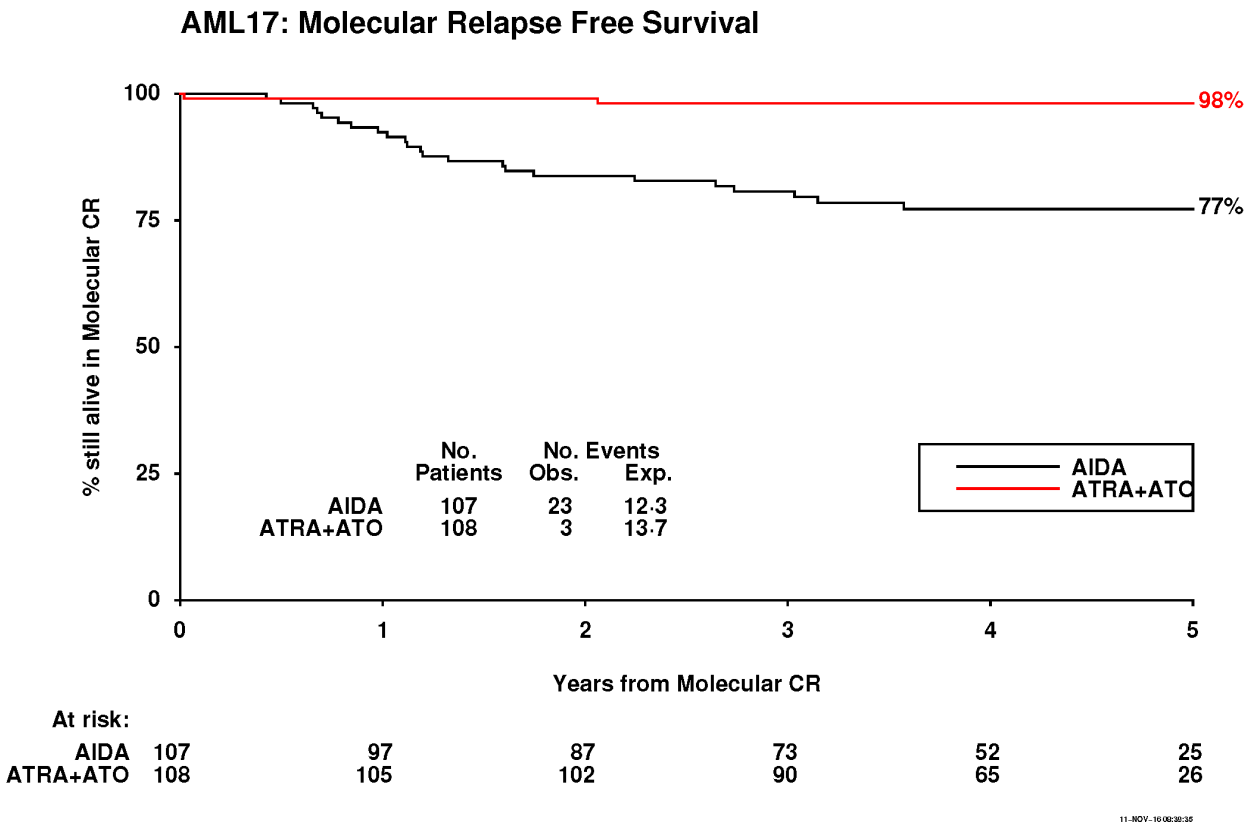
Overall Survival – low risk



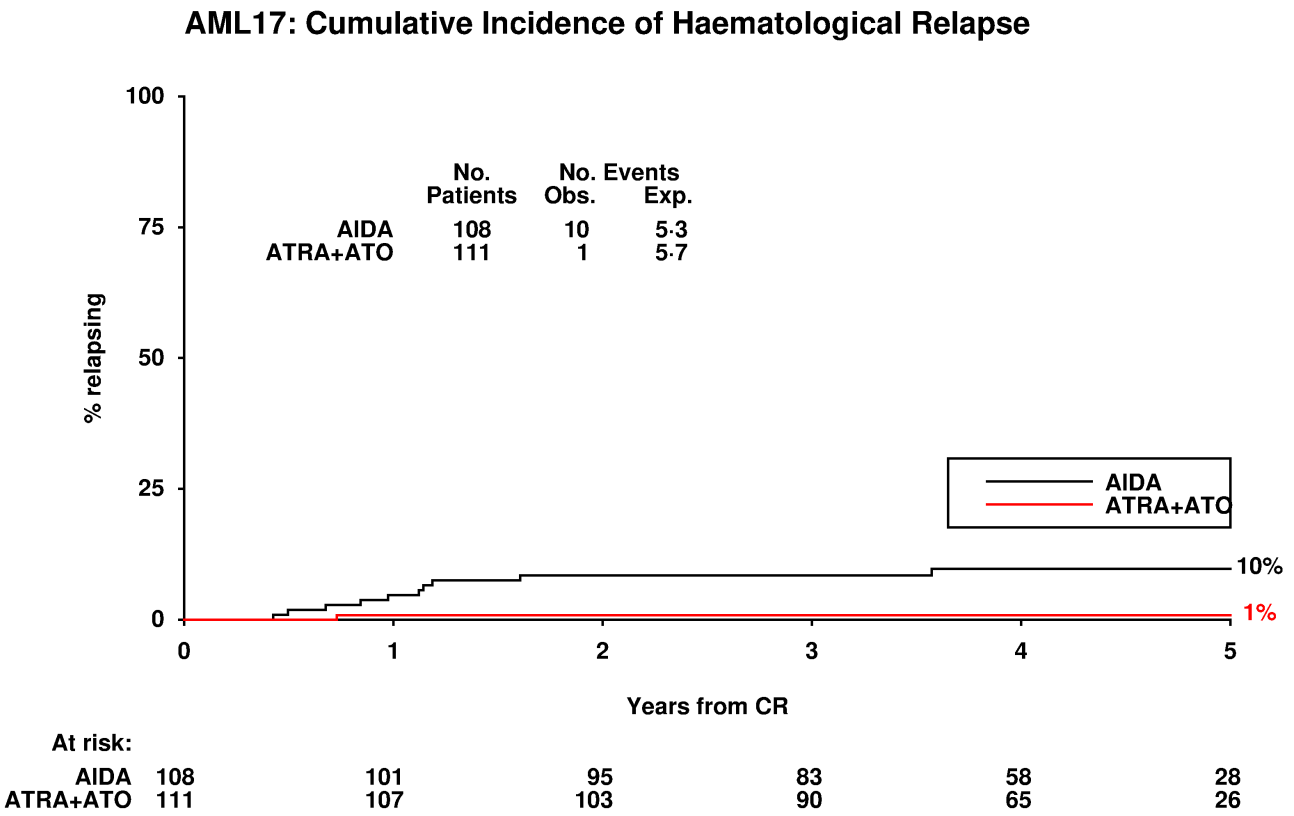
