



Acute Promyelocytic Leukemia

BHS Course - Acute Leukemia – November 2025



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MBL– KUL/VIB

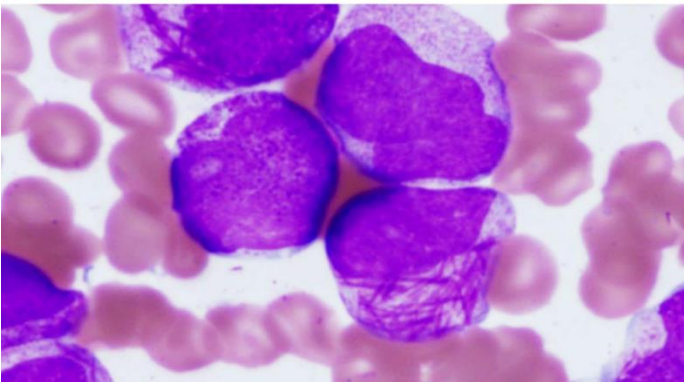


Emergency department

26 yo male patient
Spontaneous ecchymoses
Gingival bleeding
Petechiae
Weakness and effort dyspnoea

No other known disease

Bone Marrow: 80% myeloid blast infiltration



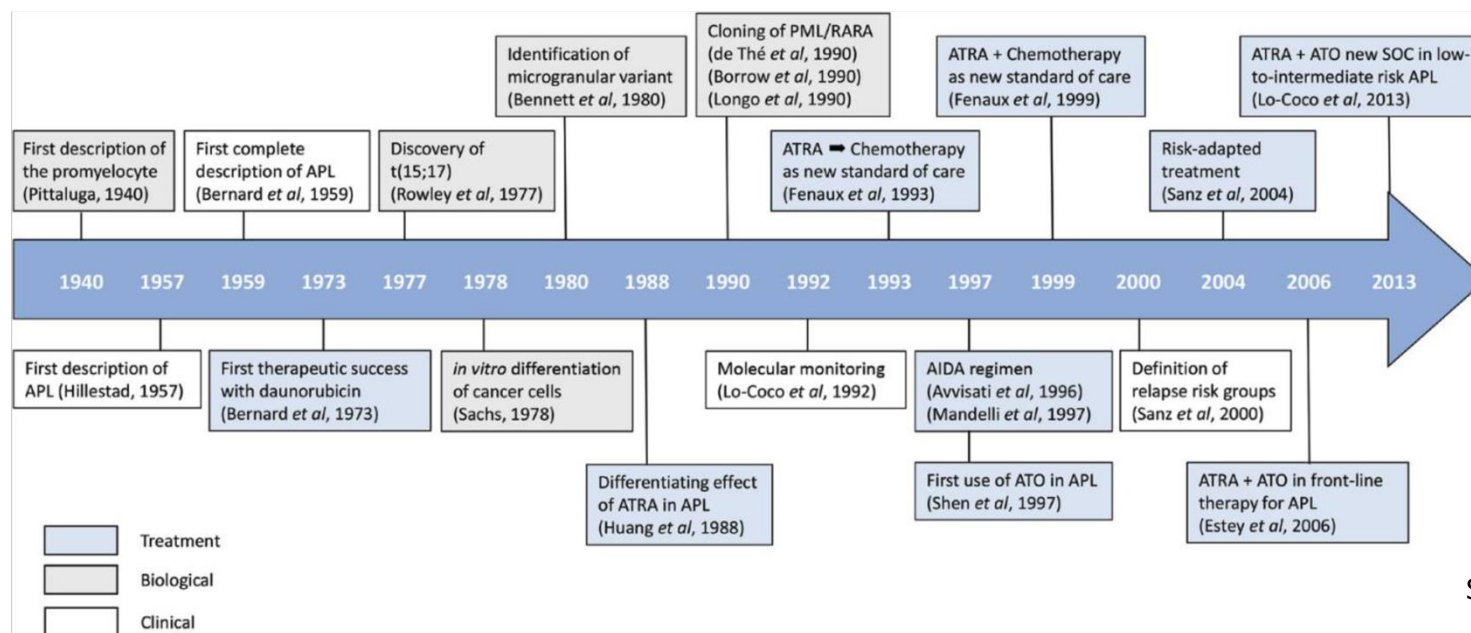
Hemoglobin	8.3 gr/dL
Platelets	54000/mcl
White blood cells	370/mcl
INR	1.5
aPTT	23 sec (NV 21.6 – 28.7 sec)
Fibrinogen	80 mg/dL
D-Dimer	15760 ng/mL

→ Acute Promyelocytic Leukemia



Acute Promyelocytic leukemia (APL)

- Distinct subtype of acute myeloid leukemia
- Medical Emergency – early recognition is crucial
- Particular morphological features (two different morphologies)
- PML-RAR α molecular hallmark
- APL is a model for target therapy (cure rates > 90%)



Acute Promyelocytic Leukemia.

By

LEIF K. HILLESTAD.

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

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

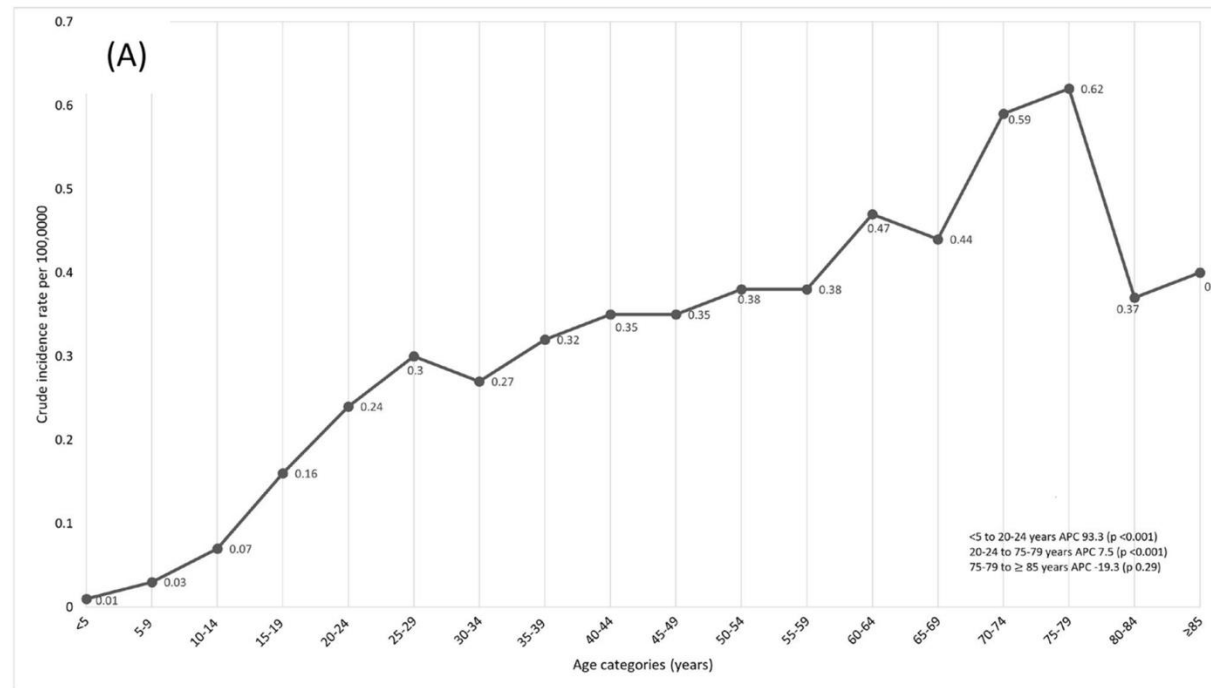
Evidence is presented for the existence of a special type of acute myelogenous leukemia. Three cases are described, characterized by 1) a very rapid fatal course of only a few weeks' duration, 2) a white blood cell picture dominated by promyelocytes, 3) a severe bleeding tendency due to fibrinolysis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

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



APL epidemiology

- 5 to 15 percent of cases of AML
- 0.32 new cases per 100,000 persons/ year in US
- Rare in childhood, increasing incidence from early adulthood
- May be secondary (15% in APL2006 trial)



Clinical Presentation

Symptoms related to **cytopenia**

Hemorrhagic findings (gingival bleeding, ecchymoses, epistaxis, or menorrhagia)

