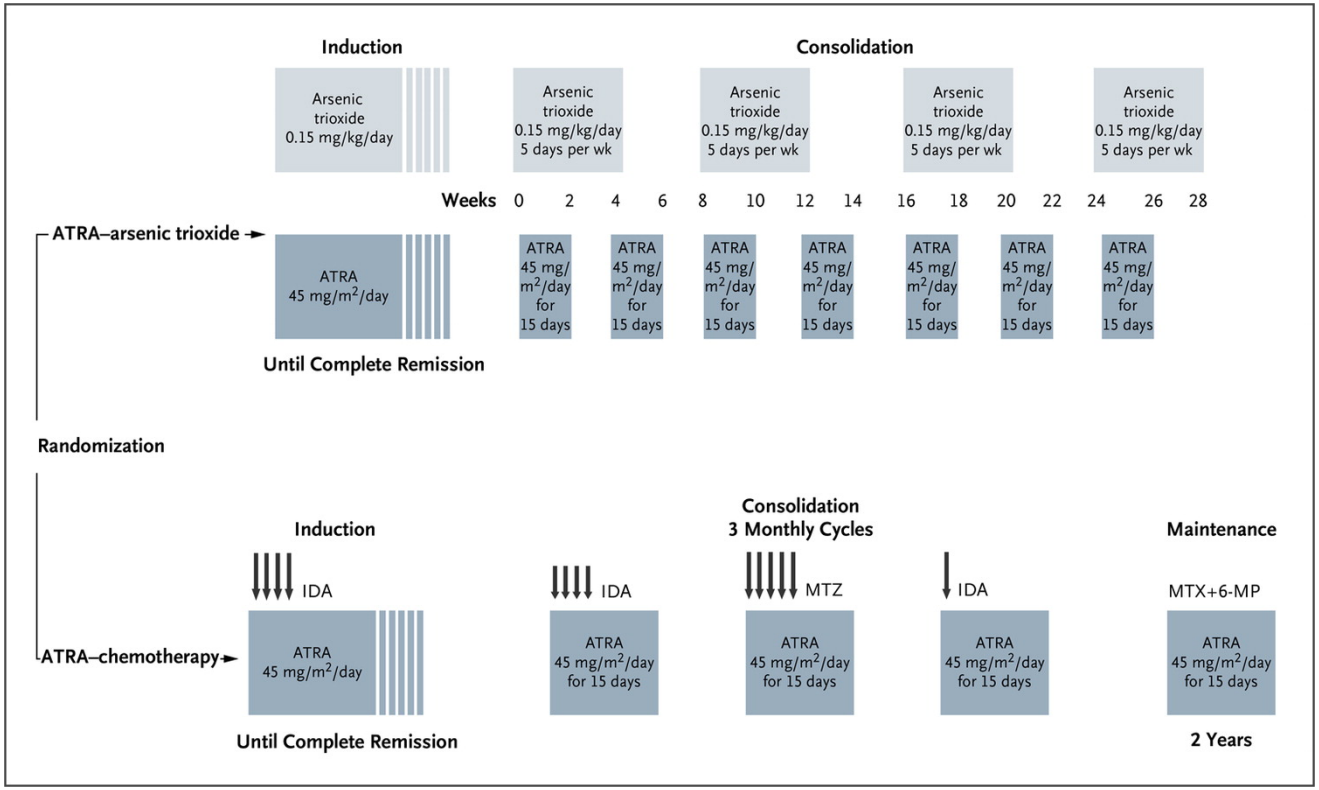
Long-term Outcome of Patients with Acute Promyelocytic Leukemia Treated with All-*Trans*-Retinoic Acid, Arsenic Trioxide, and Gemtuzumab Ozogamicin

Farhad Ravandi, Yasmin Abaza, Guillermo Garcia-Manero, Elihu Estey, Gautam Borthakur, Elias Jabbour, Stefan Faderl, Susan O'Brien, William Wierda, Sherry Pierce, Mark Brandt, Deborah McCue, Rajyalakshmi Luthra, Keyur Patel, Steven Kornblau, Tapan Kadia, Naval Daver, Courtney DiNardo, Nitin Jain, Srdan Verstovsek, Alessandra Ferrajoli, Michael Andreeff, Marina Konopleva, Zeev Estrov, Maria Foudray, David McCue, Jorge Cortes and Hagop Kantarjian

