Memorial Sloan Kettering
Cancer Center

A Cure For (Almost) Every Patient With APL

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Disclosures

- Orsenix adv bd and research funding

Why Talk About APL At All?

a. The cells are attractive and intriguing to look at

b. The molecular pathogenesis has been deciphered

c. The clinical manifestations are unique

d. The treatment is different from all other subtypes of AML

e. The disease is highly curable (almost every patient)

f. ALL OF THE ABOVE

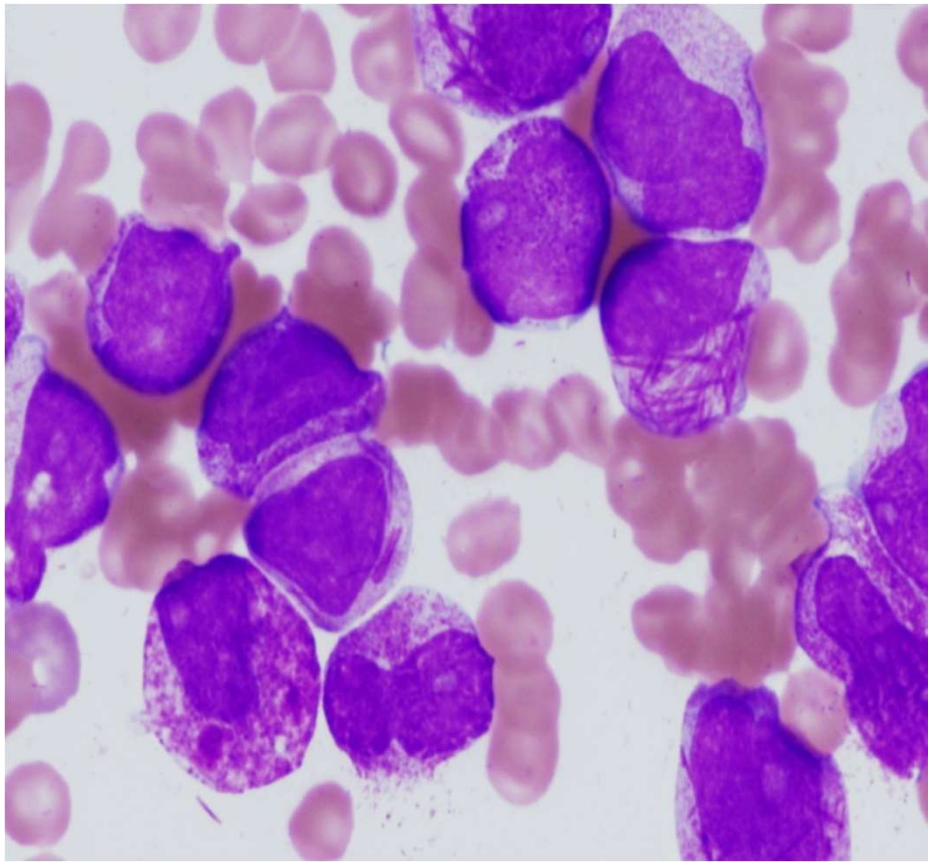
Objectives

- Describe distinguishing features of APL
- Provide approach to early death
- Address strategies for low- and high-risk disease
- Discuss role of maintenance
- Identify future directions

Acute Promyelocytic Leukemia

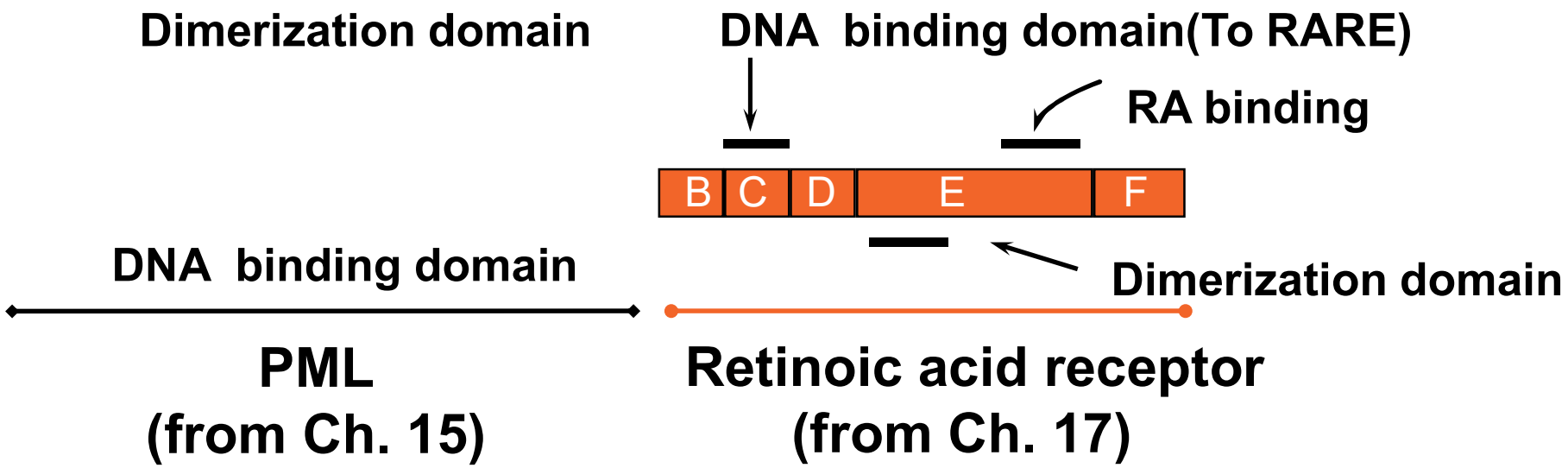
Distinguishing Features

- 10-15% adult AML; 20-30% Hispanics
- Leukopenia
- Coagulopathy
- t(15;17) chromosomal translocation
- Sensitivity to anthracyclines
- *PML-RARα* fusion transcript
- Differentiation with retinoic acid
- Apoptosis with arsenic trioxide
- Highly curable



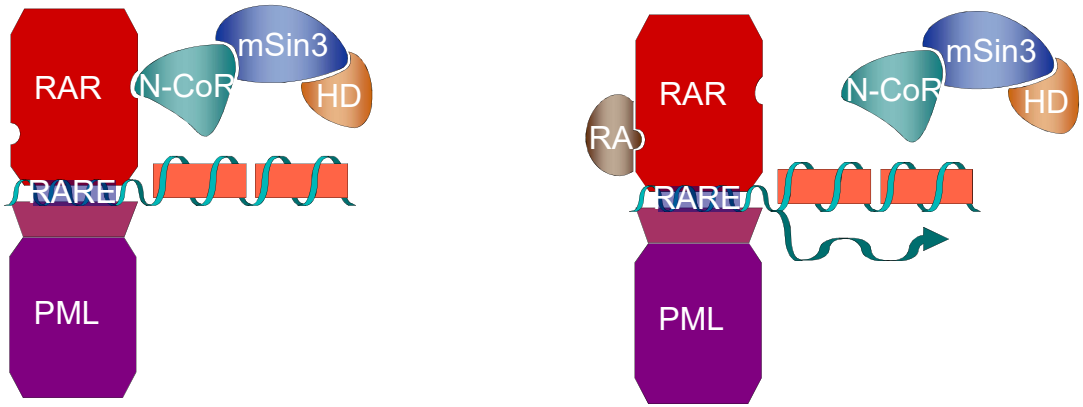
APL Specific PML/RARα Fusion Gene

t(15;17) creates fusion of PML and RARα useful for diagnosis and detection of minimal residual or recurrent disease



Molecular Basis of Leukemogenesis in APL

- RARα fuses to PML
- Increased affinity for nuclear co-repressor protein complex
- Histone deacetylase alters chromatin conformation inhibiting transcription



Grignani et al. Nature, 1998

Epidemiology

- Increased incidence in Latin Americans (Mexico, Central or South America)[1]
- 22% of AML in Peru[2]
- 75% of Latin Americans with APL have bcr1 isoform[1] suggesting genetic link

[1]Douer et al. Br J Haematol, 2003; [2]Otero et al. Blood, 1996

BCR Isoforms

	Bcr1 %	Bcr2 %	Bcr3 %
Caucasians[1]	54	8	37
Spaniards[2]	50	4	47
Italians[3]	46	2	49
Chinese[4]	67	6	27
Latin Americans[5]	75	10	15
Mexicans[6]	63	9	28

[1]*Gallagher Blood, 1997,2000* [3]*Mandelli Blood, 1997* [5]*Douer Br J Hematol, 2003*
[2]*Sanz Blood, 1999 and 2004* [4]*Chen Oncogene, 1992* [6]*Ruiz-Arguelles Leuk Lymph,2004*


Behring Strait
西域
Xiyu
Chaina

Acta Medica Scandinavica. Vol. CLIX, fasc. III, 1957.

From the Medical Department A, Rikshospitalet, Oslo. Physician in chief: Professor P. A. Owren.

Acute Promyelocytic Leukemia.

By

LEIF K. HILLESTAD.

(Submitted for publication August 13, 1957.)

Summary.

Evidence is presented for the existence of a special type of acute myelogenous leukemia. Three cases are described, characterized by 1) a very rapid fatal course of only a few weeks' duration, 2) a white blood cell picture dominated by promyelocytes, 3) a severe bleeding tendency due to fibrinolysis and thrombocytopenia, 4) a normal ESR, probably caused by the reduced fibrinogen concentration in the plasma.

It is suggested that this type is named acute promyelocytic leukemia. It seems to be the most malignant form of acute leukemia.

Dr. Jean Bernard

Showed sensitivity of APL cells to anthracyclines alone (CR rate ~ 60%)

↓

May be due to low expression of P-gp

Bernard J, Mathé G, Boulay J, Ceoard B, Chome J. Acute promyelocytic leukaemia: a study made on 20 cases. Schweiz Medical Wochenschrifte 1959

Bernard J, Weil M, Borian M, Jacquillat C, Flandrin G, Gemon MF. Acute promyelocytic leukemia: results of treatment by daunorubicin. Blood 1973

Dr. Jean Bernard, 98, Shah's Hematologist

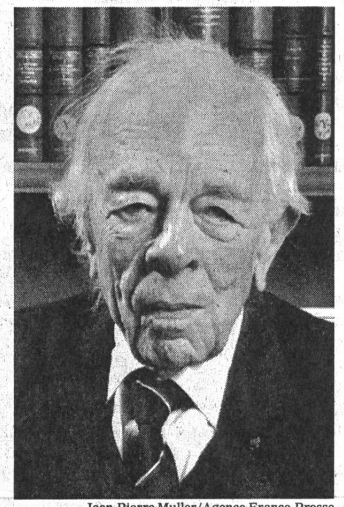
By LAWRENCE K. ALTMAN

Dr. Jean A. Bernard, a pioneering French hematologist who diagnosed the cancer that the shah of Iran kept secret for many years, and that ultimately sent him to an American hospital in a chain of events that led to the Tehran hostage crisis of 1979-81, died at his home in Paris on April 17. He was 98.

Dr. Bernard was a member of the French Academy, which announced his death.

As a prominent doctor whose name is attached to a children's bleeding disorder, Dr. Bernard occasionally consulted on patients who demanded anonymity and secrecy.

He did not know who the patient would be when a trainee of his, practicing in Iran, asked him to come to Tehran urgently in 1974. Dr. Bernard took another trainee, Dr. Georges Flandrin.



Jean-Pierre Muller/Agence France-Presse

Dr. Jean A. Bernard, in 2003.

A French doctor who was secretly flown to Iran for a diagnosis.