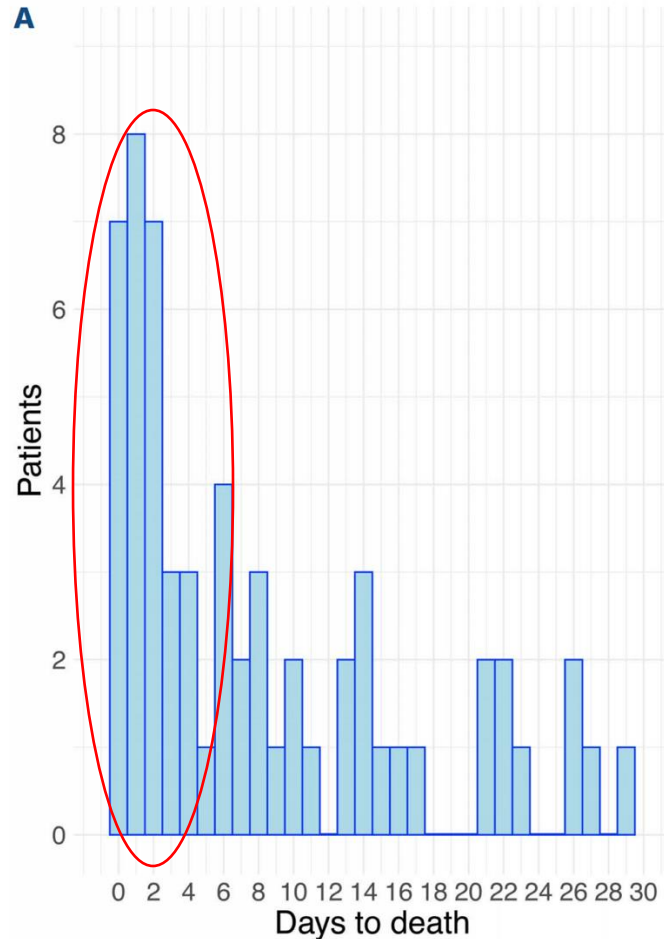
Thrombosis in about 5% of patients (cerebral, deep vein thrombosis, pulmonary embolism, and acute myocardial infarction).

Biological Work-up

Pancytopenia, low number of circulating blasts despite massive bone marrow infiltration.

Coagulopathy (PT, PTT frequently prolonged, low fibrinogen and elevated D-dimers)

Coagulopathy is responsible of early deaths in APL



Age at diagnosis

WBC	Age at diagnosis				Age at diagnosis			
	< 50	50 - 59	60 - 69	≥ 70	< 50	50 - 59	60 - 69	≥ 70
< 3.0 x 10 ⁹ /L	0	1	2	3	1	2	3	4
3.0 - 5.0 x 10 ⁹ /L	1	2	3	4	2	3	4	5
≥ 5.1 x 10 ⁹ /L	3	4	5	6	4	5	6	7

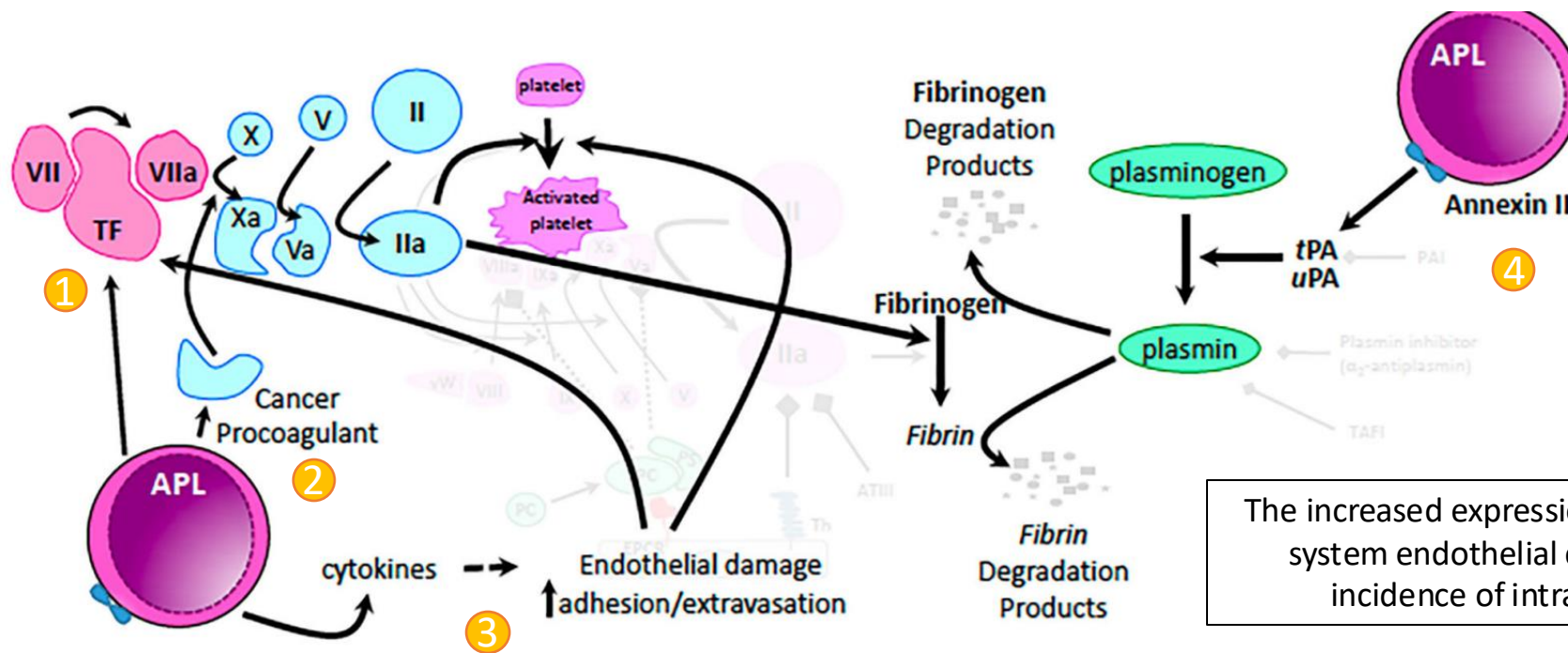
≥ 30 x 10⁹/L
< 30 x 10⁹/L

Platelets

Low risk	High risk	Very high risk
0 - 2 points	3 - 4 points	5 - 7 points
< 10 % predicted risk	10 - 30 % predicted risk	> 30 % predicted risk

Activation of Coagulation

Increased fibrinolysis



The increased expression of annexin II on central nervous system endothelial cells may contribute to the high incidence of intracerebral hemorrhage in APL

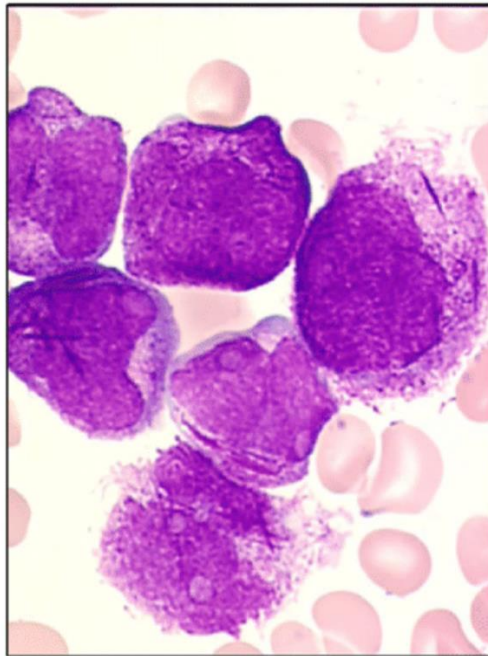
- 1- TF - **100-fold more expressed in APL than in other blasts!**
- 2- Cancer pro coagulant
- 3- Cytokines
- Massive amounts of IIa and consumptive coagulopathy.
- 4- Annexin II activates of tPA/uPA resulting in hyperfibrinolysis.

APL patients have significant lower WBC, higher D-dimers and lower Fibrinogen compared to other AML subtypes

Table 2. Comparison of the findings between APL patients and patients with other AML subtypes with DIC.

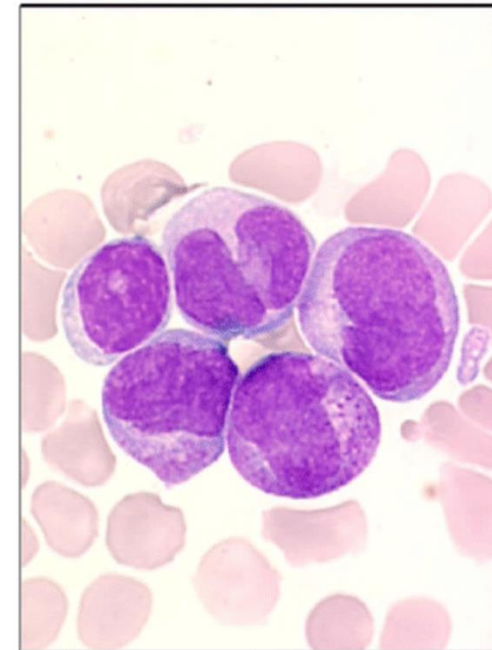
Variable	APL	Other AML subtype	<i>P</i>
Male/Female	5/9	9/6	0.272
Age (years)	49.3	57.5	0.23
WBC ($\times 10^9/L$)	14.988	70.755	0.015
Hb (g/dL)	8.03	7.36	0.412
Platelet ($\times 10^9/L$)	26.78	33.80	0.324
PT (s)	16.0	14.6	0.107
INR	1.43	1.26	0.071
aPTT (s)	28.7	29.6	0.691
FDP ($\mu g/mL$)	77.7	23.7	0.026
D-dimer (ng/mL)	7,376.2	1,315.2	0.018
Fibrinogen (mg/dL)	133.8	373.2	<0.001
LDH (U/L)	838.9	1,022.3	0.565
AST (U/L)	27.9	38.1	0.393
ALT (U/L)	21.0	36.3	0.305
Total bilirubin (mg/dL)	0.77	0.96	0.294
BUN (mg/dL)	16.6	21.1	0.518
Cr (mg/dL)	0.98	1.48	0.123
Triglyceride (mg/dL)	206.2	109.9	0.006
Cholesterol (mg/dL)	159	112	0.001
Fe ($\mu g/dL$)	135.4	120.0	0.469
TIBC ($\mu g/dL$)	264.4	206.8	0.046
Ferritin (ng/mL)	776.6	1,282.1	0.70
Transferrin (g/L)	1.79	1.29	0.005
CRP (mg/dL)	4.79	7.43	0.323
ESR (mm/h)	7.1	50.0	<0.001