Overall Survival – high risk



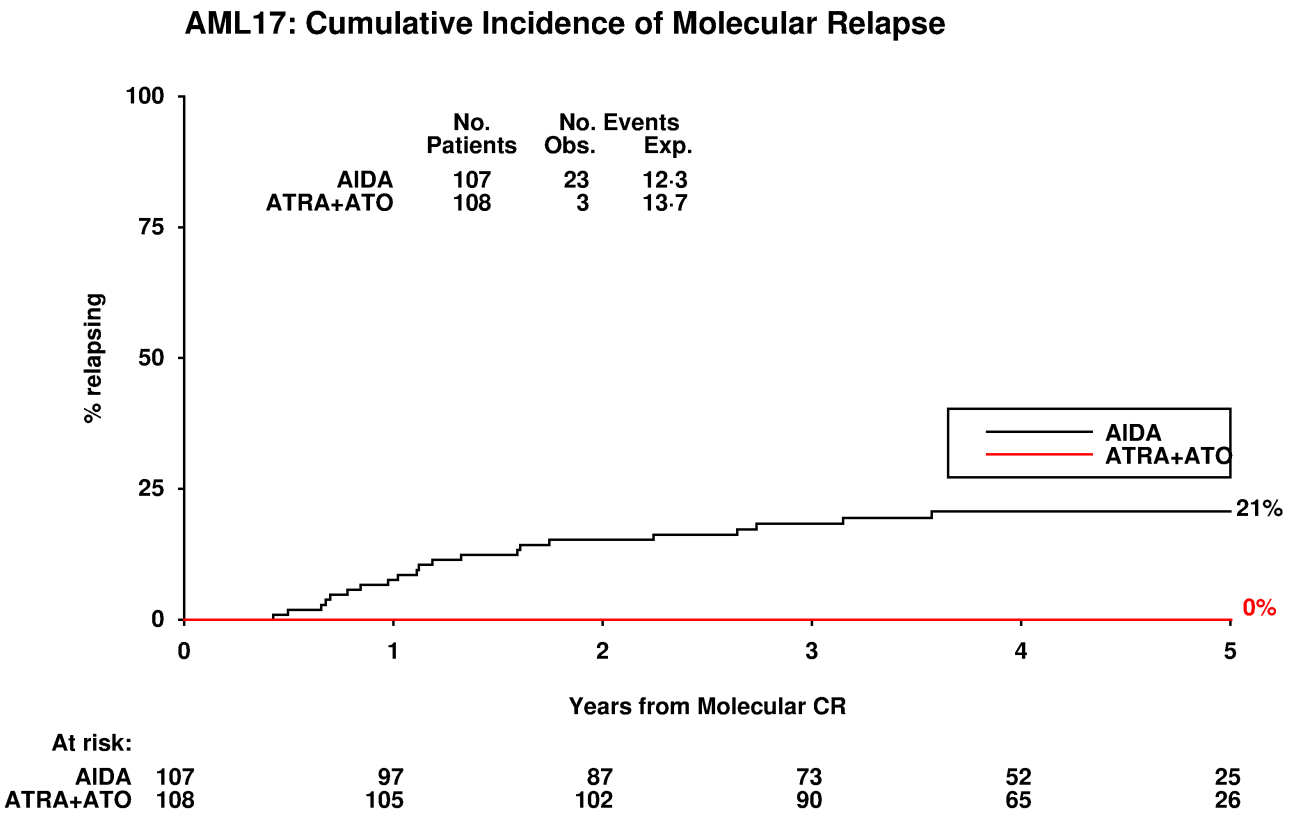
Molecular Relapse Free Survival