Department of Leukemia, University of Texas – MD Anderson Cancer Center

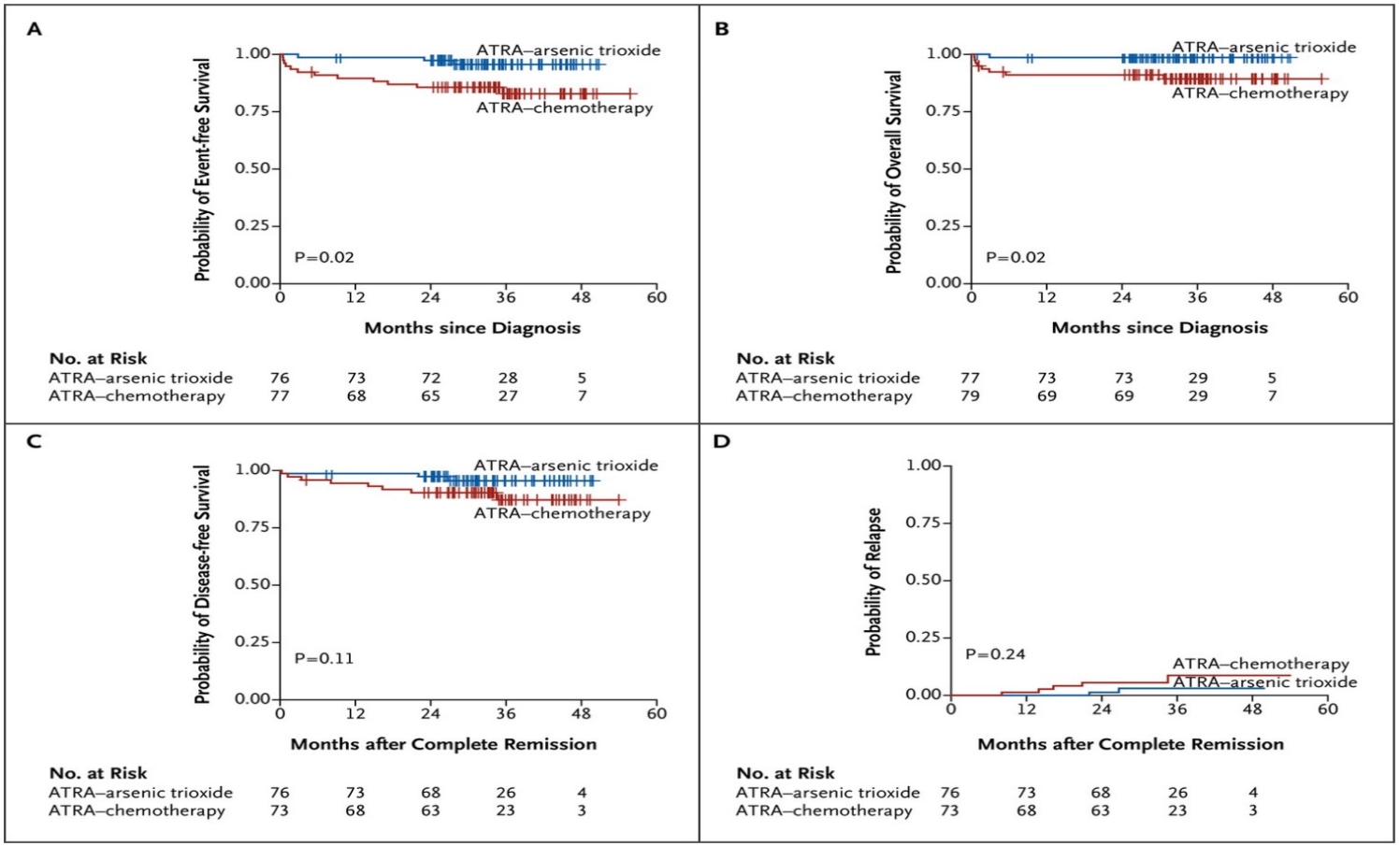
ATRA + ATO – GIMEMA, AMLSG, SAL



Lo-Coco F et al. N Engl J Med 2013;369:111-121.

The NEW ENGLAND JOURNAL of MEDICINE

ATRA + ATO: Outcomes



Lo-Coco F et al. N Engl J Med 2013;369:111-121.