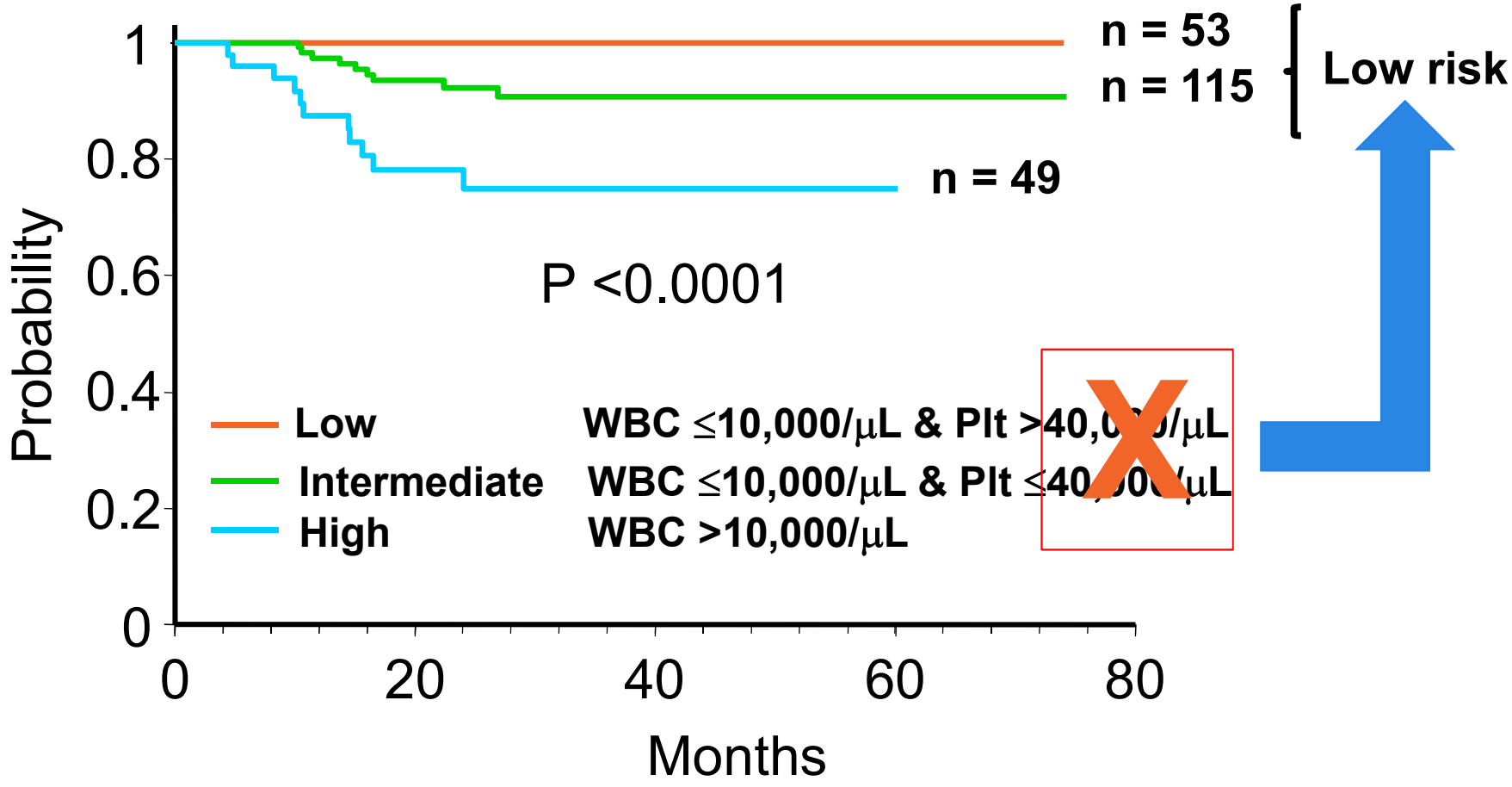
The shah died in 1980 after being treated by medical teams as he wandered the world for treatment of his cancer and its complications.

Jean Alfred Bernard was born in Paris on May 26, 1907. In 1940, he joined the French Resistance. He was caught and imprisoned until the end of World War II.

In 1947, he and Dr. Marcel Bessis developed exchange blood transfusion as a therapy for childhood leukemia. The transfusions induced what is believed to have been the first temporary remission of acute lymphoblastic leukemia in children. Prof.

GIMEMA & PETHEMA Study

Relapse-free survival



Sanz et al. Blood, 2000

Prognostic Factors in AML and APL

AML	APL
Age	WBC
PS	
WBC	
Immunophenotype	
Cytogenetics	
Molecular genetics	
MicroRNA	
MRD	

Early Death Rate in APL

Prospective Studies

Trial	N	Induction	CR%	ED%	ED Due to Bleeding%	DFS%
PETHEMA	732	ATRA + Ida	91	7	69	86
JALSG	283	ATRA/ida/ara-C	94	5	69	69
GAMLCG	142	ATRA/TAD/HAM	92	8	64	82
GIMEMA	420	ATRA + ida	94	6	32	87
AML17	119	ATRA + ida	89	6	27	70

Sanz et al. Blood, 2008; Asou et al. Blood, 2007; Lengfelder et al. Leukemia, 2009; Lo Coco et al. Blood, 2011; Burnett et al. Lancet Oncol, 2015

Early Death Rate in APL

Population-Based Studies

Study	N	ED
Jeddi	41	16%
Lehmann	99	31%
Alizadeh	137	14%
McClellan	70	26%
Chorao	63	21%
Park	1,400	18%
Ho	960	28%
Murthy*	2,367	10%

**ATRA, ATO, chemo*

Jeddi Hematology, 2008; Lehmann Leukemia, 2010; Alizadeh ASH, 2009; McClellan Haematologica, 2012, Chorao 7th Int'l APL Symp. abstr C0037, 2017; Park Blood, 2011; Ho ASH abstr 3430, 2017; Murthy ASH abstr 2468, 2017

Early Death Rate in APL

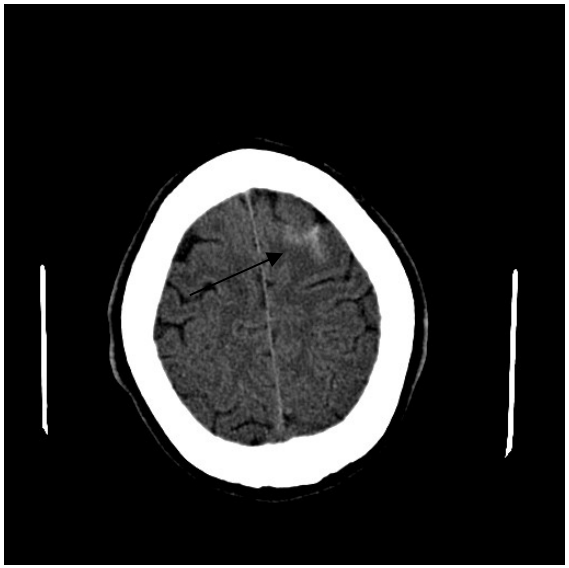
ATRA/ATO-Based Studies

Study	N	ED
Zhu	309	5%
Ravandi	187	4%
Platzbecker	77	1%
Lo Coco	77	0

Zhu et al., Ravandi et al., Platzbecker et al. 7th Int'l Symp on APL abstr C0008, C0028, P0027, 2017; ASH abstr 2618, 2017; Lo Coco et al. NEJM, 2013

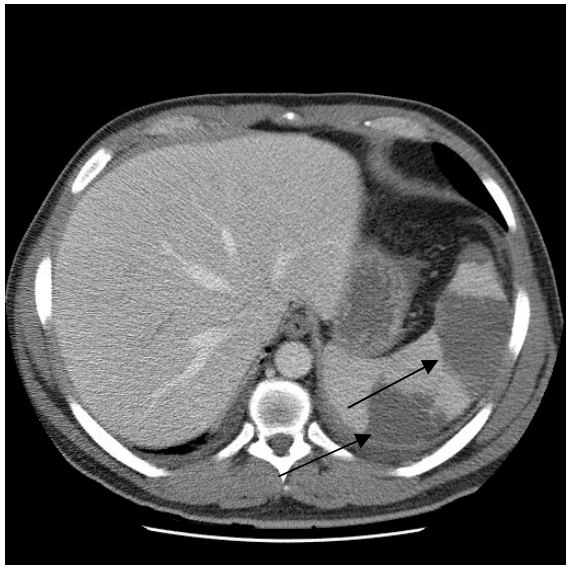
The Coagulopathy Associated with APL

Various Manifestations Reflect Complexity

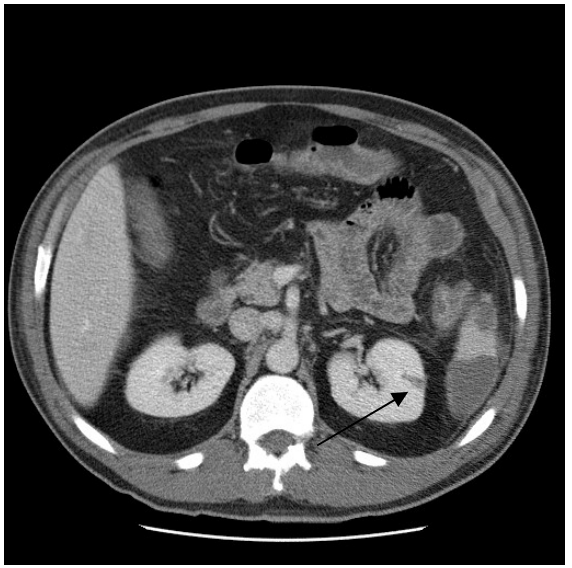


Subarachnoid hemorrhage

At diagnosis



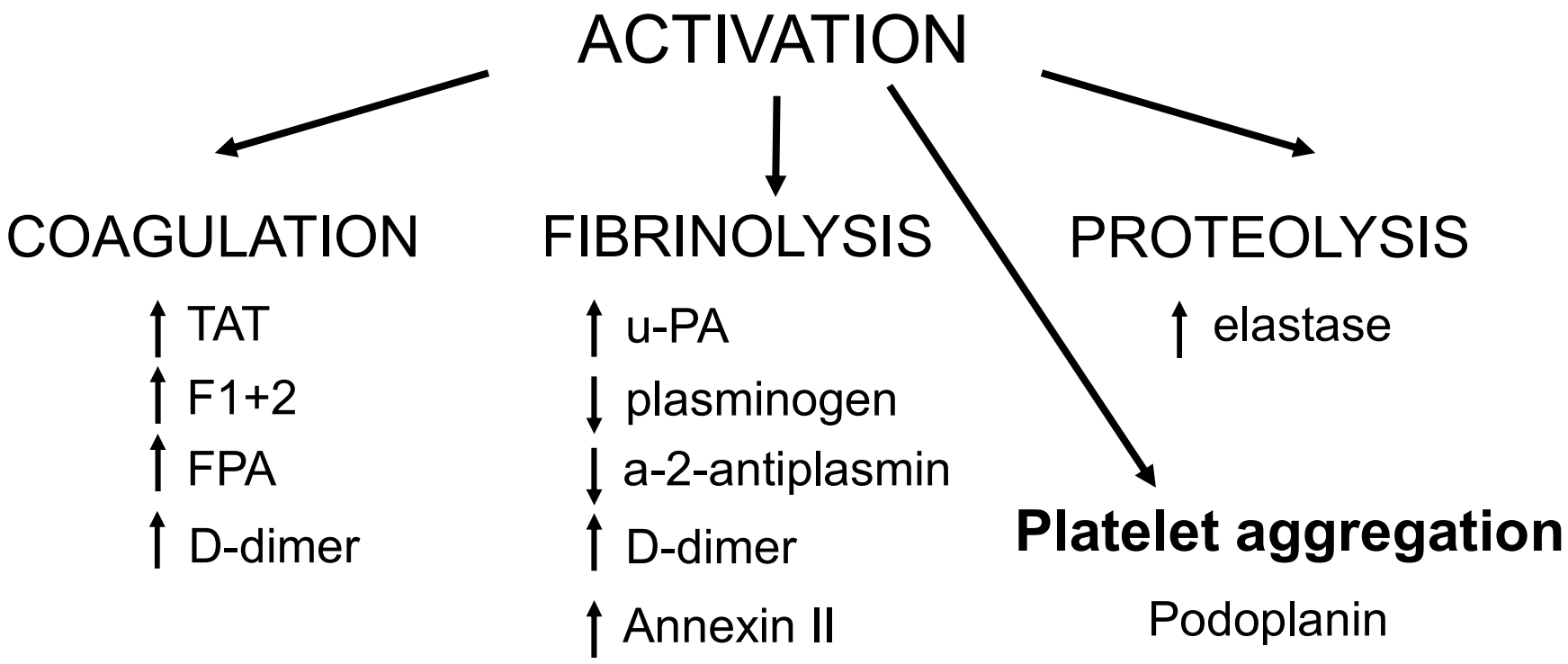
Splenic infarction



Splenic and renal infarction

2 weeks after starting induction with ATRA + chemotherapy

Pathogenesis of the Coagulopathy
(It's not just DIC)



Podoplanin as a Novel Contributor to Coagulopathy in APL

- Glycoprotein binds to *CLEC2* receptor on platelets, induces platelet aggregation causing separation of blood and lymphatic vessels during embryogenesis
- Not expressed on all other sorted cell populations from normal blood or marrow including normal promyelocytes
- Ectopically expressed on APL promyelocytes
- ATRA reduces bleeding by decreasing Podoplanin expression (<10% by day 4)

Lavallee et al. Leukemia, 2018

Early Death in APL

- **Has emerged as the major limitation to cure (not resistance)**
- Higher than reported in clinical trials
- May be reduced if ATRA given in ERs at first suspicion
- May be lower with ATRA/ATO induction
- Should be high priority for education of wide variety of health care providers (guidelines, ECOG-ACRIN EA9131 outreach protocol)