Cumulative Incidence of Frank Relapse



Cumulative Incidence of Molecular Relapse



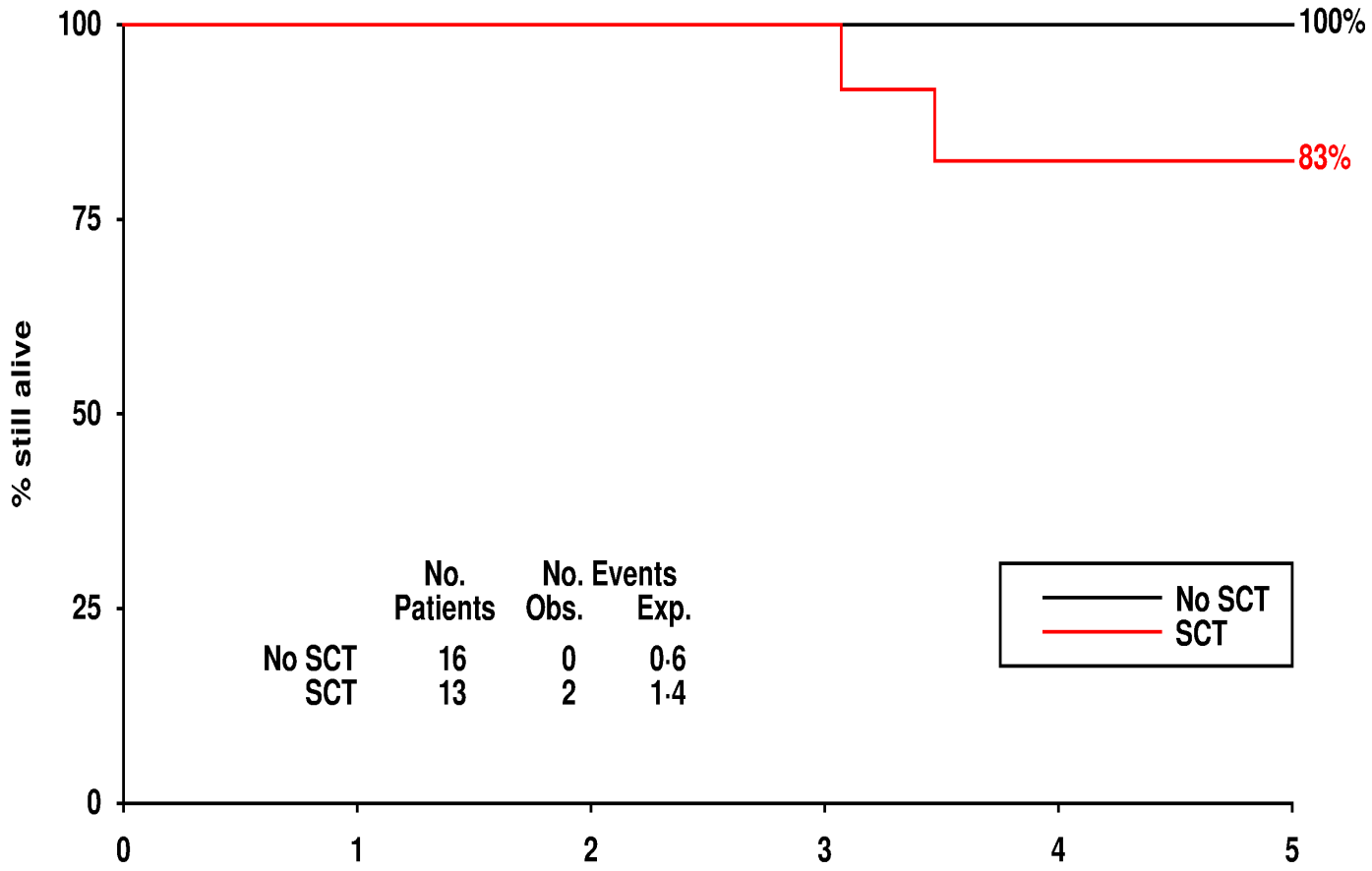
Response to AML17 schedule ATO of patients relapsing post AIDA