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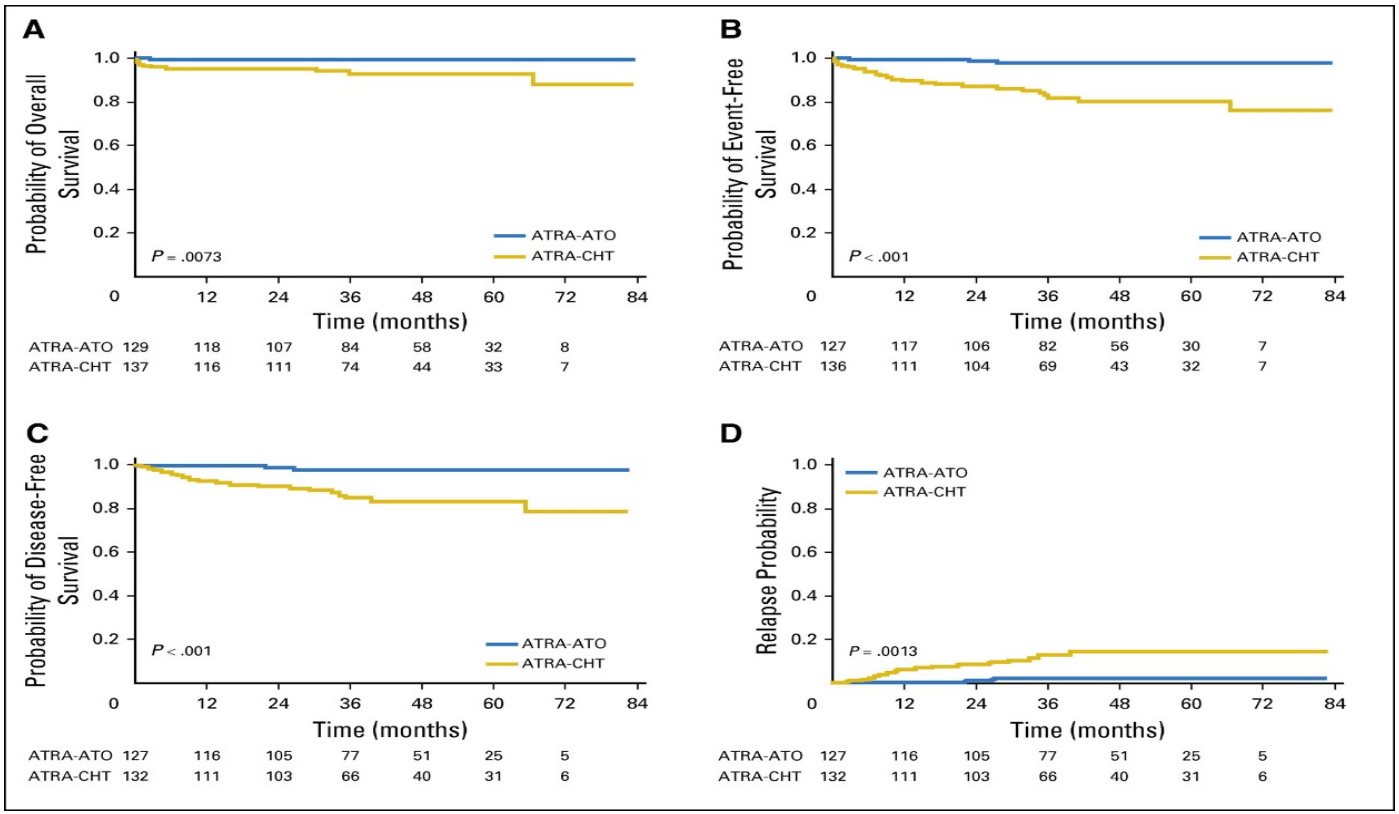
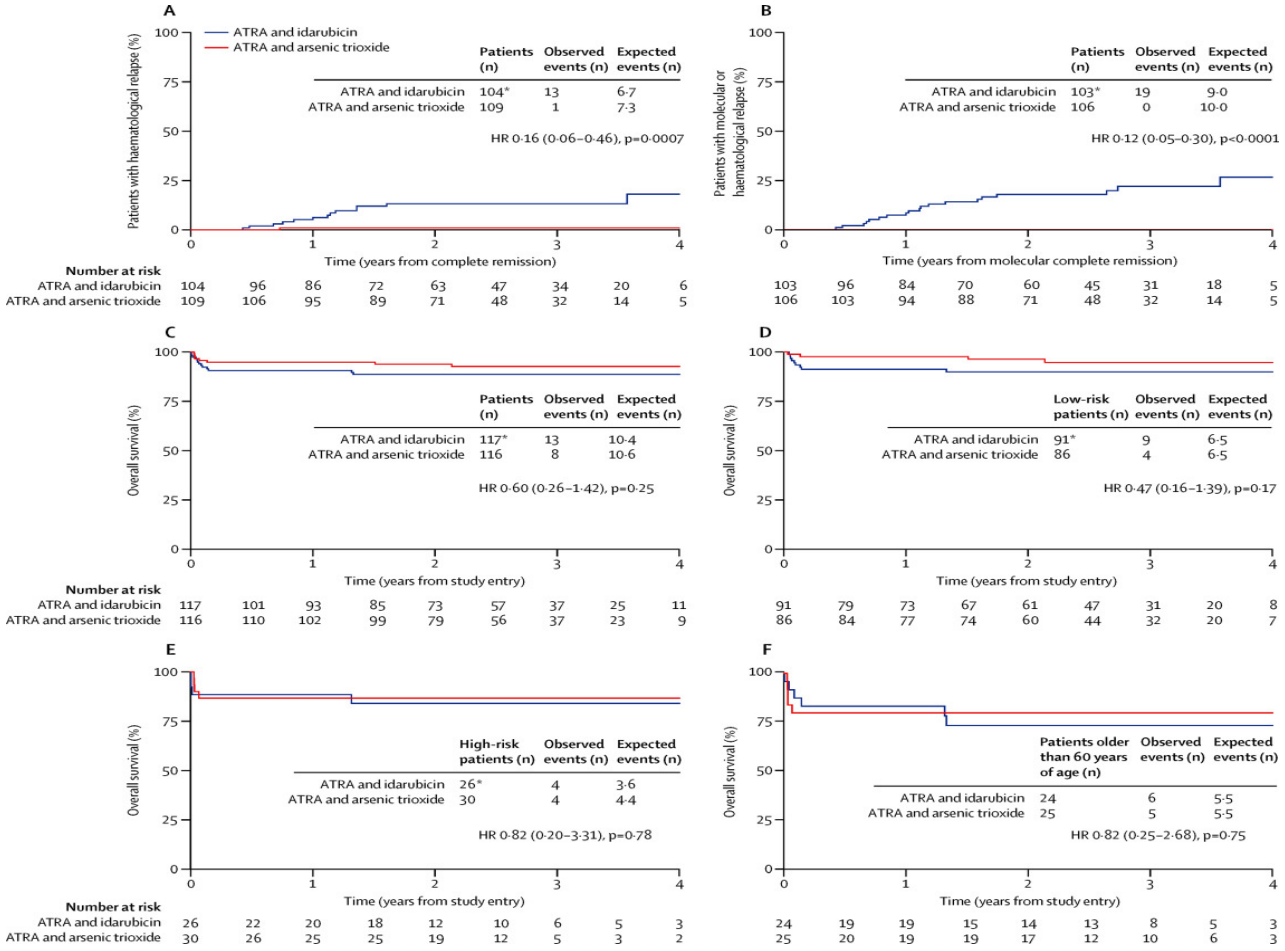
ATRA + ATO: Long-Term Follow-up