75% typical (macrogranular) – M3



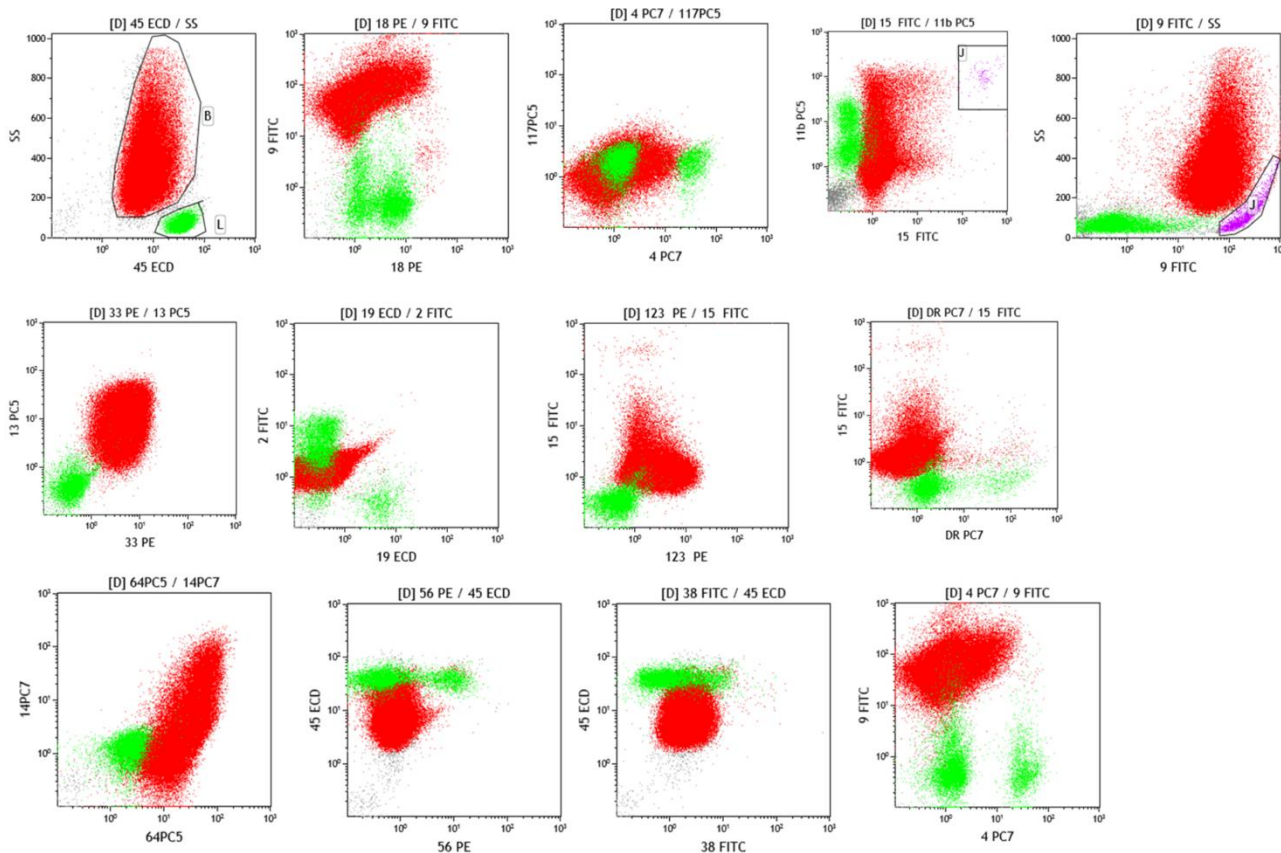
Low white blood cell count
Reniform nuclei
Purple granulations and Auer rods, faggots

25% microgranular variant – M3v



Higher white blood cell count
Reniform nuclei
Few granulations (better seen at electronic microscope)

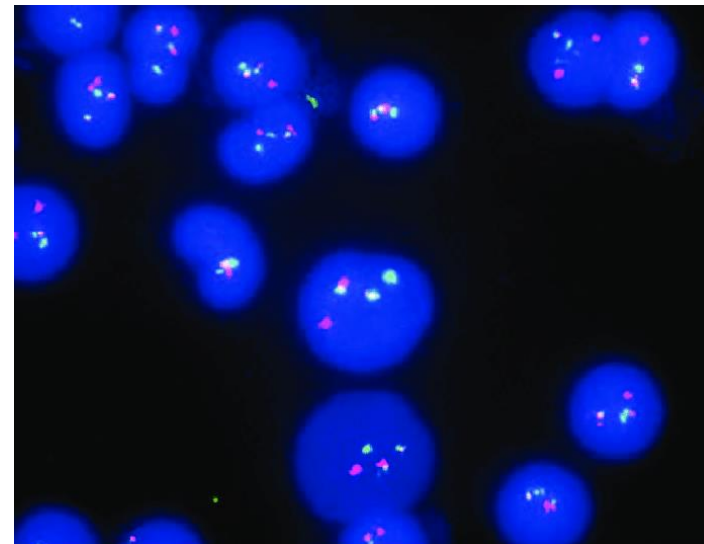
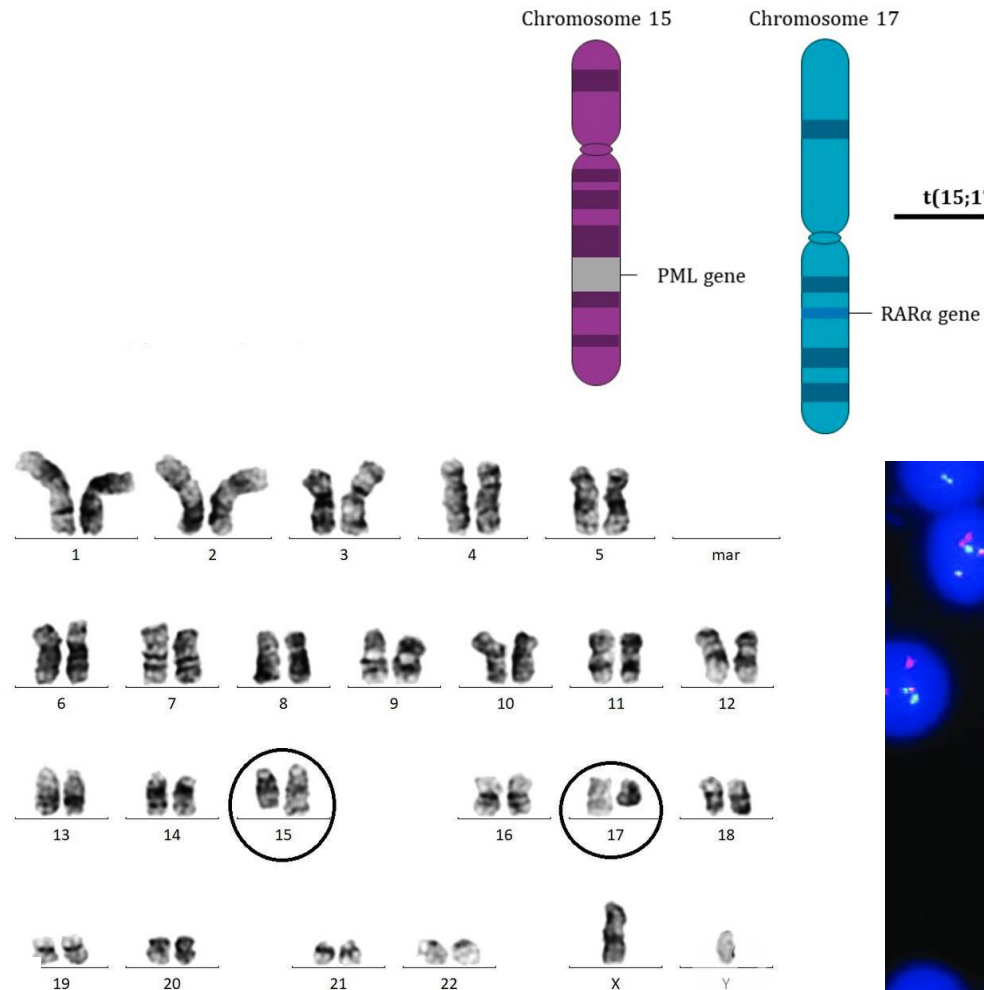
CD34-/partial or weak +, HLA-DR -, CD13+, CD33+, CD11b-, CD15-, CD117 weak/variable, MPO+.