Prevention of Early Death in APL

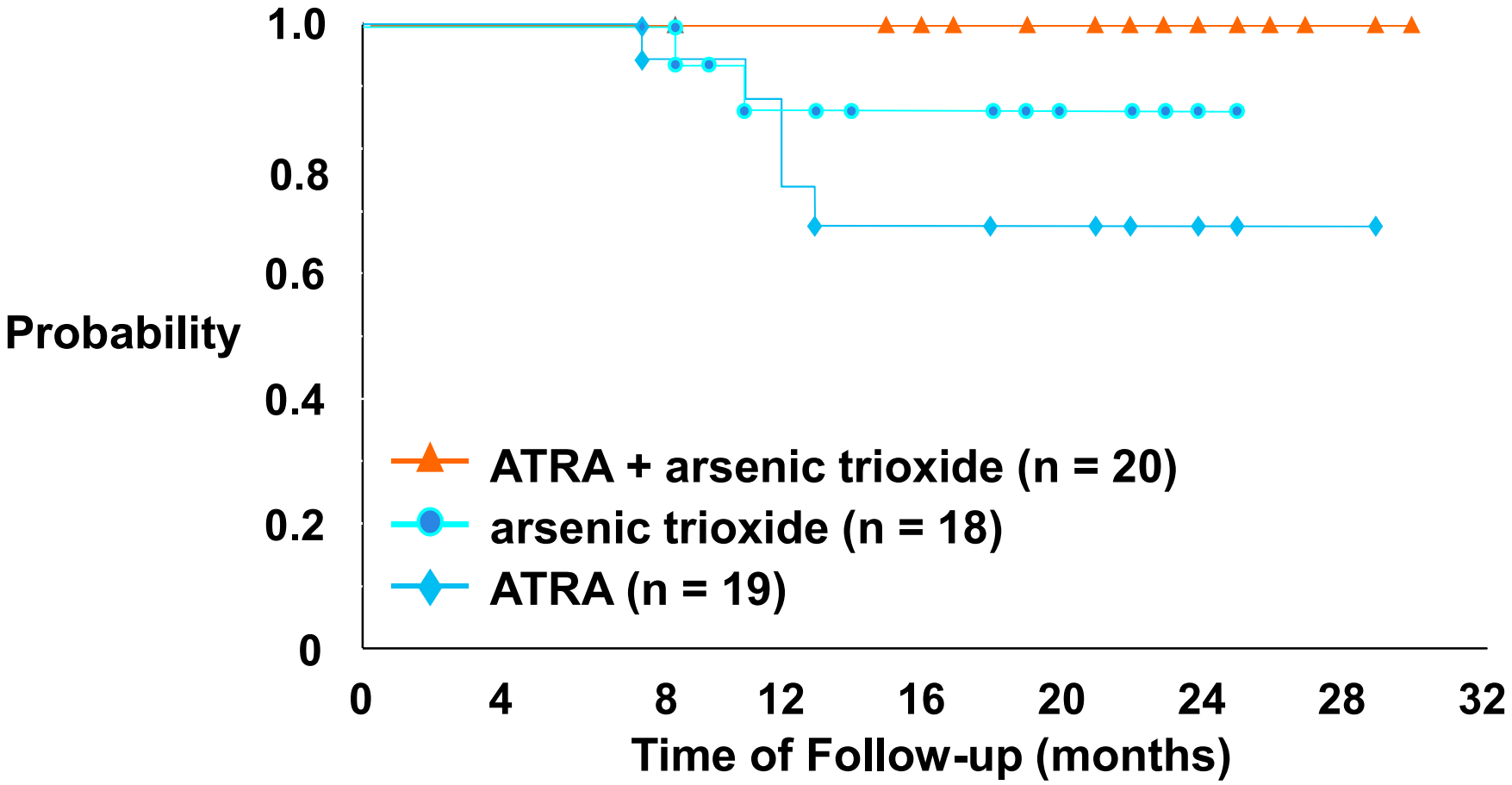
- Start ATRA at first suspicion (based on clinical hx and review of peripheral smear), BEFORE MARROW AND BEFORE DIAGNOSIS CONFIRMED GENETICALLY
- Frequent plt transfusion to ≥50,000/μL
- Cryo to maintain fibrinogen ≥150 mg/dL
- No heparin, altho not studied in ATRA era
- No antifibrinolytics
- ABO identical blood components and washed red cells and plts

Rodeghiero et al. Blood, 1990; Tallman et al. Leukemia Res, 2004; Sanz et al. Blood, 2008; Sahai et al. Leuk Res, 2017

Important Concepts in Induction in APL

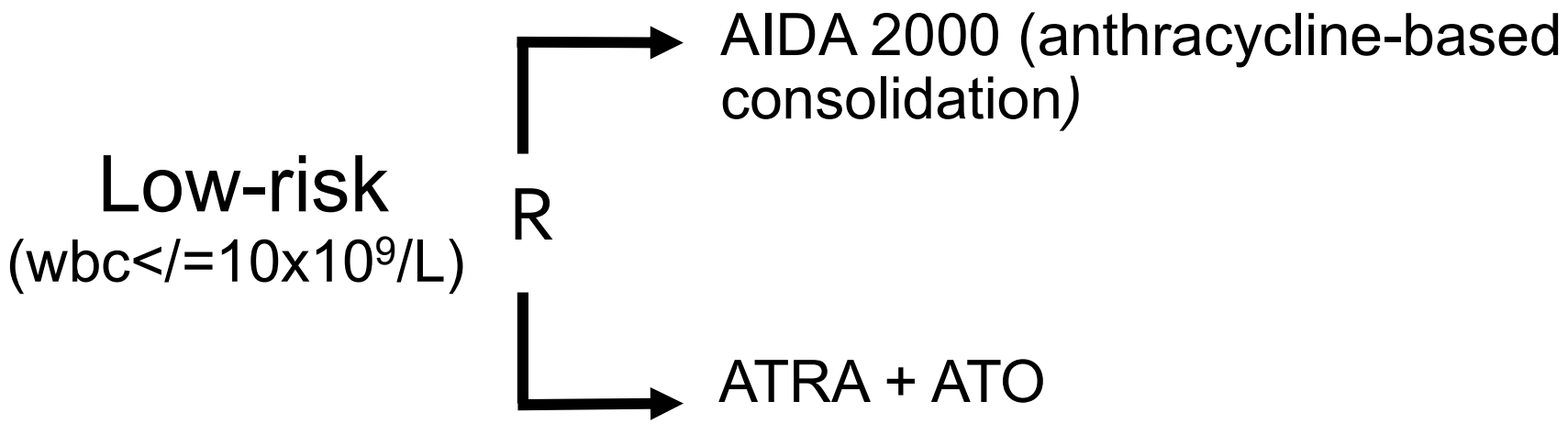
- No modification based on additional cyto abn (? complex), therapy-related etiology, *FLT3* mutations, *PML* isoform, or morphology (M3V), ? CD56
- Bone marrow not needed on day 14 AND not at CR
  - No primary resistance (secondary is very rare, point mutations in RAR in ligand binding domain and in PML at site of arsenic binding)
  - No prognostic importance of cyto/molecular genetics in CR1 at end of induction
- Maybe no marrow needed at presentation for some pts if diagnosis unequivocal

Disease-Free Survival By Treatment Group



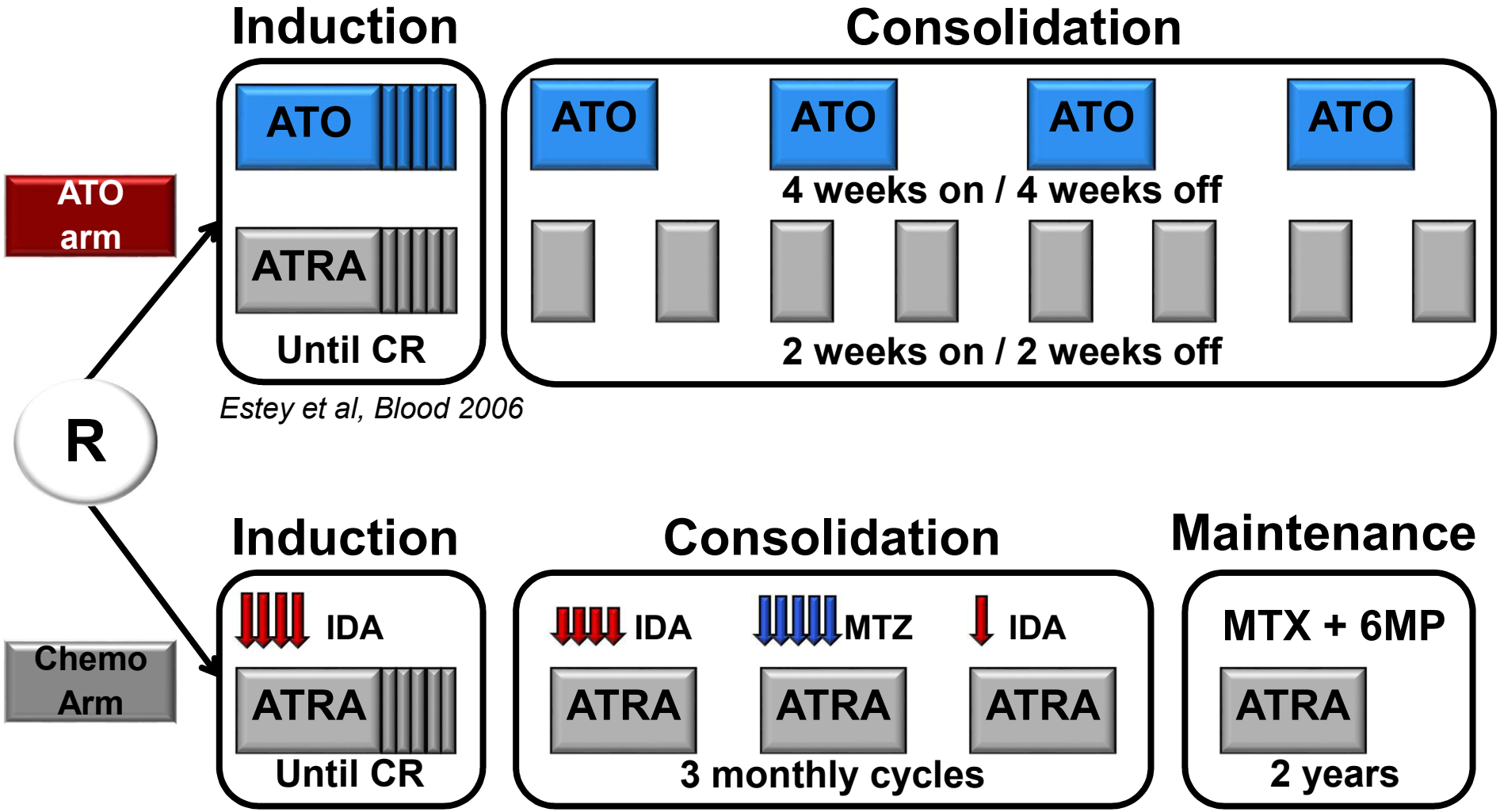
Shen et al. PNAS, 2004

GIMEMA /SAL/AMLSG-APL0406



APL 0406 Study

Treatment Schema



Lo Coco et al. NEJM, 2013

Induction Outcome

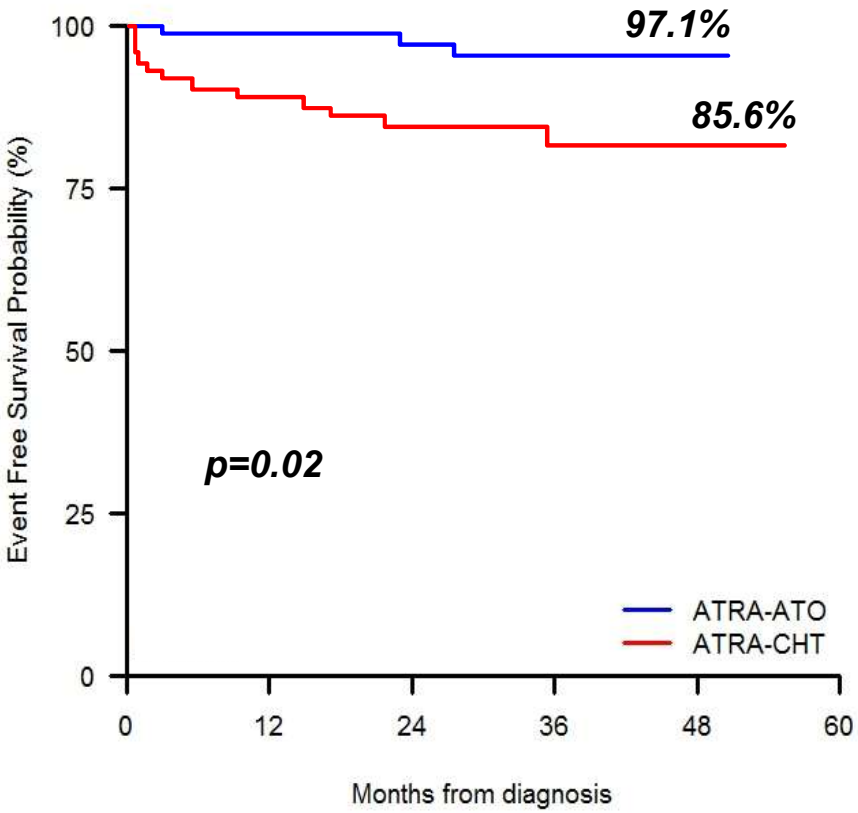
	ATRA + ATO	ATRA + Chemo
No. of patients	75	79
CR, (%)	75 (100%)	75 (95%)
Induction death	0	4*
Resistant disease	0	0