Platzbecker U, et al JCO 2017, 35, 605-612

ATRA + ATO: UK NCRI

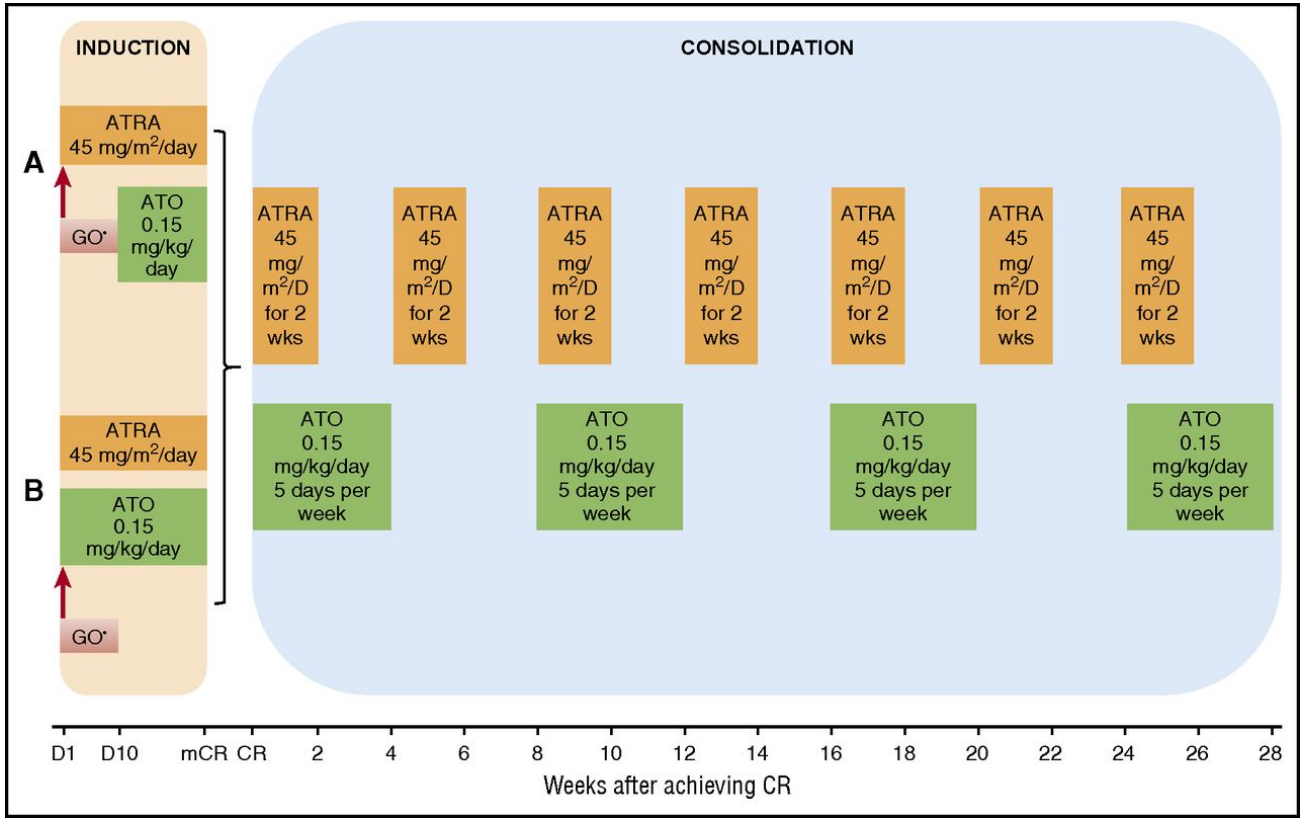


Burnett AK, et al, Lancet Oncology, 2015, 16(13), 1295-1305

ATRA + ATO ± GO: MDACC

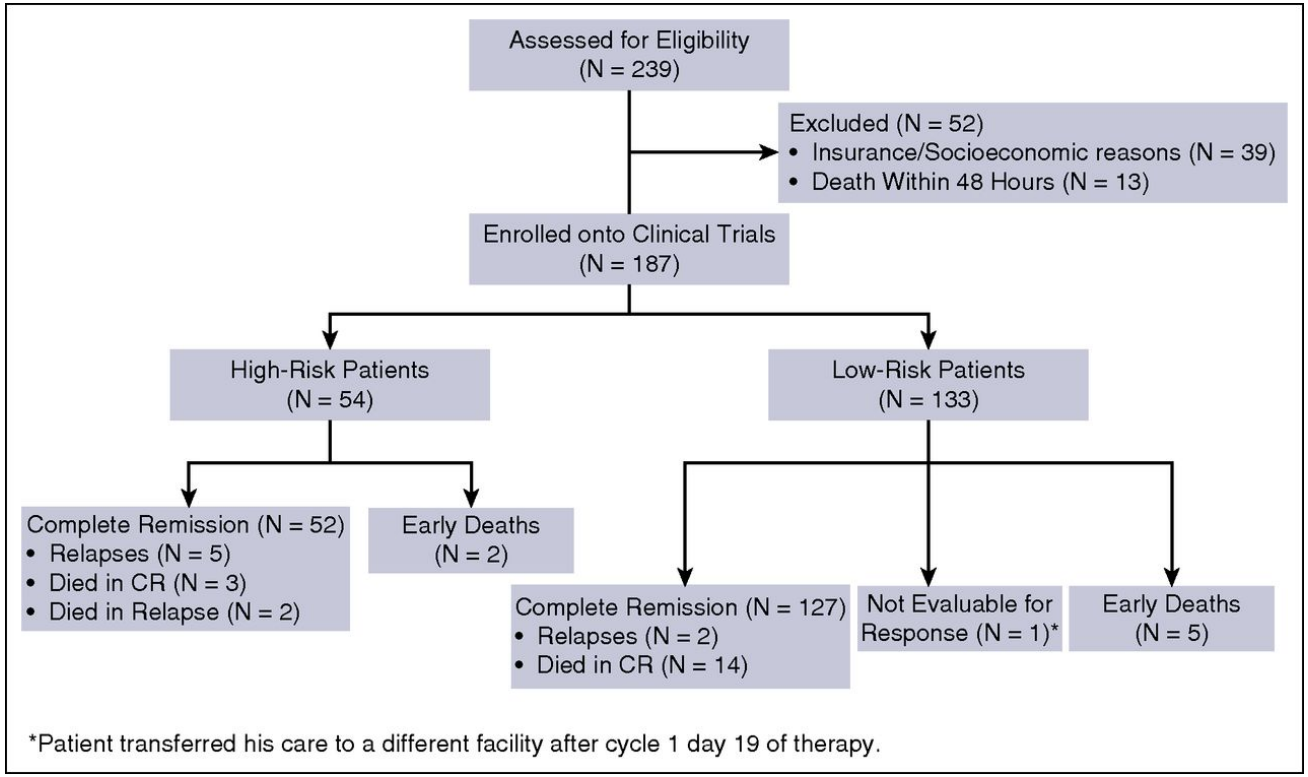
- Between July 2002 and May 2015, 239 patients with newly diagnosed APL seen at MDACC
- Three phase 2 studies : ID01-014, NCT01409161, NCT00413166
- 187 patients enrolled
- Reasons for excluding remaining 52 (22%)
  - Insurance/Socio-economic
  - Death within 48 hors of hospitalization

ATRA + ATO ± GO: Treatment Regimen



Abaza Y, et al. Blood 2017;129:1275-1283

ATRA + ATO ± GO: Patient Disposition



Abaza Y, et al. Blood 2017;129:1275-1283

Patient Characteristics

Characteristics (N = 187)	Number (%)	Median (range)
Age, y		50 (14-84)
≥60	52 (28)	
Sex		
Male	97 (52)	
Risk category		
High-risk	54 (29)	
Low-risk	133 (71)	
Leukocyte count ($\times 10^9$/L)		2.2 (0.3-187.9)
Platelet count ($\times 10^9$/L)		36 (3-261)
Cytogenetics		
t(15;17)	122 (65)	
t(15;17) + other cytogenetic	45 (24)	
Diploid (RT-PCR +)	10 (5)	
ND/IM (RT-PCR$^+$)	10 (5)	
FAB morphology		
M3	163 (87)	
M3v	22 (12)	
PML-RARA isoforms		
Short	78 (42)	
Long	105 (56)	
Both	4 (2)	

Mutation Analysis

Molecular Feature	Performed N	Detected N(%)	High Risk N(%)	Standard Risk N(%)
PML-RARA	187	187		
FLT3-ITD	152	59 (39)	(66)	(28)
FLT3-TKD	153	18 (12)	(13)	(11)
RAS	145	7 (5)	(2)	(6)
CEBPA	39	1 (3)		