100% sensitivity and 99% specificity for APL

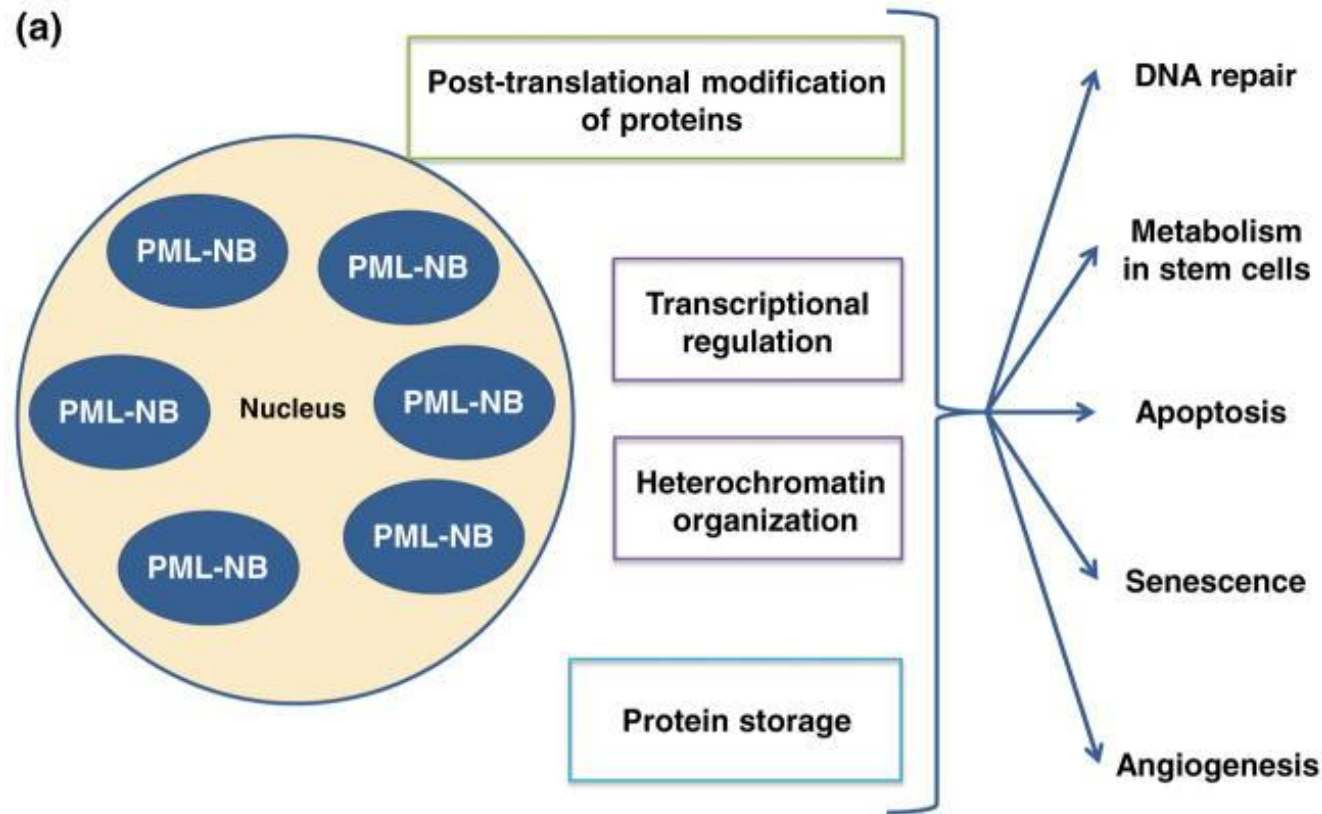
CD33 targetable with Gemtuzumab Ozogamicin

Translocation t(15;17)(q24;q21)

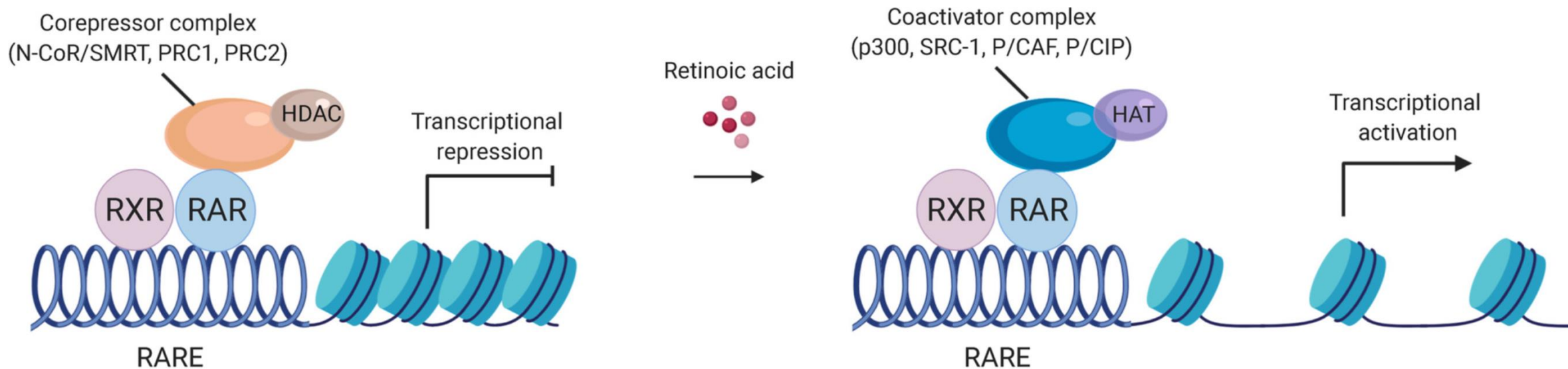


PML
RAR α
PML/RAR α

PML proteins multimerize to form multi-protein sub-nuclear structures called PML-nuclear bodies



RAR α promotes transcriptional activation and myeloid differentiation in physiological conditions