* Differentiation syndrome (2), ischemic CVA (1) and pneumonia (1)

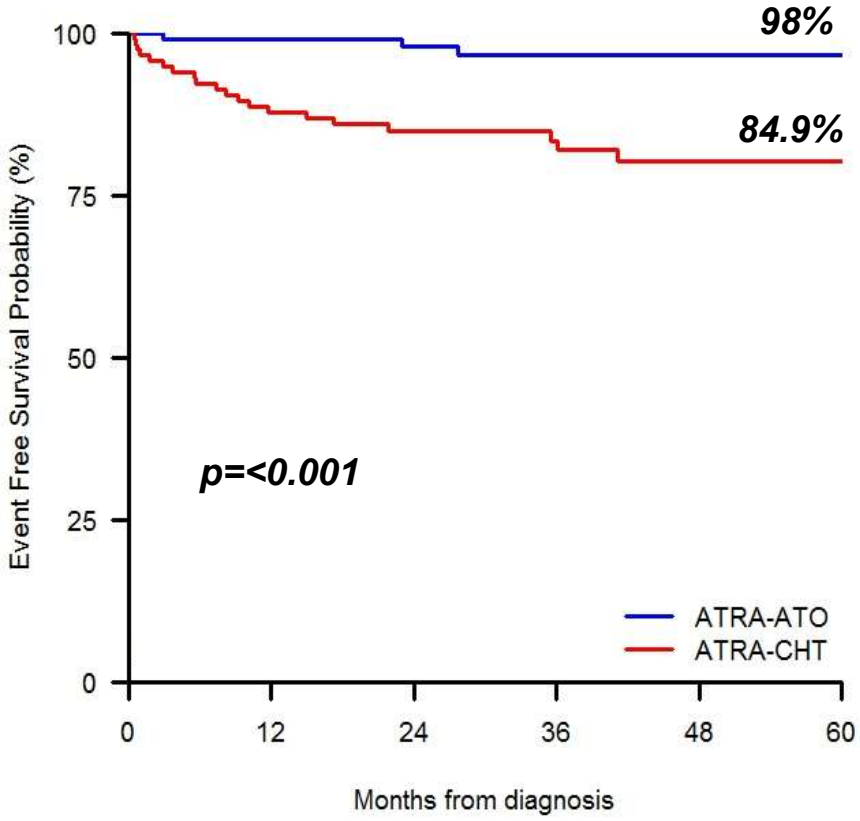
Event-Free Survival

Primary objective

Initial series



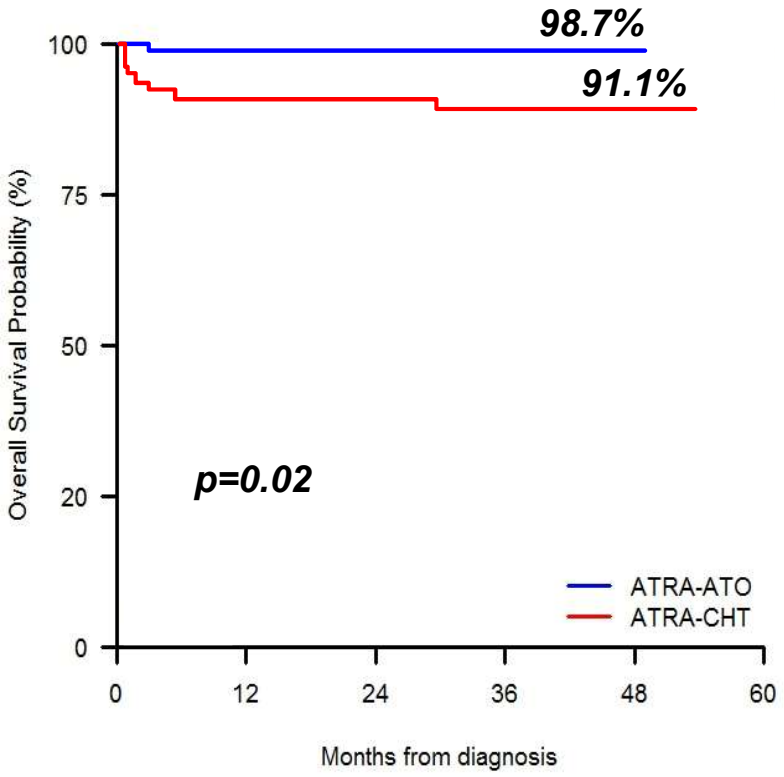
Final series



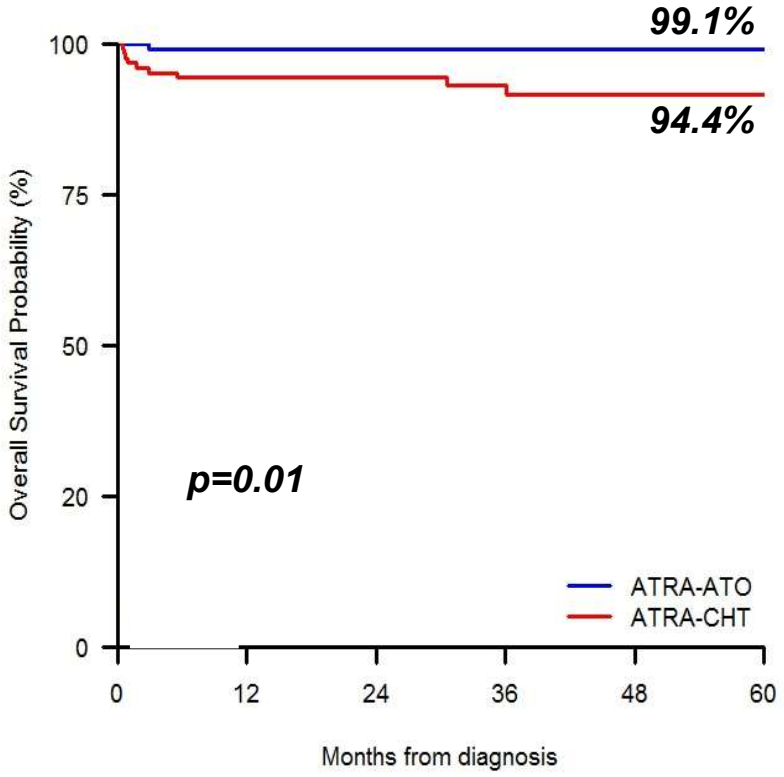
Lo Coco et al. NEJM, 2013 and J Clin Oncol, 2017

Overall Survival

Initial series



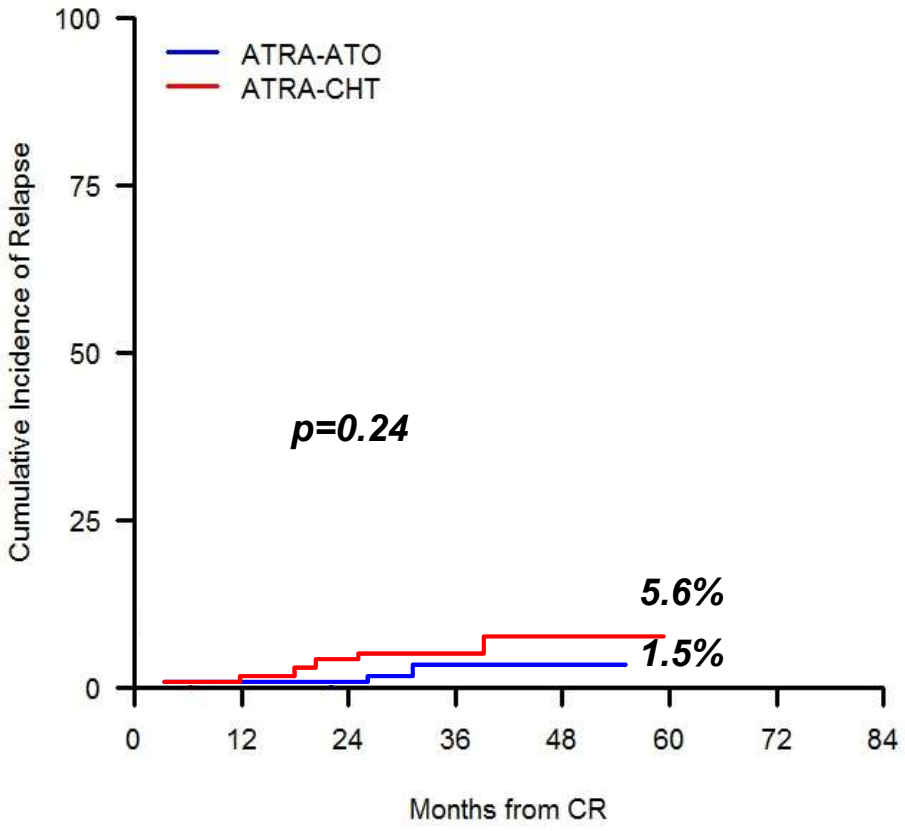
Final series



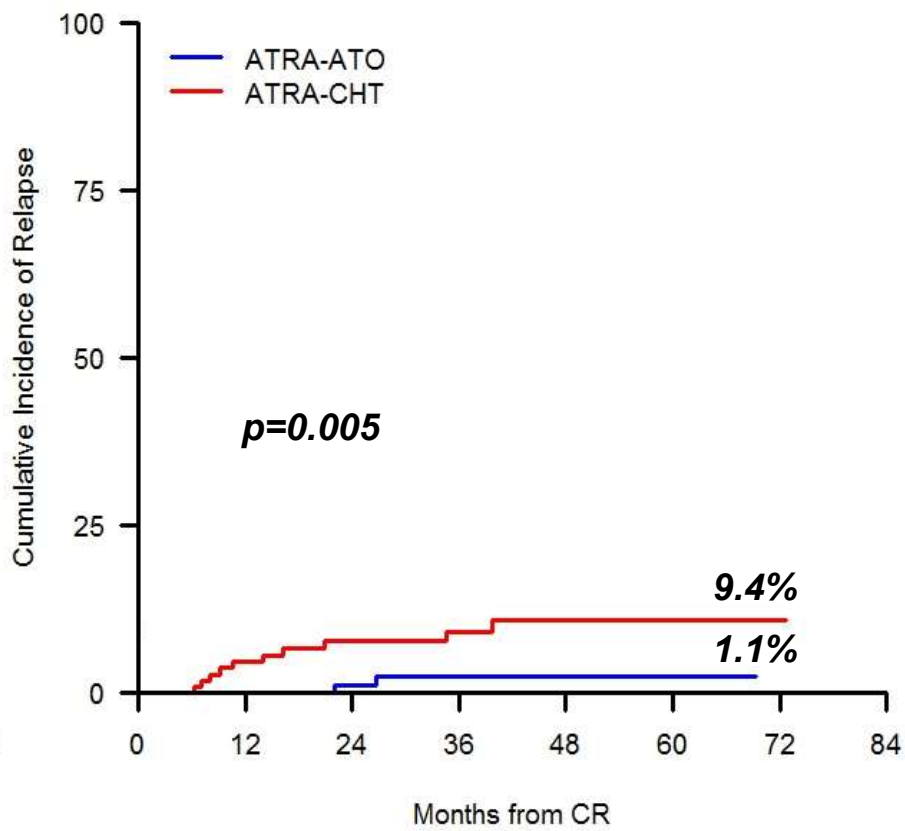
Lo Coco et al. NEJM, 2013 and J Clin Oncol, 2017