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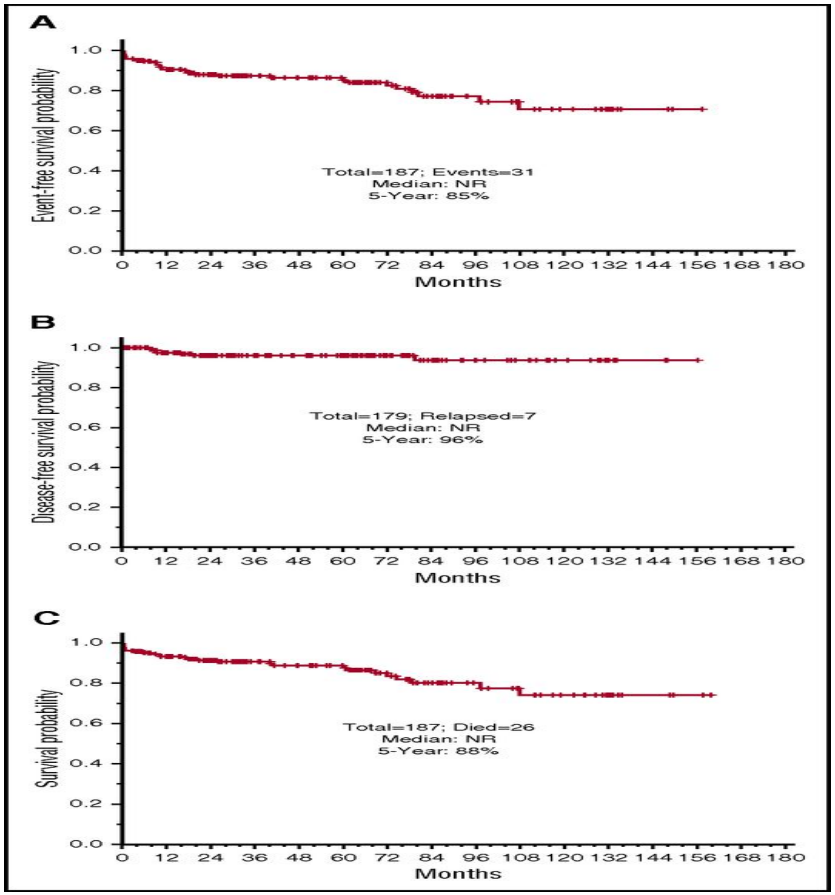
Details of Leucocytosis and Cytoreductive Therapy

- 179 patients (96%) achieved CR after induction (Low risk 96%, high risk 96%)
- 176 achieved complete molecular remission (2 withdrew consent; 1 lost to f/u)
- 53 High risk patients received cytoreductive therapy;
  - 45 (83%) received GO,
  - 7 (13%) received Idarubicin,
  - 1 (2%) received both and
  - 1 did not receive any
- 96 Low risk patients (72%) developed leukocytosis
  - Median WBC 19.8 x 10^9/L, range 10.3-195 x 10^9/L
  - reached at a median of 10 days (range 2- 26 days)
- Among them 60 received cytoreductive therapy
  - GO in 51, Idarubicin in 9
- No patients received GO for molecular persistence or relapse

Survival outcomes for the whole population



Median F/U 47.6 months, Range 2.7 – 159.7 months

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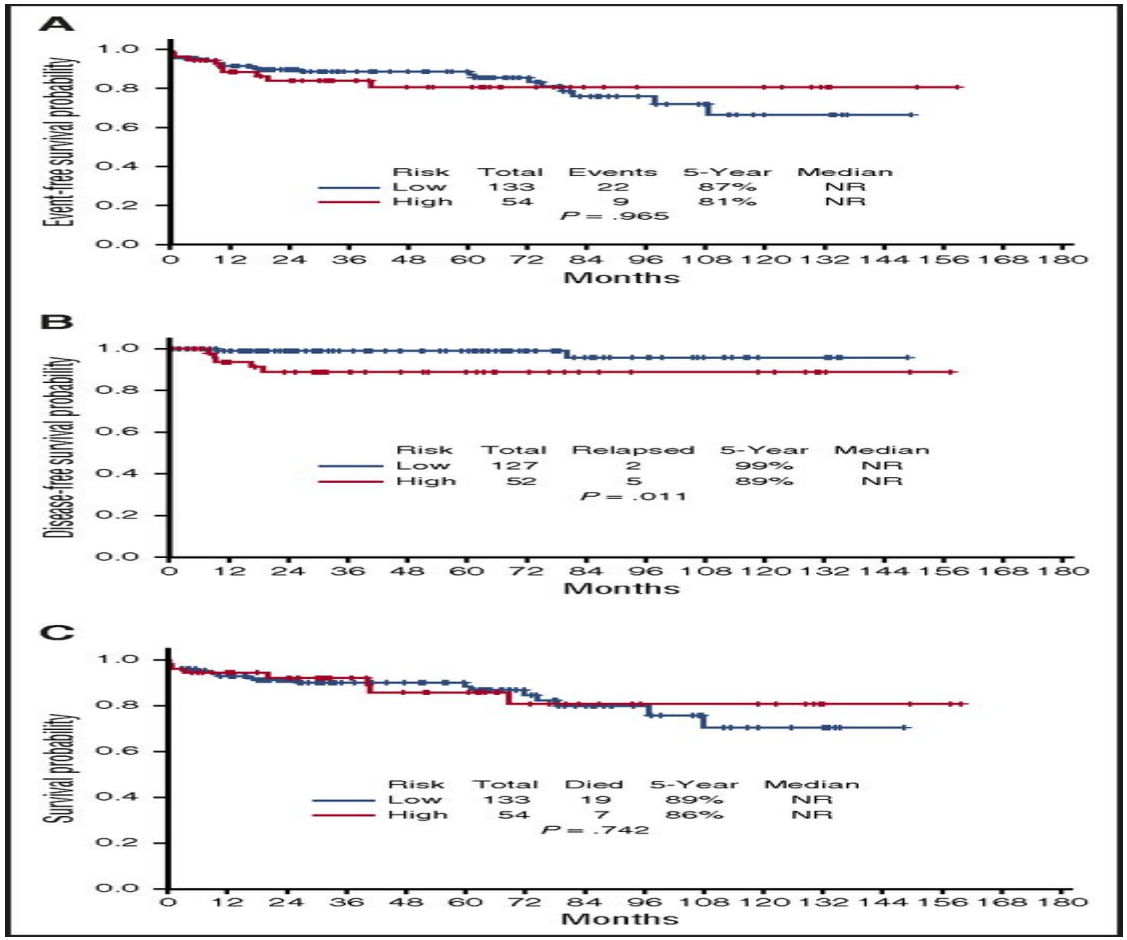
Outcomes by risk subsets