Myeloid differentiation

Physiological role of PML

Physiological role of RAR α

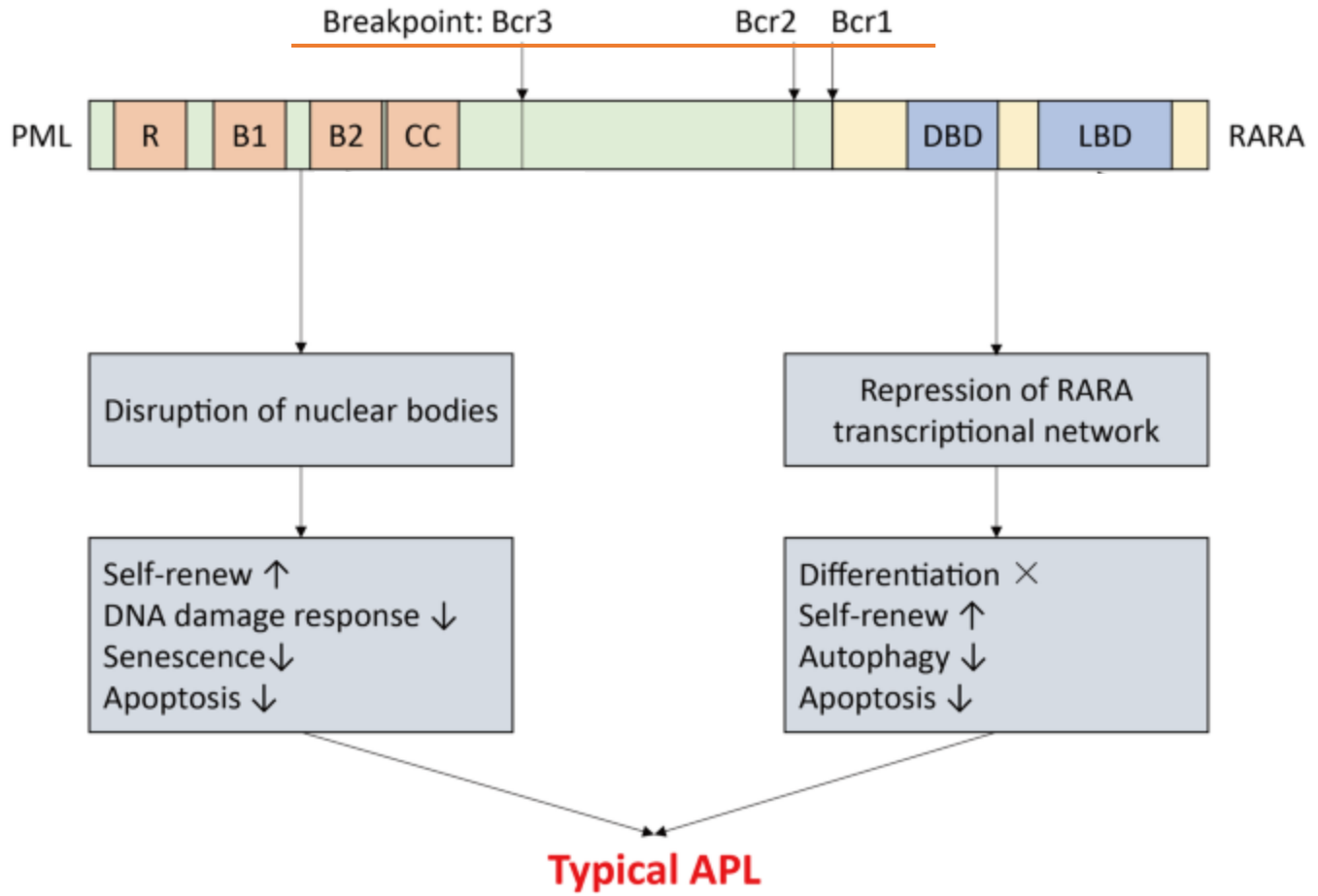
Fusion PML/RAR α

MRD Marker

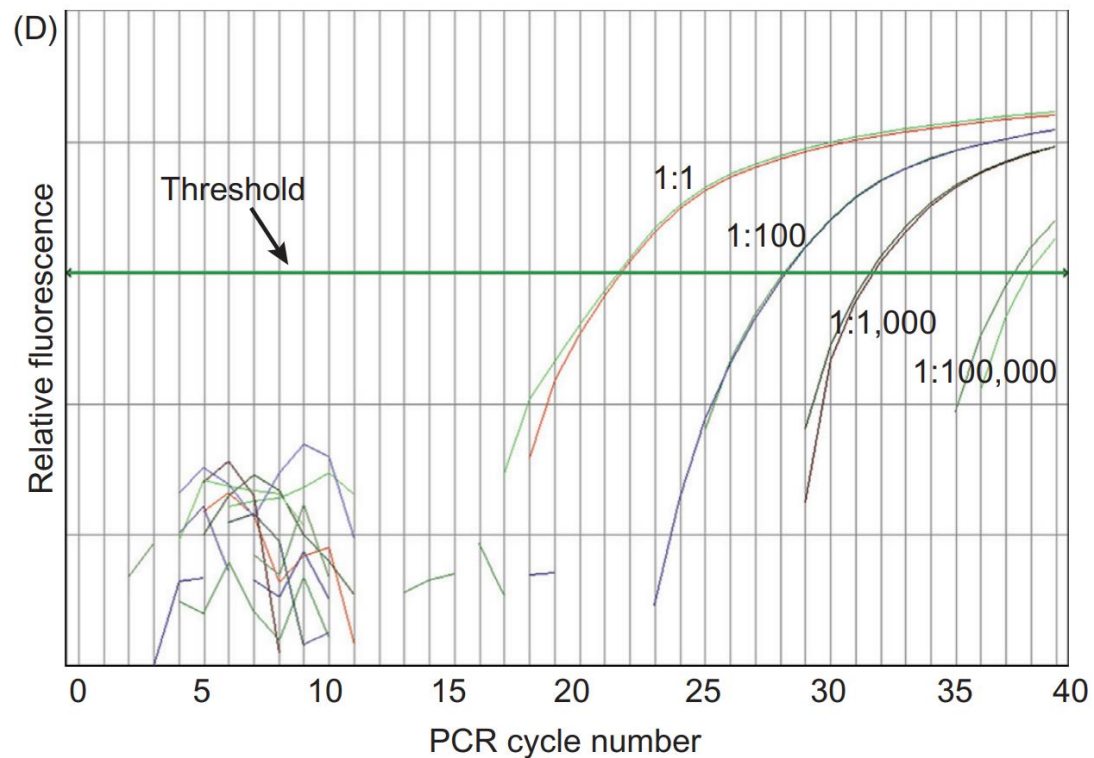
APL Variants

Associated Mutations

PML-RARA/t(15;17)



PML/RAR α as marker of Minimal Residual Disease (MRD)

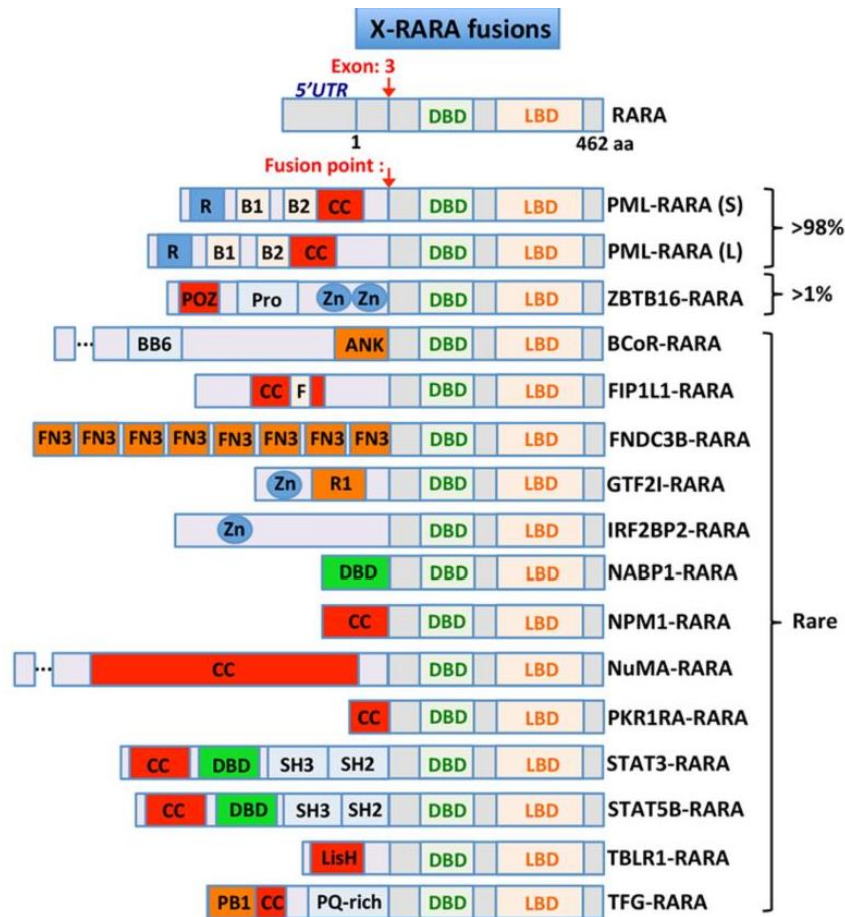


Behdad and Betz, Diagnostic Molecular Pathology 2017

PML-RAR α

- Unique to APL (disease hallmark)
- Strongly correlated with pathogenesis
- Ideal marker for residual disease monitoring
- Targeted by specific therapies

APL variants



Associated mutations

FLT3 – ITD

Confers R to ATRA-induced differentiation, abrogated with ATO

More likely to present with high white blood count

WT1 mutation

In association with FLT3mut, worsens prognosis

Anthracyclines

ATRA

ATRA + Chemo

ATO

ATRA-ATO in No HR APL

ATRA-ATO +/- chemo in HR APL

APL Treatment Evolution, moving towards a chemo-free strategy

- Anthracyclines
- ATRA
- ATRA + Chemotherapy (IDA)
- ATO
- ATRA+ ATO in non-high risk patients
- ATRA+ ATO+/- chemo (GO/IDA) and ATRA-ATO in all and **high** risk APL

Anthracyclines as APL treatment



BLOOD

The Journal of Hematology

VOL. XLI, NO. 4

APRIL 1973

Acute Promyelocytic Leukemia: Results of Treatment by Daunorubicin

By Jean Bernard, Marise Weil, Michel Boiron, Claude Jacquillat,
Georges Flandrin, and Marie-François Gemon