Cumulative Incidence of Relapse

Initial series

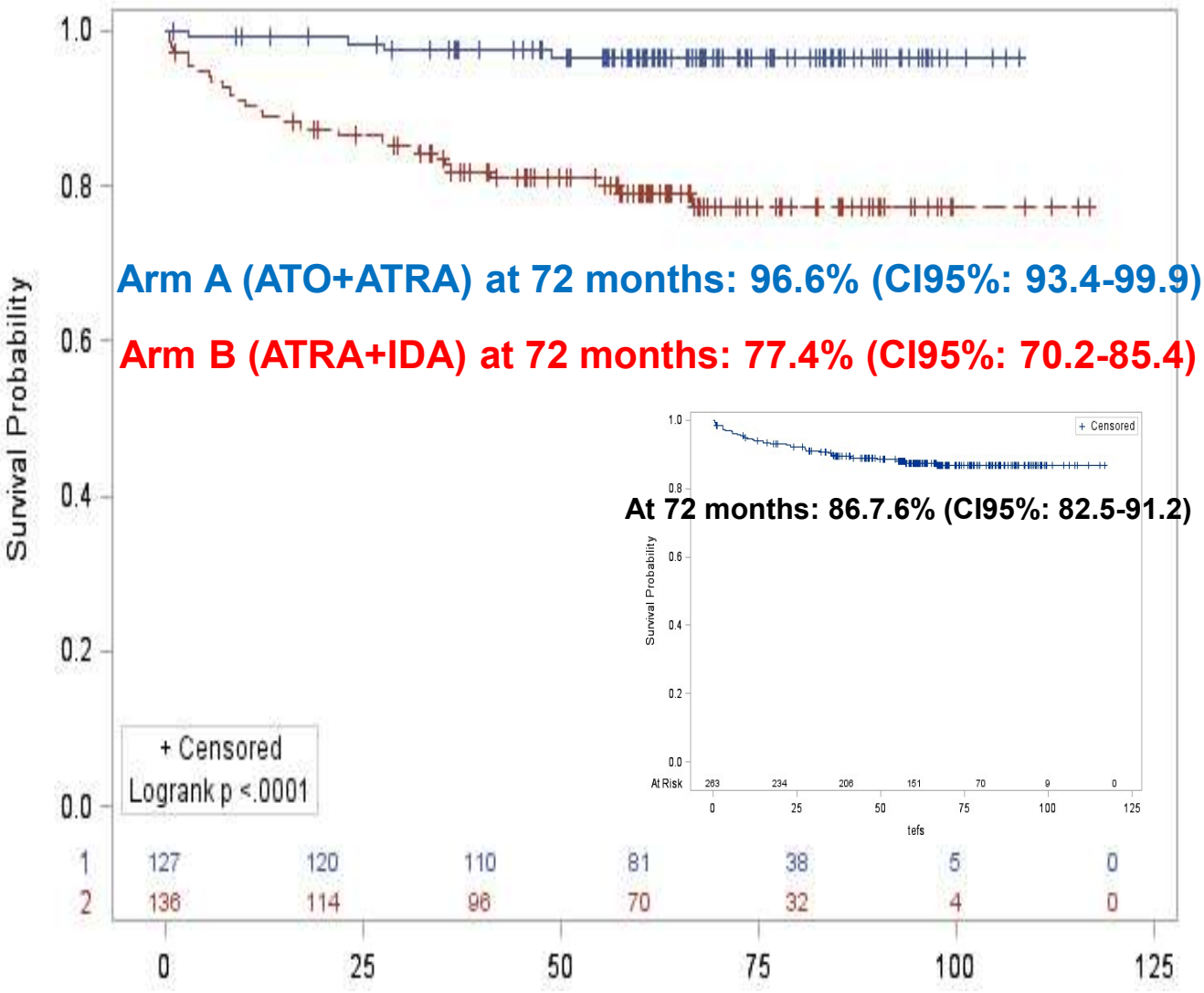


Final series



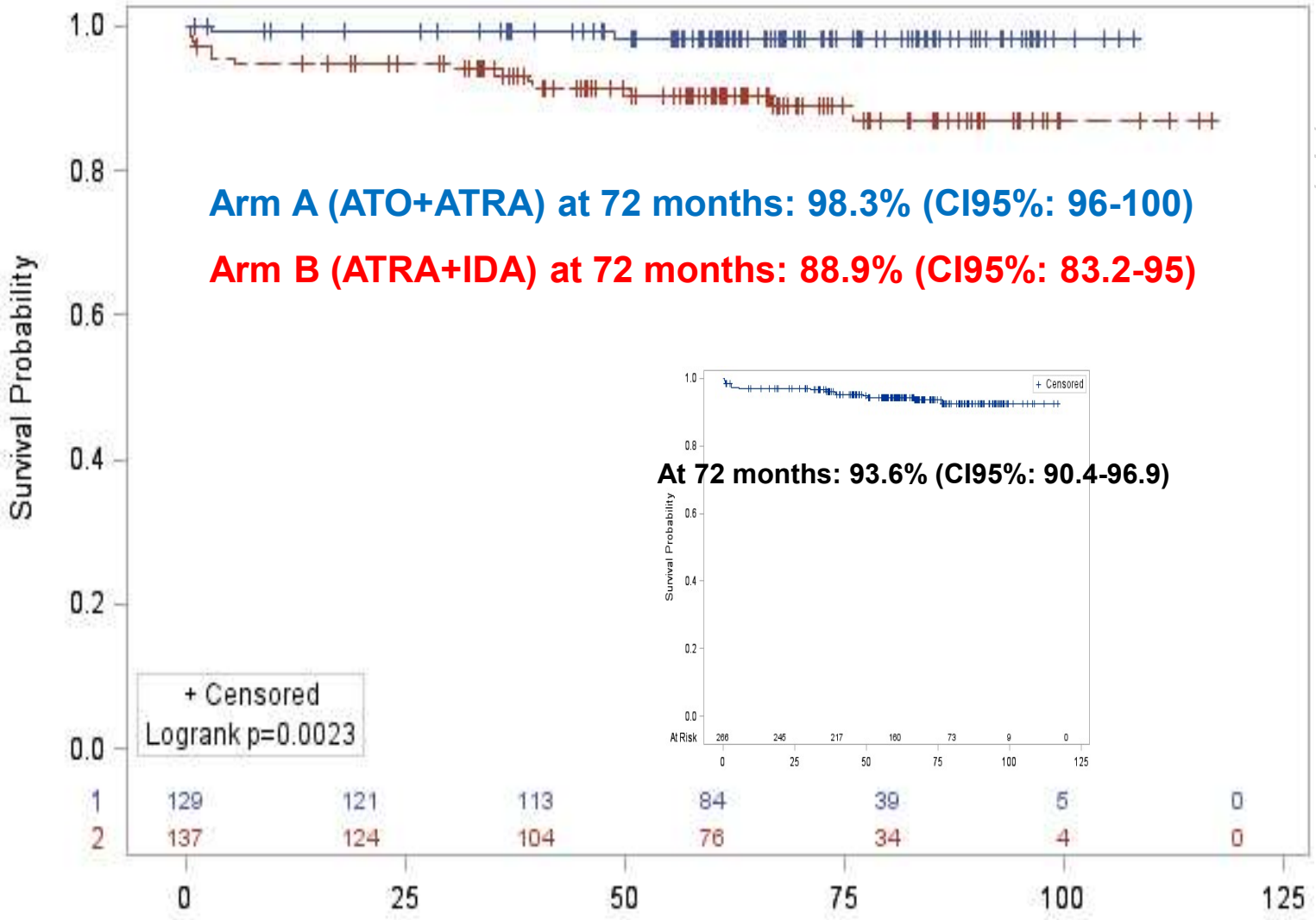
Lo Coco et al. NEJM, 2013 and J Clin Oncol, 2017

Event-Free Survival



Overall Survival

Memorial Sloan Kettering Cancer Center



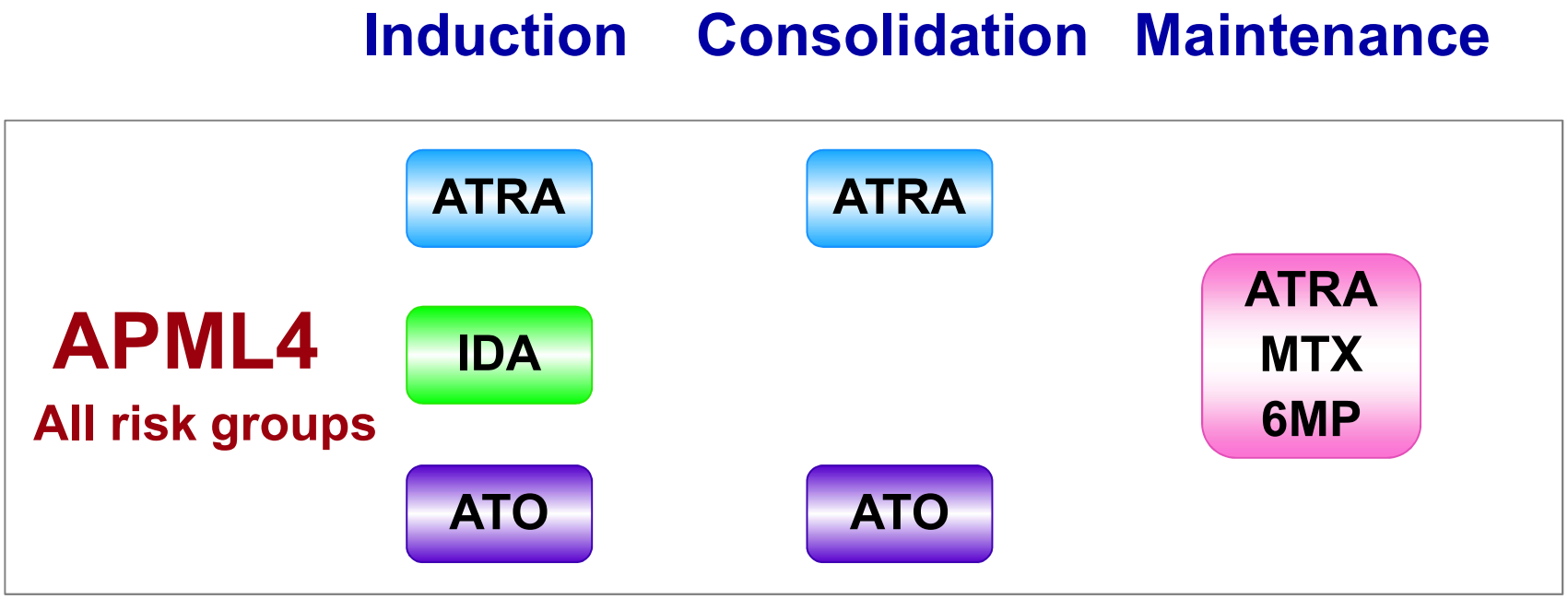
Avvisati et al. 7th Intern'l Symposium on APL, Rome, 2017

Events as of September 20, 2017
APL0406

EVENT	ATRA-ATO	AIDA	Total
Induction Death	0	4	4
Death in CR	2	5	7
Molecular resistance	0	2	2
Relapses	2	17	19
Secondary AML	0	1	1
Total	4	29	33