- In AML17 a total of 189 patients were treated with AIDA
- 30 patients relapsed following AIDA therapy (including 5 with CNS disease)
- 1 patient died in relapse before any salvage could be initiated
- 29 patients were treated with the same attenuated ATO+ATRA schedule
- 18 were treated at molecular relapse, reflecting the value of centralized MRD monitoring
- **All 29 treated patients achieved molecular CR post ATO+ATRA**

Survival after ATO/ATRA salvage

- Of the 29 patients 13 were transplanted in molecular remission (10 autograft, 3 allograft) including 4 of the 5 patients with CNS disease
- 16 patients were treated with a full course (induction plus 4 consolidation) of ATO/ATRA alone without chemotherapy
- 3/16 patients had a second molecular relapse after ATO + ATRA salvage (1 later transplanted and 2 not transplanted)
- All patients treated with ATO/ATRA alone remain alive

AML17 (AIDA): Overall Survival from Relapse



At risk:

No SCT	16	12	7	6	3	1
SCT	13	13	13	12	7	1

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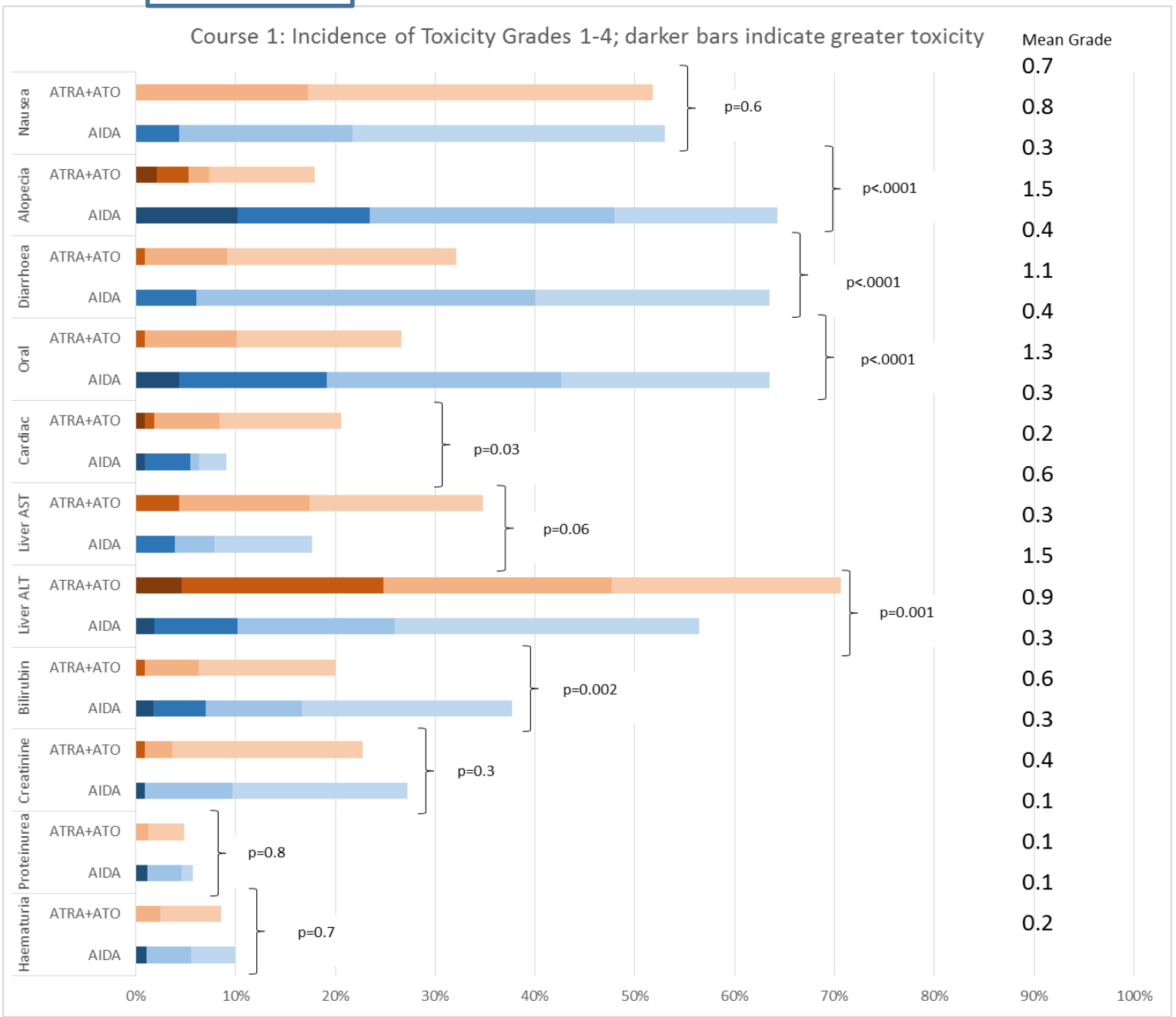
AML17 APL: Conclusions

- Updated analysis confirms that ATO+ATRA results in superior EFS at 5 years (93% vs 79%, p=0.007) compared to AIDA
- No patient on ATRA+ATO who achieved molecular negativity experienced relapse (CIMR 0% vs 21%, p<.0001)
- The attenuated ATO schedule was effective and safe in the upfront and relapsed setting
- No overall survival benefit was seen with ATO primarily because of excellent results of salvage therapy with ATO with the majority of patients treated at molecular relapse and survival of 96% at 3years
- The attenuated schedule (n=63 vs 140 doses) & (1190mg vs 1470mg)/ 70kg patient, which has patient convenience and cost implications seems adequate