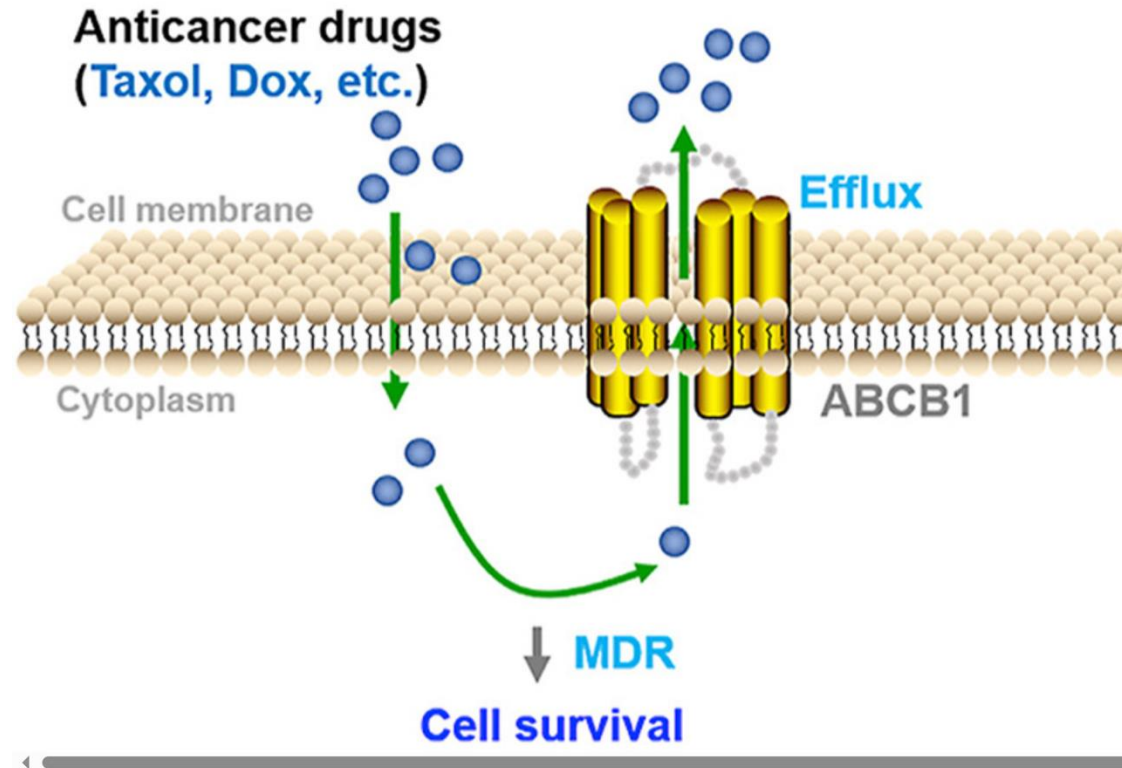
Jean Bernard: Daunorubicin + massive platelet transfusions

- Up to 80% CR, 40 to 50% prolonged CR
- High sensitivity of APL to **anthracyclines**

British Journal of Haematology, 1995, 90, 369-374

Low incidence of MDR1 expression in acute promyelocytic leukaemia

DORIS DRACH, SHOURONG ZHAO, JOHANNES DRACH AND MICHAEL ANDREEFF *Department of Hematology, Section of Experimental Hematology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, U.S.A.*



Anthracyclines

ATRA

ATRA + Chemo

ATO

ATRA-ATO in No HR APL

ATRA-ATO +/- chemo in HR APL

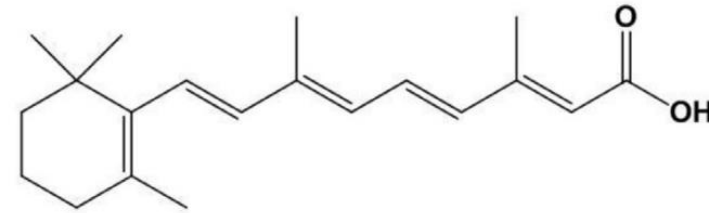
All-trans retinoic acid (ATRA)

➤ Vitamin A derivative, differentiation induction

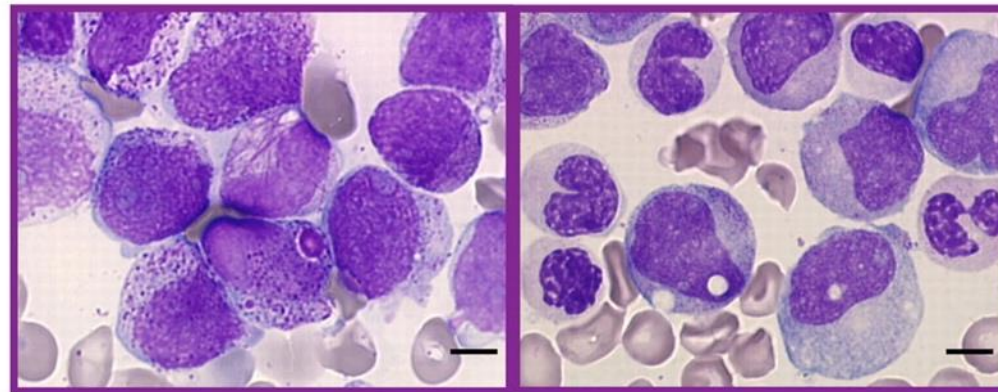
➤ 1988: All transretinoic acid (ATRA)

➤ 90% complete remissions, through differentiation of APL cells

➤ No long-lasting CR, relapsed within a few months, despite continuous ATRA treatment



ATRA



Untreated

Differentiation by RA

Continuous Treatment With All-Trans Retinoic Acid Causes a Progressive Reduction in Plasma Drug Concentrations: Implications for Relapse and Retinoid “Resistance” in Patients With Acute Promyelocytic Leukemia

By Josephia Muindi, Stanley R. Frankel, Wilson H. Miller Jr, Ann Jakubowski, David A. Scheinberg, Charles W. Young, Ethan Dmitrovsky, and Raymond P. Warrell Jr

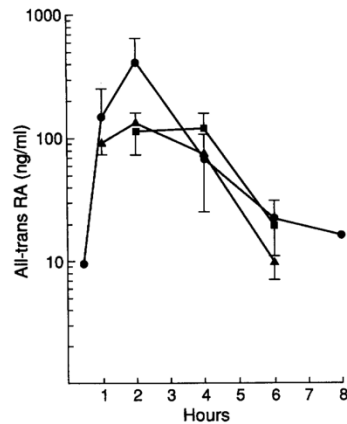


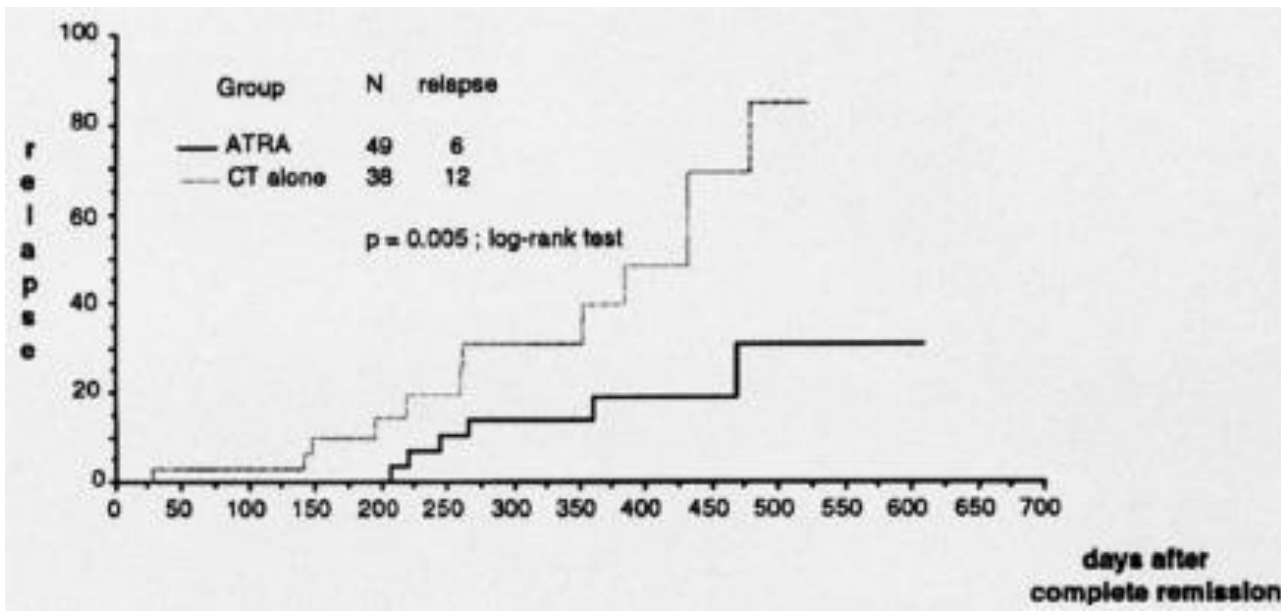
Fig 1. Plasma concentrations (\pm SEM) of all-trans RA after the administration of a single oral dose (45 mg/m²) on day 1 of treatment in three patients (●), at the time of relapse (Δ), and at relapse (■) after treatment with a single dose of 90 mg/m². The calculated plasma AUC concentrations were significantly lower at the time of relapse compared with day 1 and were not increased despite the twofold escalation in dose.

Decrease in ATRA plasma levels in prolonged administration.
 ATRA induces increase of CytP450 which catabolises ATRA.