Avvisati et al. Intern'l APL Symposium. Rome, 2017

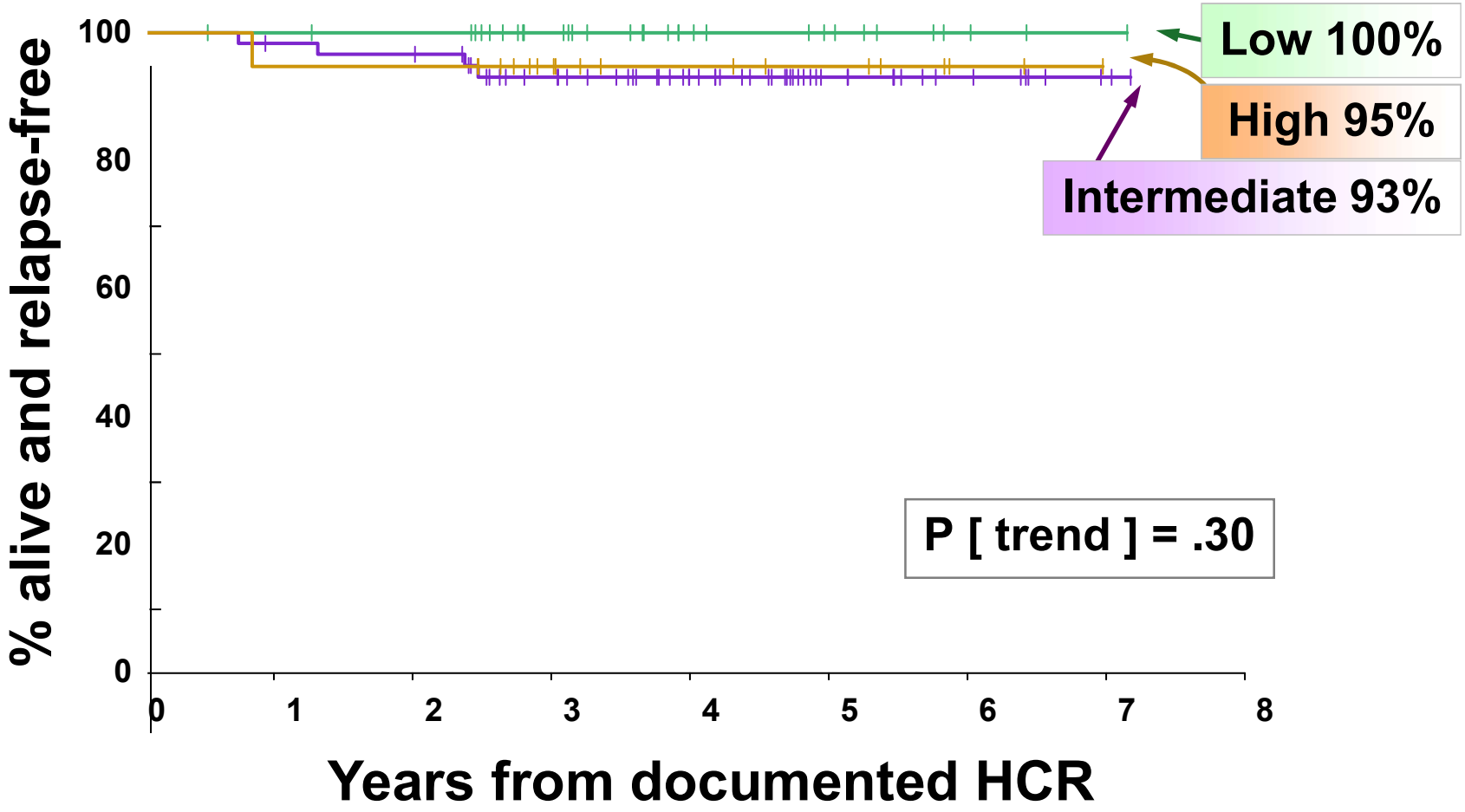
APML4 Trial



Iland et al. Blood, 2012

APML4

DFS by Sanz Risk Category



Iland et al. Blood, 2012 and Lancet Haematol, 2015

High-Risk APL
ATRA + Risk-Adapted Chemo vs APML4

	Number	Median follow-up (months)	IDA equivalent (mg/m^2)	AraC (g/m^2)	DFS	CIR	OS
PETHEMA LPA2005	118	28	122	5.8	82%	14%	79%
European APL2000	74	103	99	22.8	-	7%	88%
GIMEMA AIDA2000	129	59	122	6.3	85%	9%	83%
ALLG APML4	23	50	48	0	95%	5%	87%

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Sanz et al. Blood, 2010; Adès et al. Am J Hematol, 2013; Lo Coco et al. Blood, 2010;Sanz et al. Best Pract Res Clin Haematol, 2003; Iland et al. ASH, 2014

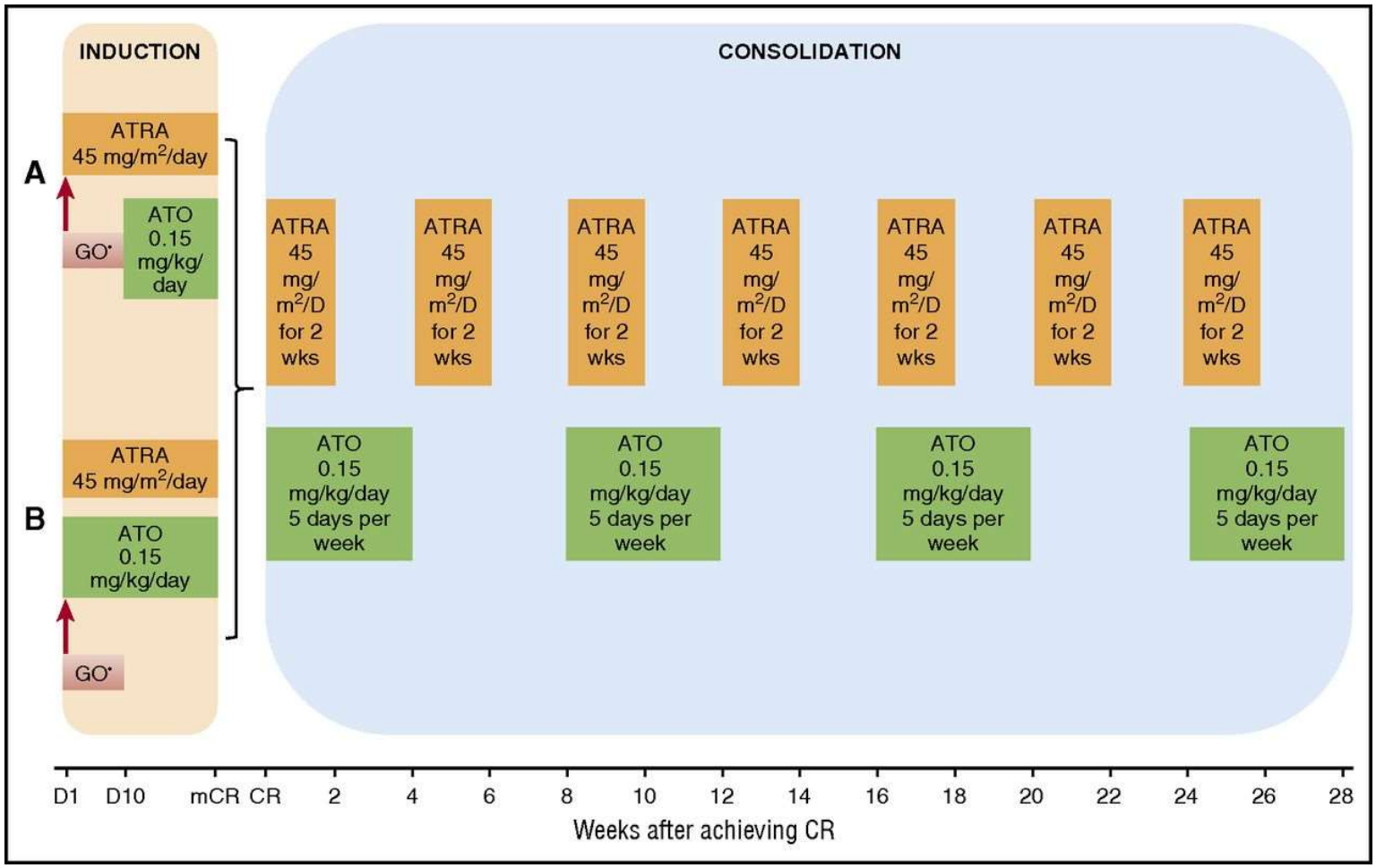
Gemtuzumab Ozogomicin in APL

Study	N	Disease Status	CR%	Mol CR%
Estey[1]	19	De novo	84%	100%
LoCoco[2]	16	Mol. Relapse	NA	100%

[1]Estey et al. Blood, 2002[2;] Lo Coco et al. Blood, 2004

ATRA + ATO ± GO

Long-term follow-up

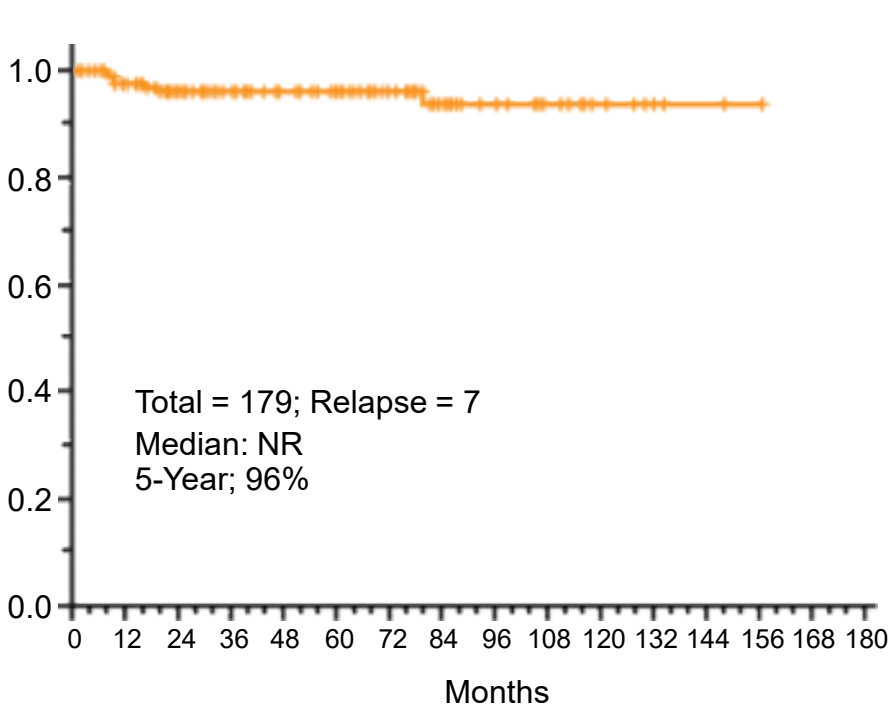


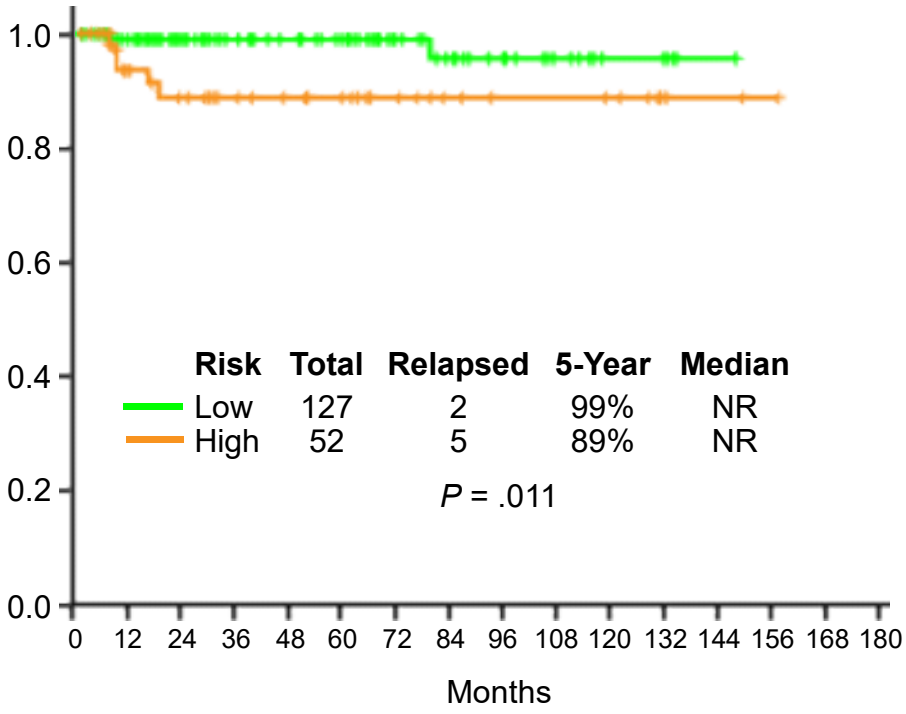
Estey et al. Blood 2006; Abaza et al. Blood 2017

ATRA + ATO ± GO

Long-term follow-up

Disease-free survival





Abaza et al. Blood, 2017

Induction

- ATRA + ATO for low-risk
- ATRA + ATO + ida (or GO) for high-risk

  or

- ATRA + ida
- CNS prophylaxis for high-risk (IT x 6 or twice with each consolidation-no data, but I do it)

Consolidation

- ATRA + ATO
  - Low-risk: 4 courses (Lo Coco)
  - High-risk: 2 [with ida in induction (Iland)]

OR

- 2-3 cycles anthracycline-based chemo (leads to molecular CR in 95%)
  - ATRA for 2 weeks with each cycle, based on historical comparisons of consecutive series

- High-risk patients require either
  - ATO in induction or consolidation
  - IDAC in consolidation

Mandelli et al. Blood, 1997; Diverio et al. Blood, 1999; Sanz et al. Blood, 2009; Powell et al. Blood, 2010

Maintenance

- Maint likely depends on intensity of chemotherapy-based induction and consolidation
- If chemotherapy-based treatment, give maint, esp in high-risk, with ATRA + 6-MP/MTX for 1-2 yrs
- If ATRA + ATO given, maint not needed in low-risk, ? High-risk, but I give it
- Don’t “mix and match”

MRD Monitoring

- Low- and intermediate-risk: 1% OS benefit at 5 yrs
- High-risk: 10% OS benefit at 5 years
- Low-risk: MRD monitoring can be reasonably discontinued and pts followed carefully once molecularly negative
- High-risk: continue MRD monitoring every three months for 3 years