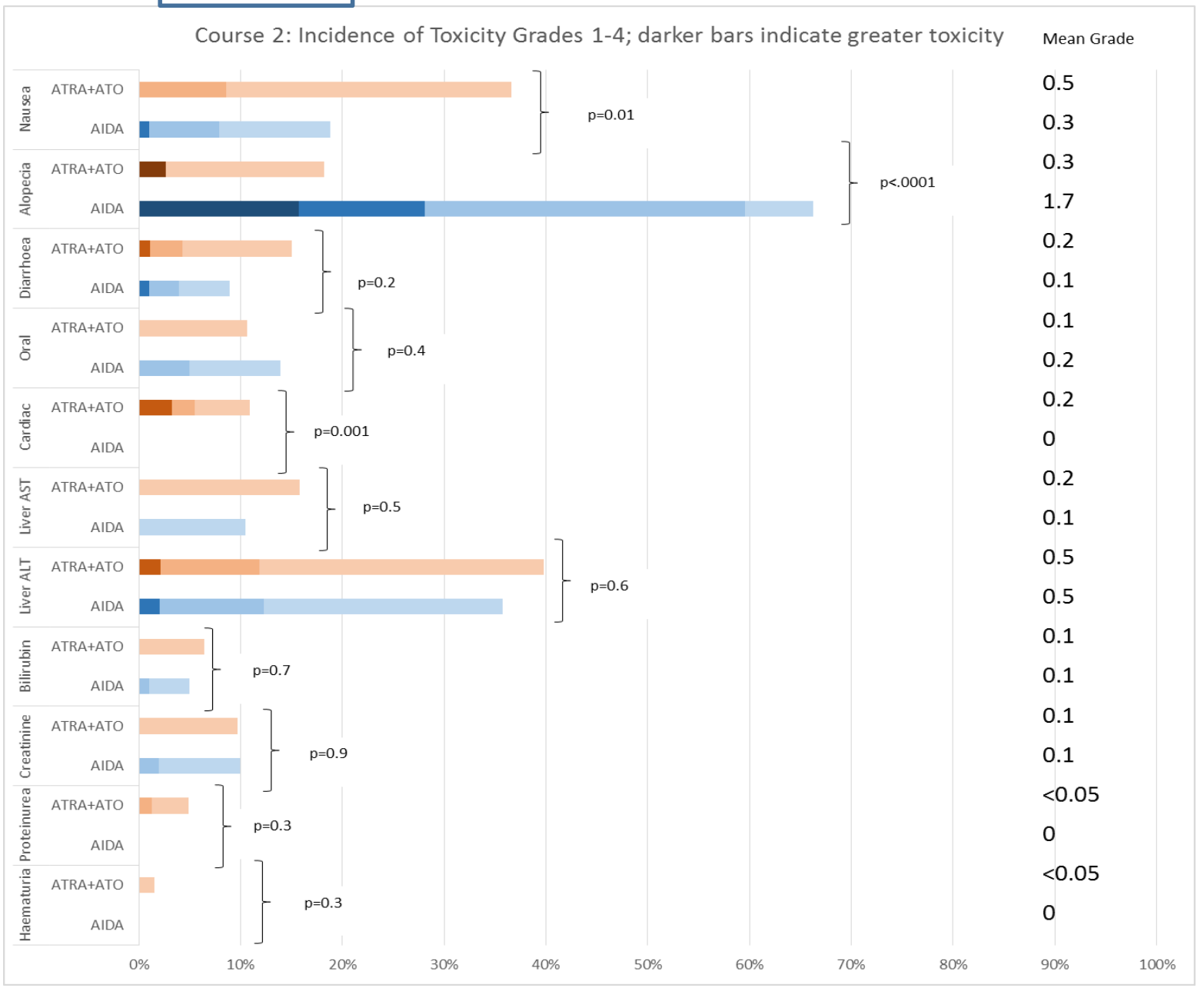
AML17 APL: Conclusions

- In contrast to AIDA the low relapse risk with ATO negates the need for MRD monitoring once molecular CR has been achieved - usually following course 2.
- However molecular surveillance for 3 years remains important in those with relapsed disease treated with ATO/ ATRA.