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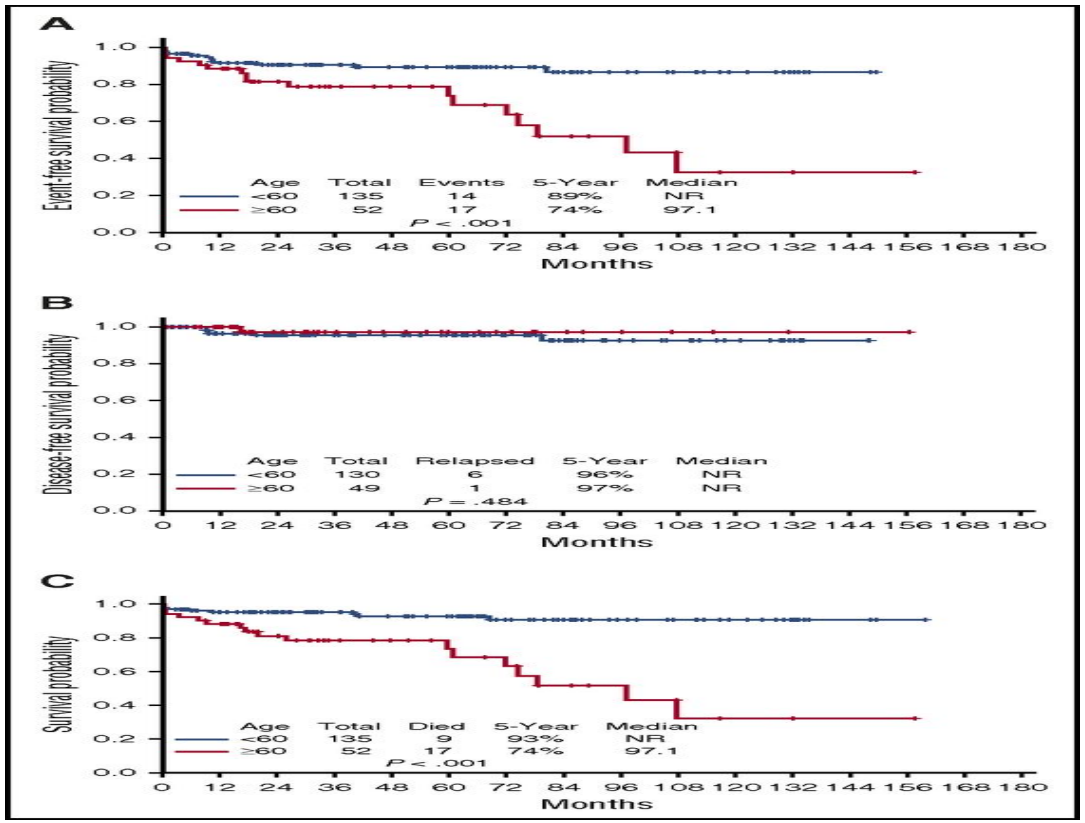
Outcomes by age