Grimwade et al. J Clin Oncol, 2009; Grimwade and Tallman Leukemia Res, 2010

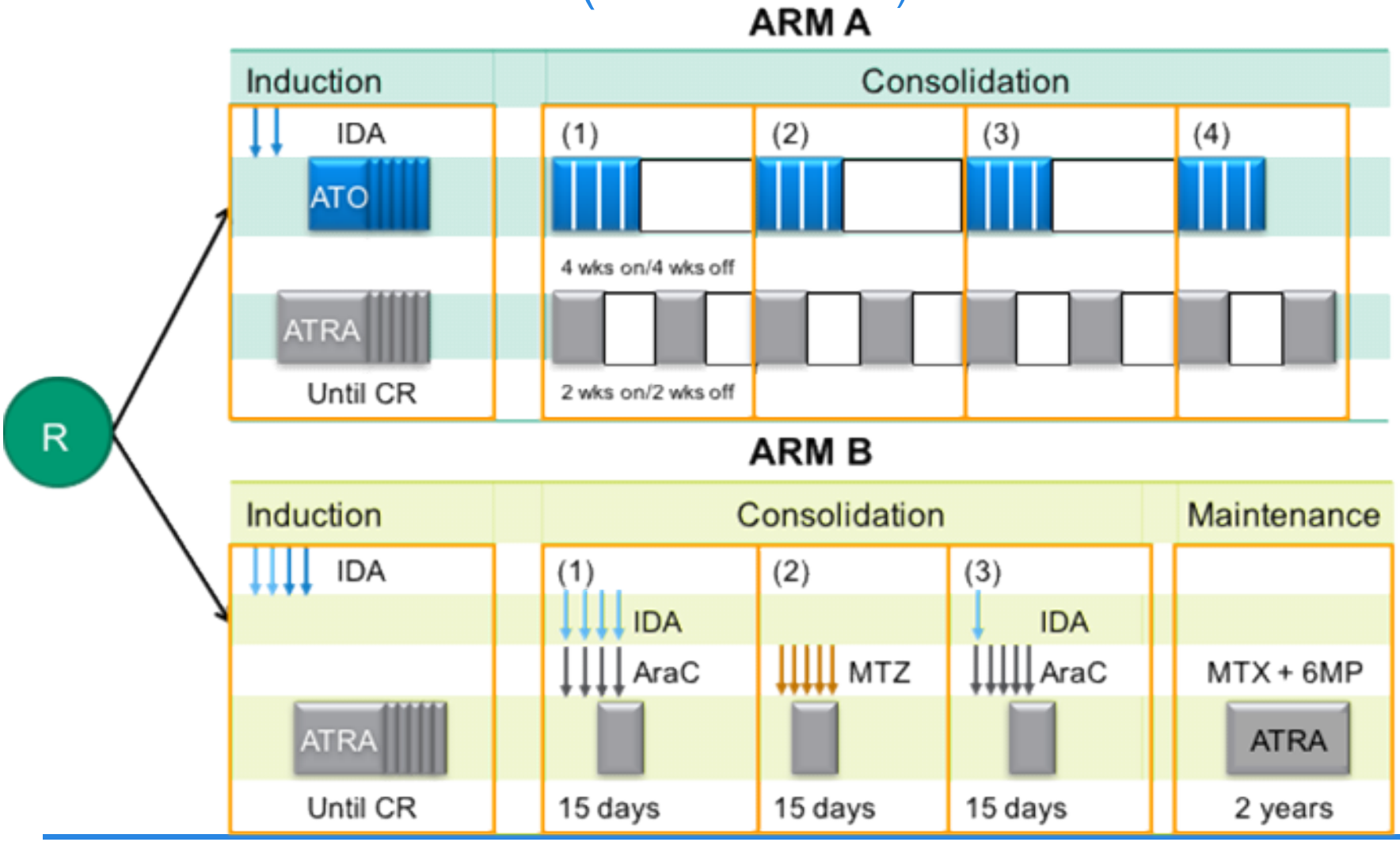
Future Directions

- Decrease early death

- Optimize/refine treatment for high-risk patients
  - APOLLO trial
  - Tamibarotene
- Novel strategies
  - Alternative schedules/doses of arsenic
  - Oral arsenic

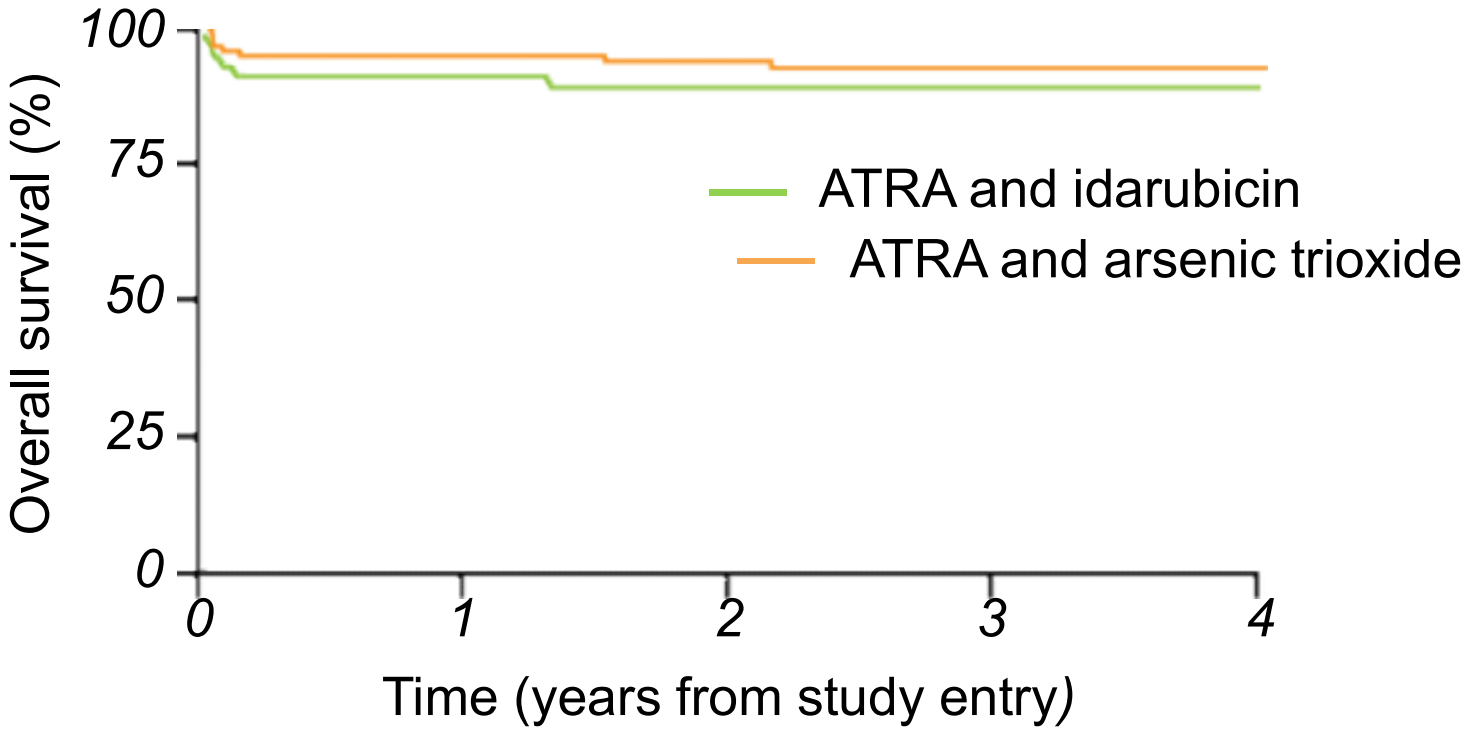
High-risk APL

Pan-European randomized trial in high-risk APL (APOLLO trial)



Overall Survival in the Intention-to-Treat Population

Twice Weekly Arsenic



Burnett et al. Lancet Oncol, 2015

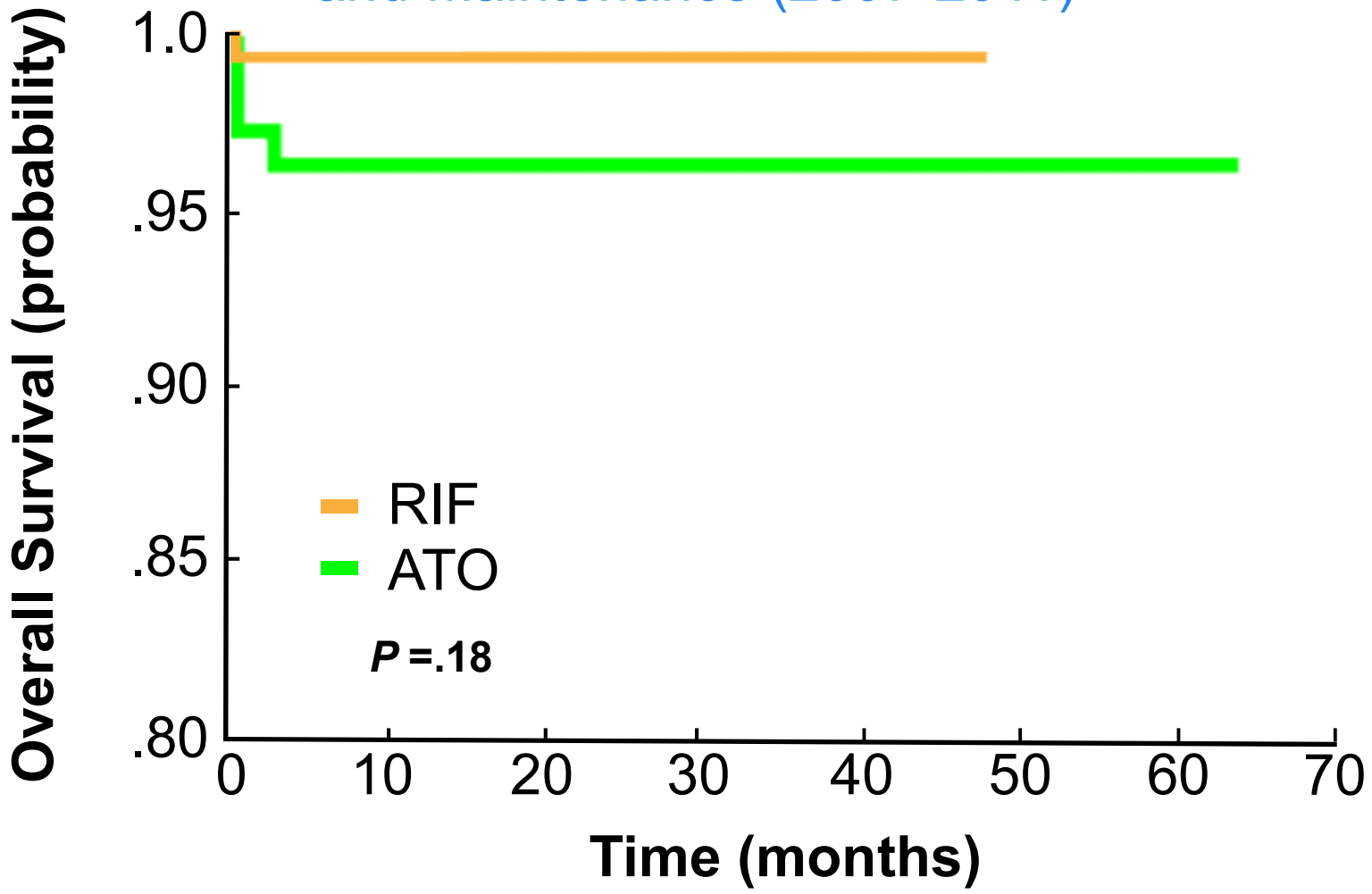
Tamibarotene Maintenance

- Synthetic retinoid with
  - 10 x potency in inducing differentiation vs ATRA
  - Enhanced stability
  - Low affinity for cellular RAS-binding proteins
- Randomized trial of Tamibarotene (n=134) vs ATRA (n=135) for 14 days every 3 months for 2 years after chemotherapy
- RFS at 7 years: 93% Tami vs 84% ATRA (p=0.027)
- RFS in high-risk: 89% vs 62% (p=0.034)

Takeshita et al. Leukemia, 2019

Overall Survival

Randomized Trial of Oral Arsenic RIF vs ATO for Induction and Maintenance (2007-2011)



Zhu et al. J Clin Oncol, 2013

Randomized Trial of Oral ATO (RIF) + ATRA vs IV ATO + ATRA In Non High-Risk Patients 2014-2017

- Randomized trial, 2:1, N=109
- Noninferiority trial, such that difference not >10%
- CR rate oral: 100% vs IV: 94% (p=.12)
- EFS at 2 yrs oral: 97% vs IV: 94%
- Conclusion: oral ATO not inferior to IV