- ATRA-Chemotherapy combination
- ATRA **intermittently** administered

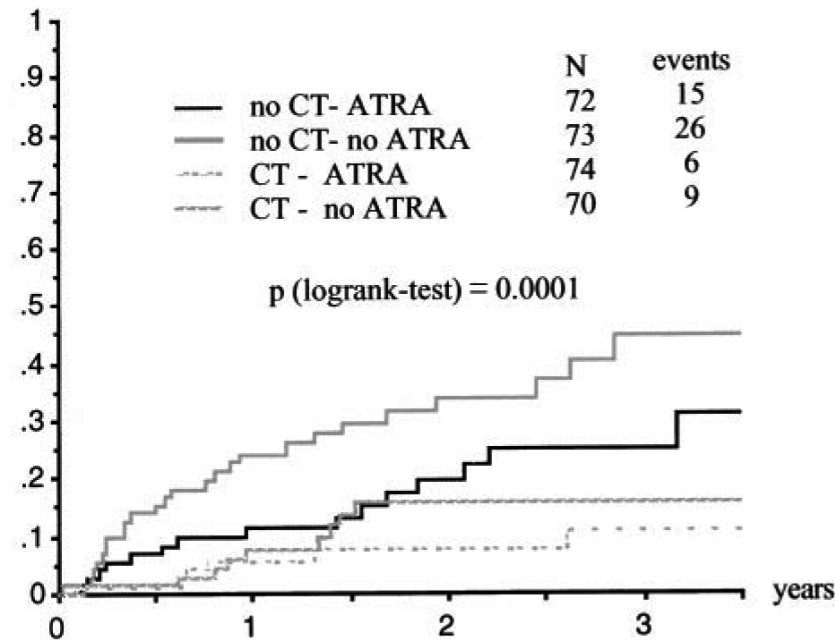
ATRA + Chemotherapy

- 1991: ATRA+ chemotherapy better than chemotherapy alone
- 90% CR, 25 % relapses



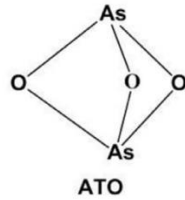
Maintenance with ATRA

➤ 1997: maintenance treatment with ATRA and low dose chemotherapy reduces relapses

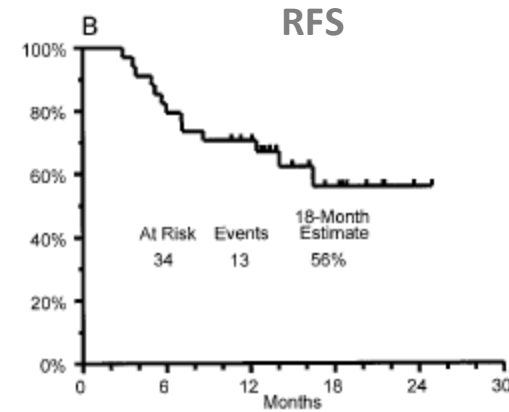
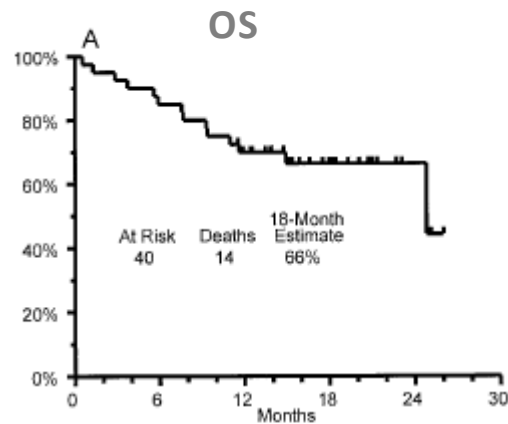


Relapse according to maintenance treatment group

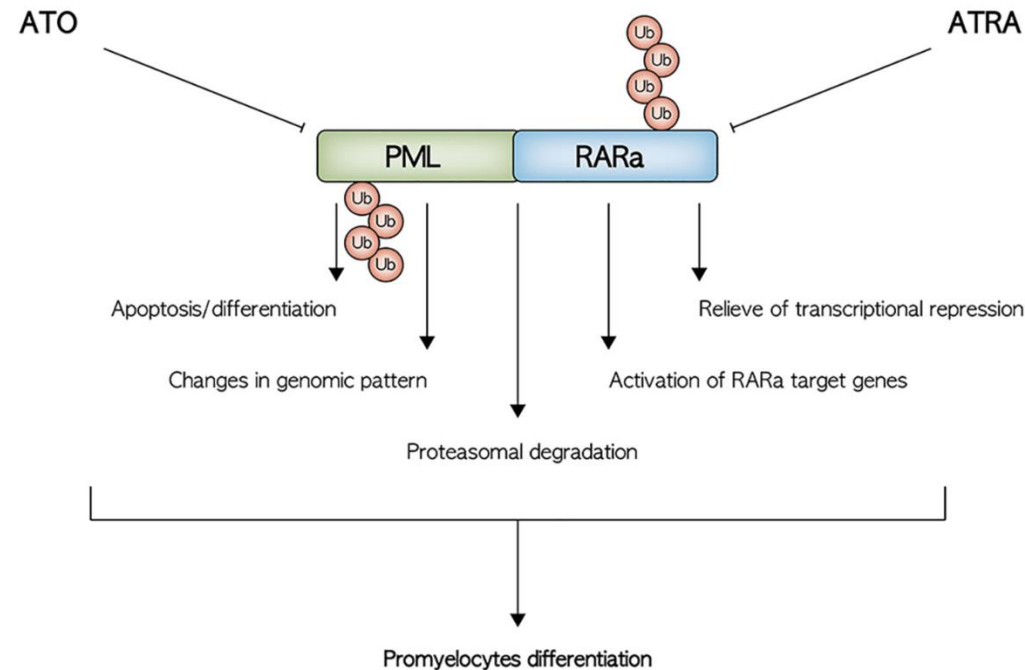
Arsenic trioxide (ATO) in APL



- High efficacy of ATO in APL reported in 1992 by a Chinese study, confirmed in a randomized US study
- Approved by FDA for relapsed APL in 2000



- ATRA and ATO both degrade PML/RARA
 - ATRA degrades PML/RARA through its RARa moiety and relieve transcriptional repression
 - ATO degrades PML/RARA through its PML moiety

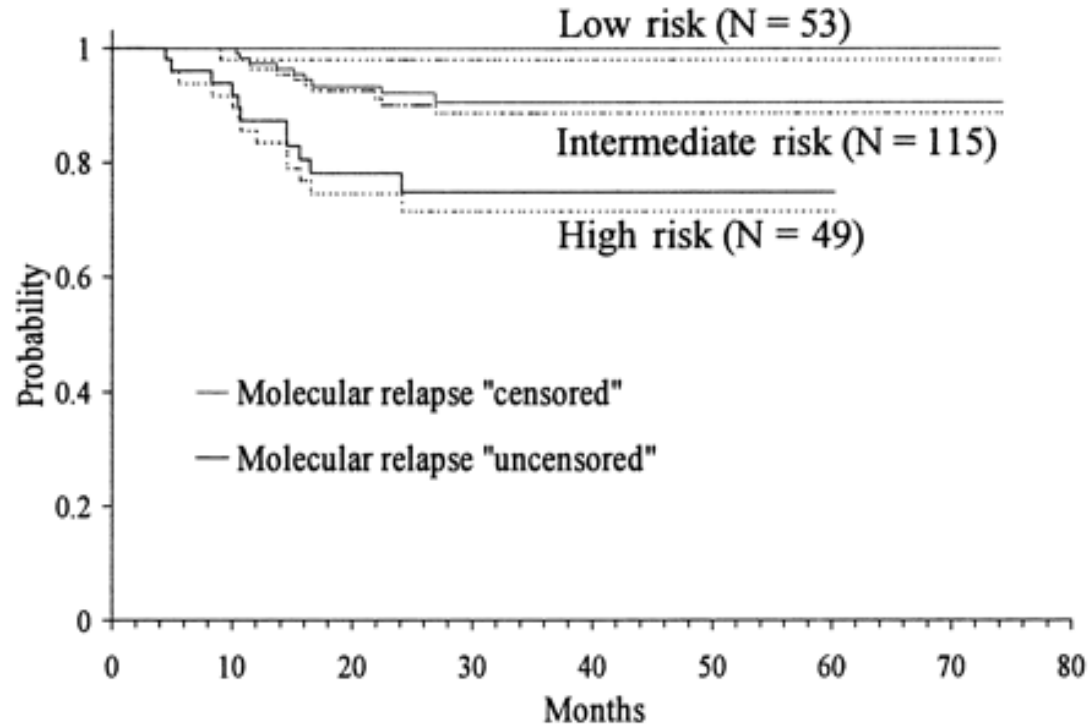


Risk-assessment, "Sanz-score"