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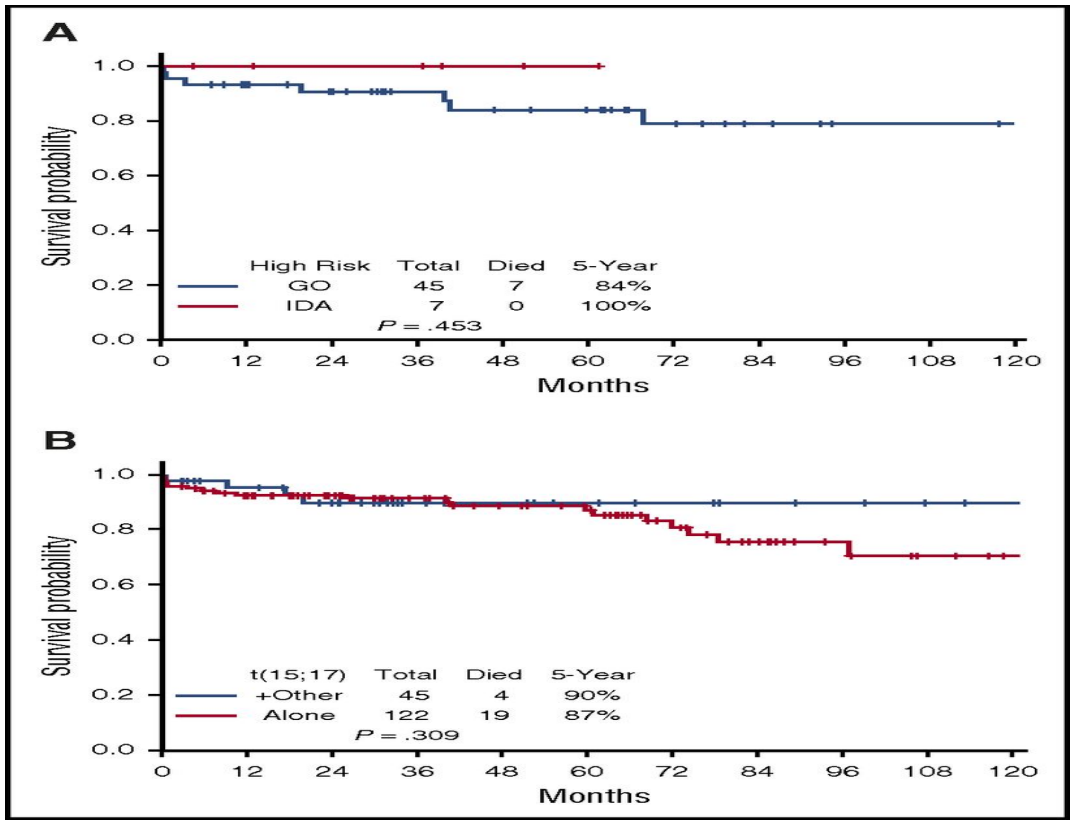
Survival for specified subsets



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Characteristics of Relapsed Patients

7 patients relapsed including 3 with CNS relapse

Patient no.	Risk category	Age (y)	Sex	Cytogenetics	FLT3 status	Time to first relapse (mo)	Type of first relapse
1	High	52	F	Diploid	ND	9.2	Molecular*
2	Low	42	M	46XY t(15;17) [20]	ND	79.5	Hematological/ molecular
3	High	38	M	46XY t(15;17) [19]	ND	9	Hematological/ molecular
4	High	79	M	46XY t(15;17), der (17) i (17) (q10) [18]; 46 XY [2]	Neg	12.4	Molecular*
5	High	18	M	46XY t(15;17) [19]	ND	9.4	Molecular*
6	Low	19	F	Diploid	Neg	9.5	Hematological
7	High	35	M	46XY t(15;17) [16]; 46 idem, del 7 [1]; 46 XY [3]	Neg	7.9	Hematological

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Causes of Death

- **26 (14%) patients died:**
  - **7 during induction, 2 refractory relapse, and 17 died in CR**

Patient (N = 17)	Age (y)	CR duration (mo)	Cause of death	Response at time of death
1	69	69.9	Stage IV GIST	CR
2	77	8	Prostate cancer	CR
3	75	60	Prostate cancer	CR
4	60	96.2	H&N cancer	CR
5	47	4.9	Prostate cancer	CR
6	64	77.5	Melanoma	CR
7	74	73.4	Pancreatic cancer	CR
8	70	16.5	Melanoma	CR
9	69	58.4	ESRD on HD	CR
10	75	15.7	ESRD on HD	CR
11	38	9	Pneumococcal meningitis	CR
12	64	0.9	Sepsis/pneumonia	CR
13	21	9.3	Infection and pulmonary embolism	CR
14	69	7	CHF and cardiac arrest	CR
15	81	25.2	Unknown	CR
16	81	106.8	Unknown	CR
17	43	39.2	Unknown	CR

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Grade 3-4 adverse events

Toxicity	N (%)
Infections	44 (23.5)
QT prolongation	14 (7.5)
Hemorrhage	10 (5)
Hepatotoxicity	27 (14)

Differentiation syndrome occurred in 21 patients (11%); managed successfully in all

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Conclusions

- ATRA plus ATO is effective in frontline therapy of standard risk APL
- Addition of GO in high risk patients and in low risk patients whose WBC rises is safe
- Excellent outcome in high risk patients
- No incidence of veno-occlusive disease of liver
- No significant cardiac arrhythmias with careful monitoring and replacement of electrolytes
- Most failures after the initial period related to death from other causes
- Few late relapses after first year