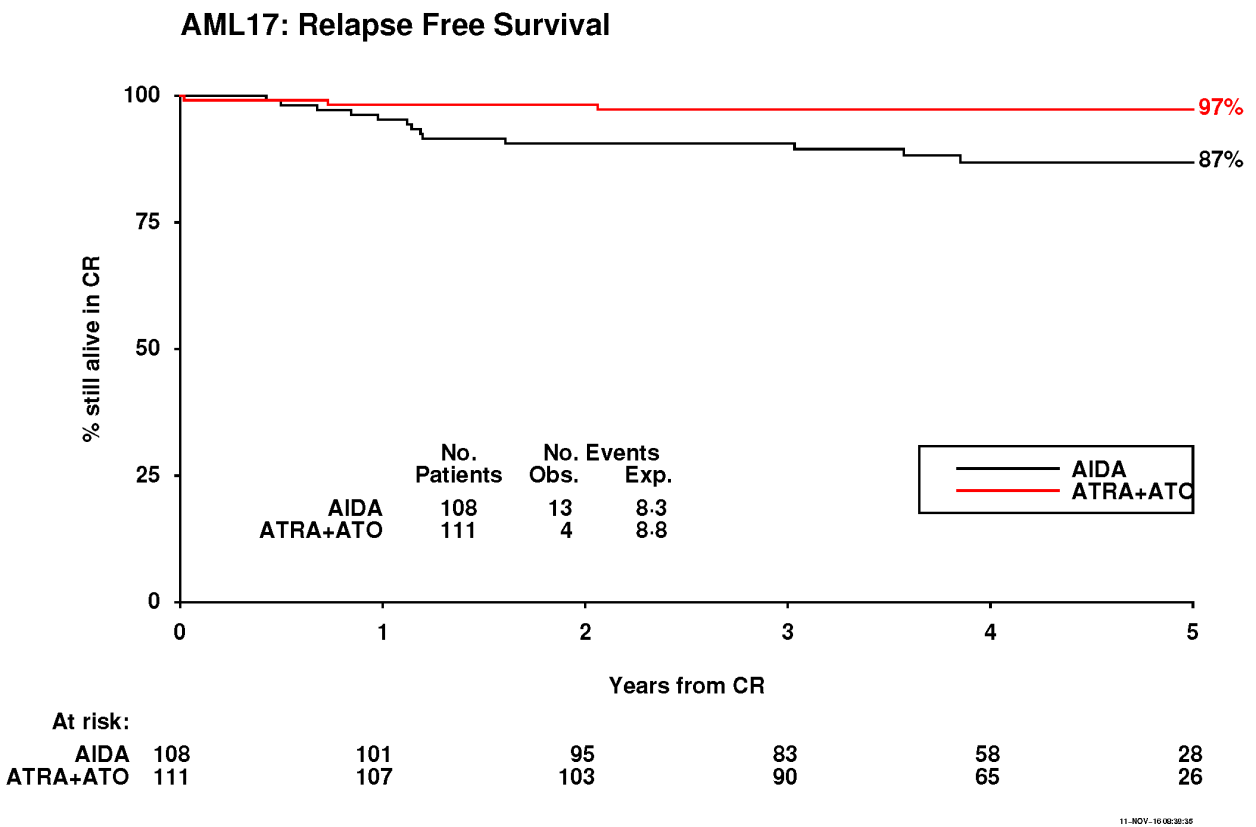
Course 1


Course 1: Incidence of Toxicity Grades 1-4; darker bars indicate greater toxicity
Mean Grade
Nausea
ATRA+ATO
AIDA
0.7
0.8
p=0.6
Alopecia
ATRA+ATO
AIDA
0.3
1.5
p<.0001
Diarrhoea
ATRA+ATO
AIDA
0.4
1.1
p<.0001
Oral
ATRA+ATO
AIDA
0.4
1.3
p<.0001
Cardiac
ATRA+ATO
AIDA
0.3
0.2
p=0.03
Liver AST
ATRA+ATO
AIDA
0.6
0.3
p=0.06
Liver ALT
ATRA+ATO
AIDA
1.5
0.9
p=0.001
Bilirubin
ATRA+ATO
AIDA
0.3
0.6
p=0.002
Creatinine
ATRA+ATO
AIDA
0.3
0.4
p=0.3
Proteinurea
ATRA+ATO
AIDA
0.1
0.1
p=0.8
Haematuria
ATRA+ATO
AIDA
0.1
0.2
p=0.7
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

Course 2


Course 2: Incidence of Toxicity Grades 1-4; darker bars indicate greater toxicity
Mean Grade
Nausea
ATRA+ATO
AIDA
p=0.01
0.5
0.3
Alopecia
ATRA+ATO
AIDA
p<.0001
0.3
1.7
Diarrhoea
ATRA+ATO
AIDA
p=0.2
0.2
0.1
Oral
ATRA+ATO
AIDA
p=0.4
0.1
0.2
Cardiac
ATRA+ATO
AIDA
p=0.001
0.2
0
Liver AST
ATRA+ATO
AIDA
p=0.5
0.2
0.1
Liver ALT
ATRA+ATO
AIDA
p=0.6
0.5
0.5
Bilirubin
ATRA+ATO
AIDA
p=0.7
0.1
0.1
Creatinine
ATRA+ATO
AIDA
p=0.9
0.1
0.1
Proteinurea
ATRA+ATO
AIDA
p=0.3
<0.05
0
Haematuria
ATRA+ATO
AIDA
p=0.3
<0.05
0
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

Haematological Relapse Free Survival



Arsenic trioxide in patients with myelodysplastic syndromes: a phase II multicenter study.

Vey N, Bosly A, Guerci A, Feremans W, Dombret H, Dreyfus F, Bowen D, Burnett A, Dennis M, Ribrag V, Casadevall N, Legros L, Fenaux P.

J Clin Oncol. 2006 Jun 1;24(16):2465-71