Zhu et al. Lancet Oncol, 2018

ORH-2014:
Novel Oral Formulation of Arsenic Trioxide

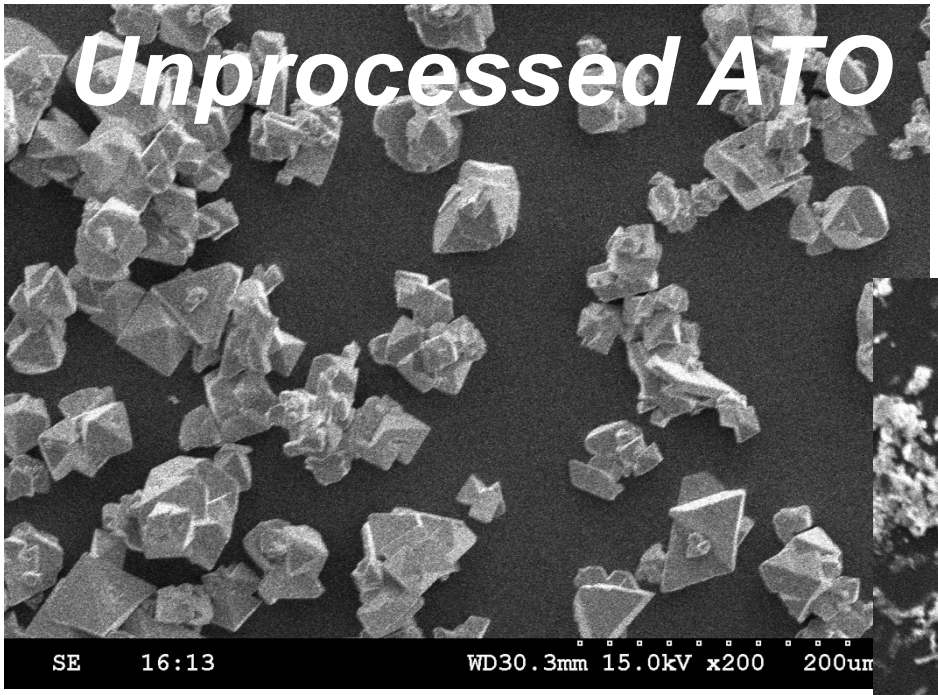
Arsenic Trioxide (ATO) vs ORH-2014

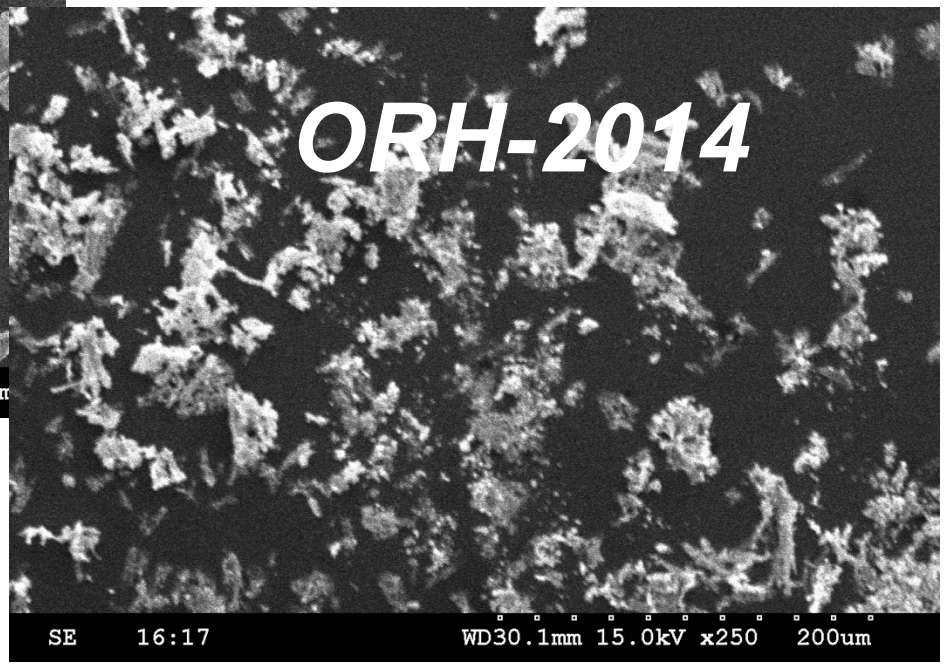
Improved Physical Properties

- Particle Size
  - 2.0 microns (ORH-2014) vs 40 microns (ATO)
- Surface Area
  - 40x higher for ORH-2014 vs ATO
- Solubility
  - 20x higher for ORH-2014 vs ATO

- Improved Pharmaceutical Properties
  - Dissolution
    - >90% for ORH-2014 vs 10% for ATO
  - Bioavailability (Dog)
    - 100% for ORH-2014 vs <10% for ATO

ORH-2014 vs ATO
Physical Properties





Oral Arsenic ORH-2014
Phase I Trial

- N=12
- Hematologic malignancies
- Med age 77 yrs (45-81)
- NO DLTs or drug-related SAEs ex 1 gr 3 QT prolongation
- 15 mg Cmax comparable to ATO IV dose and AUC from 0-24 hrs was 36% vs 30%
- ORH-2014 is safe, bioavailable, and provides requied ATO exposure compared to IV drug

Ravandi et al. Haematologica, 2019

Additional Distinguishing Features of APL

- Current strategies are directed at less chemo and APL can be cured with no chemo
- Disease is as sensitive among older adults as younger
- Treatment of relapsed disease effective (for late relapse highly effective)
- Auto not allo is treatment of choice in CR2
- **We now cure all but the very few patients who present with catastrophic bleeding**

Is APL a Leukemia?

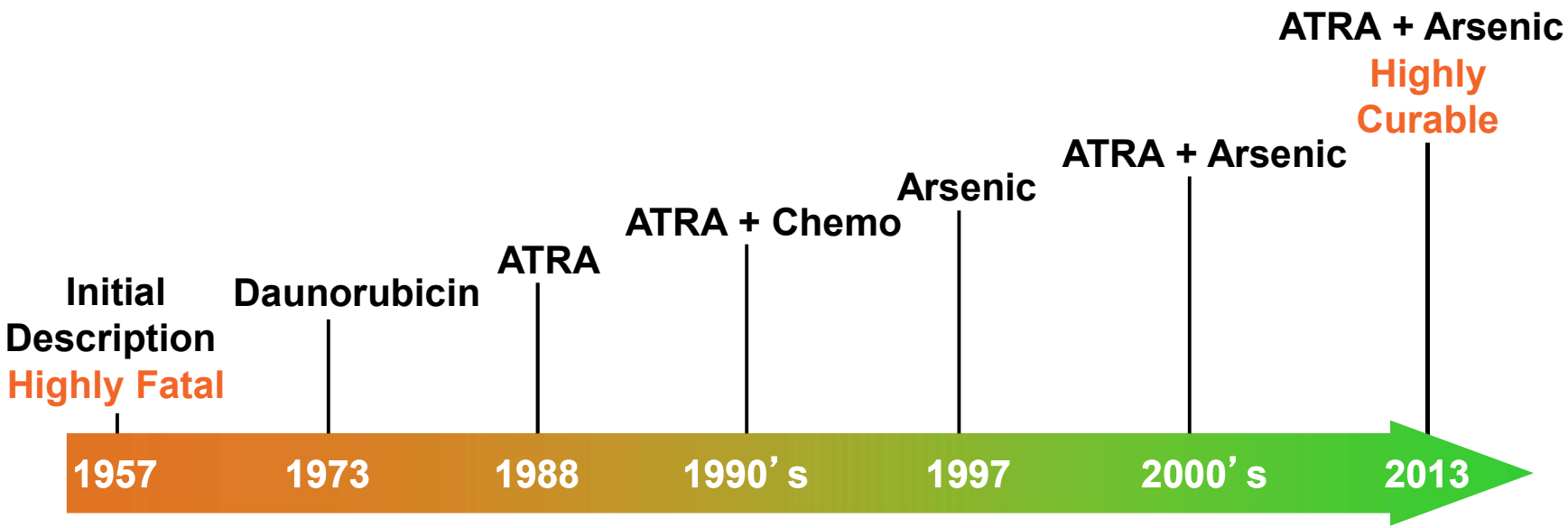
Acute Promyelocytic Leukemia: Another Pseudoleukemia?

"Perhaps combinations of agents such as trans-retinoic acid and a-interferon" will enhance treatment results in acute promyelocytic leukemia in the future. Another pseudoleukemia could be on the way out".

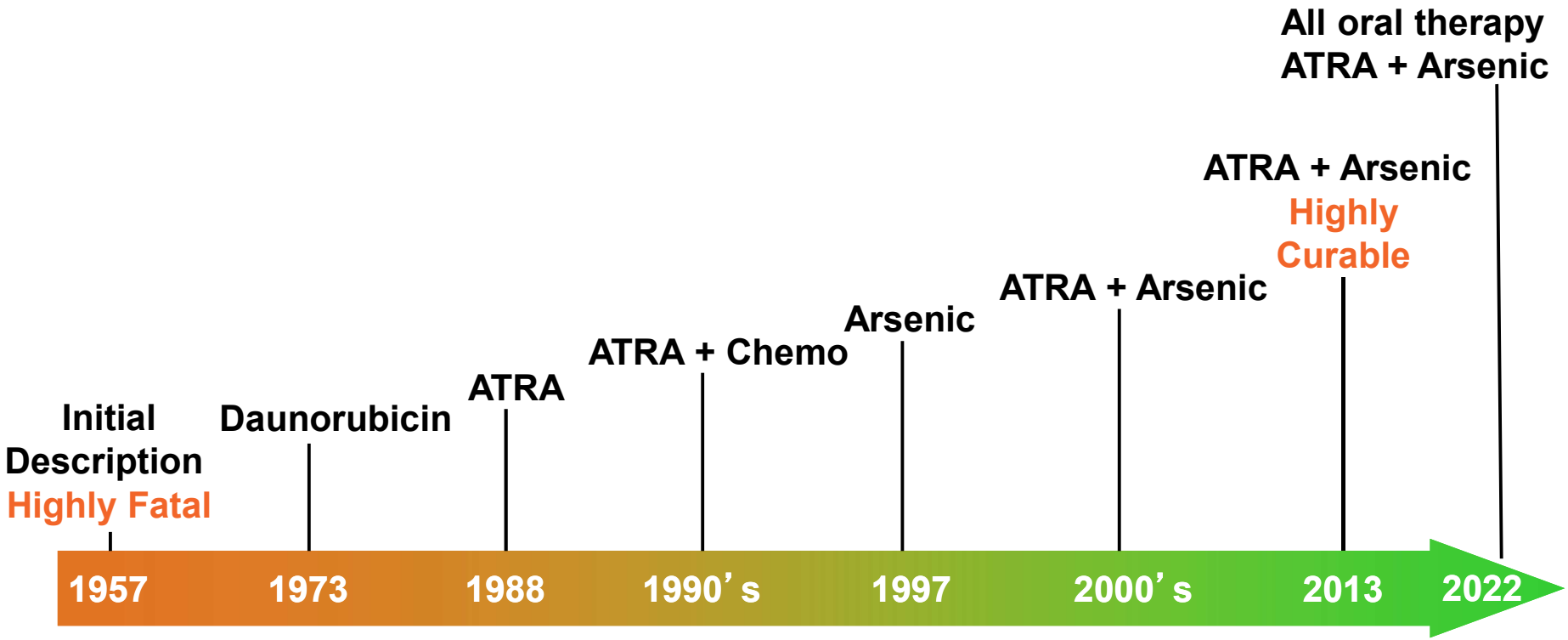
Peter H. Wierrnik

Albert Einstein Cancer Center Bronx. *NY*

Milestones in the Development of Curative Strategies in APL



Milestones in the Development of Curative Strategies in APL



Acknowledgements

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Memorial Sloan Kettering Cancer Center

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International Consortium on Acute Leukemi

A 27-year-old man presents with oropharyngeal bleeding and is found to have multiple large ecchymoses on the upper and lower extremities. The white blood cell count is 35,000/uL and the platelets are 12,000/uL. A diagnosis of APL is made. The PML-RARalpha is detected. In addition, cytogenetics show a trisomy 8 and a FLT3-ITD mutation is present. Aggressive blood product support is initiated. Which of the following represents the best initial treatment approach?

a. ATRA plus ATO
b. ATRA plus ATO plus idarubicin
c. ATRA plus ATO plus intermediate-dose ara-C
d. ATRA plus ATO plus intermediate-dose ara-C plus ida
e. A combination of ATRA, ATO and chemotherapy followed by hematopoietic cell transplantation

Discussion

This pt has high-risk APL since the presenting WBC is >10,000/uL. Among low-risk patients recent studies have shown that almost all patients can be cured with the combination of ATRA and ATO given without cytotoxic chemotherapy (Lococo et al. NEHM, 2013). Among high-risk patients, the highest cure rates appear to be obtained with ATRA, ATO and an anthracycline, commonly idarubicin (Iland et al. Blood, 2012). Gemtuzumab ozogamicin can be substituted for the idarubicin (Abaza et al. Blood, 2107). Successful induction in both low- and high-risk patients can be carried out without cytarabine. There is no role for either allogeneic nor autologous transplantation in APL. The only role for autologous transplantation is in molecular CR2 following reinduction for relapsed patients (Chakrabarty et al. BBMT, 2014. There is no major influence of additional cytogenetic abnormalities (Cervera et al. Haematologica, 20100. The same is believed to be true regarding FLT3-ITD mutations.