➤ **High risk:**
WBC >10.000/mm³

➤ **Int risk:**
WBC < 10.000/mm³
Platelets <40.000/mm³

➤ **Low risk:**
WBC < 10.000/mm³ and
Platelets >40.000/mm³



APL0406 randomized trial for NON-high risk patients



ESTABLISHED IN 1812

JULY 11, 2013

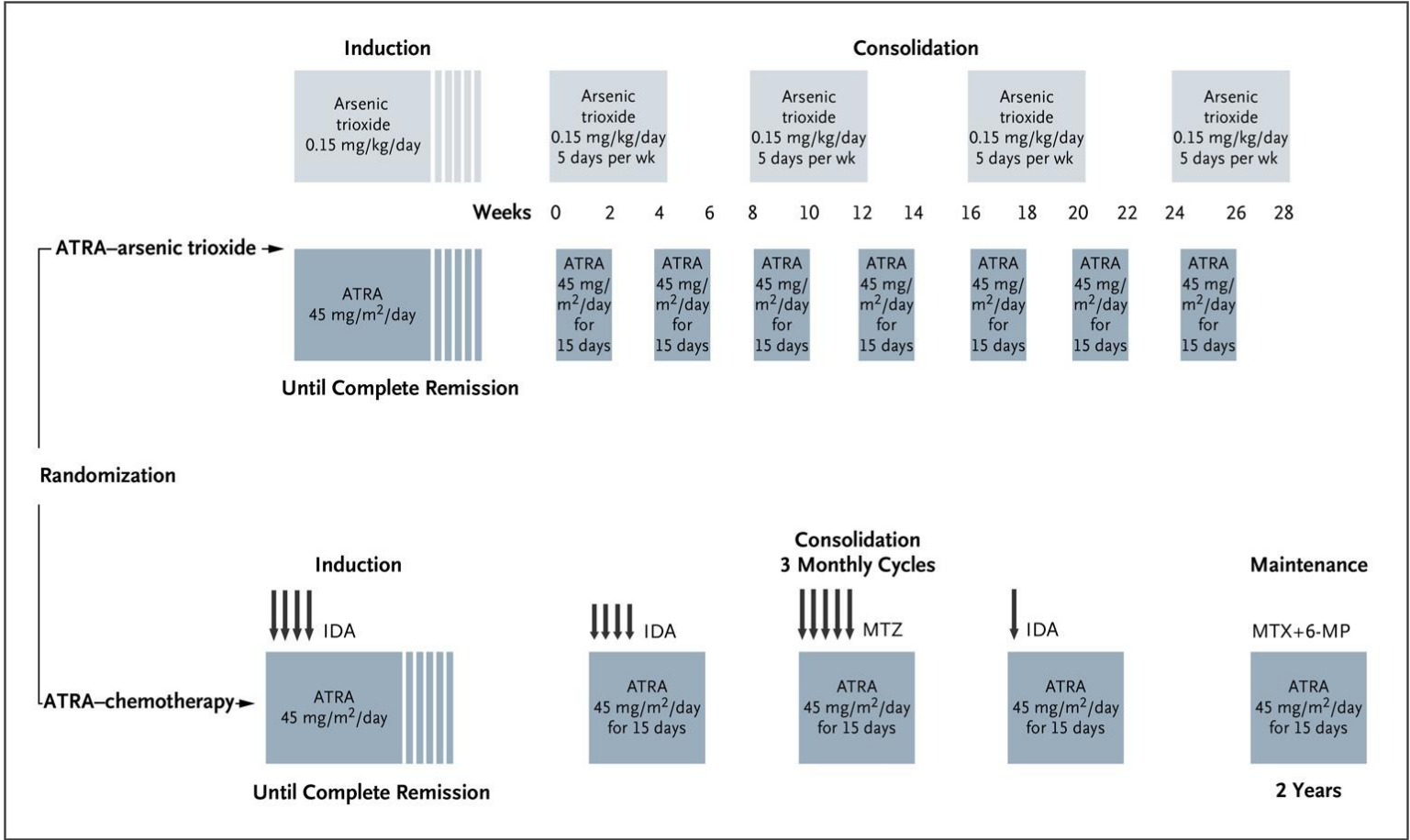
VOL. 369 NO. 2

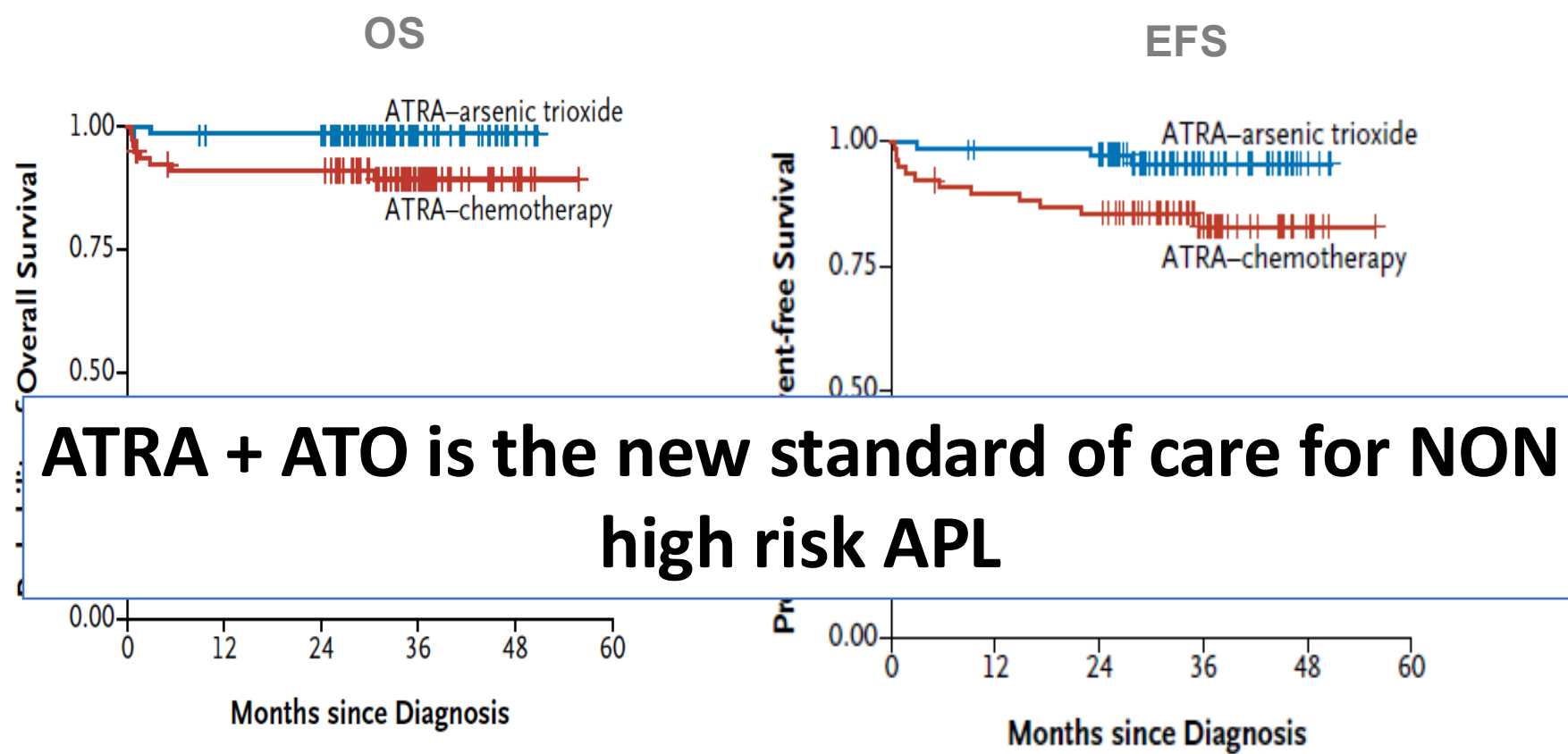
Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia

F. Lo-Coco, G. Avvisati, M. Vignetti, C. Thiede, S.M. Orlando, S. Iacobelli, F. Ferrara, P. Fazi, L. Cicconi, E. Di Bona, G. Specchia, S. Sica, M. Divona, A. Levis, W. Fiedler, E. Cerqui, M. Breccia, G. Fioritoni, H.R. Salih, M. Cazzola, L. Melillo, A.M. Carella, C.H. Brandts, E. Morra, M. von Lilienfeld-Toal, B. Hertenstein, M. Wattad, M. Lübbert, M. Hänel, N. Schmitz, H. Link, M.G. Kropp, A. Rambaldi, G. La Nasa, M. Luppi, F. Ciceri, O. Finizio, A. Venditti, F. Fabbiano, K. Döhner, M. Sauer, A. Ganser, S. Amadori, F. Mandelli, H. Döhner, G. Ehninger, R.F. Schlenk, and U. Platzbecker for Gruppo Italiano Malattie Ematologiche dell'Adulto, the German–Austrian Acute Myeloid Leukemia Study Group, and Study Alliance Leukemia

APL0406 randomized trial for NON-high risk patients ATRA-ATO versus AIDA

APL
Low/intermediate Sanz
risk
(WBC $\leq 10 \times 10^9/L$)





NON-high risk patients

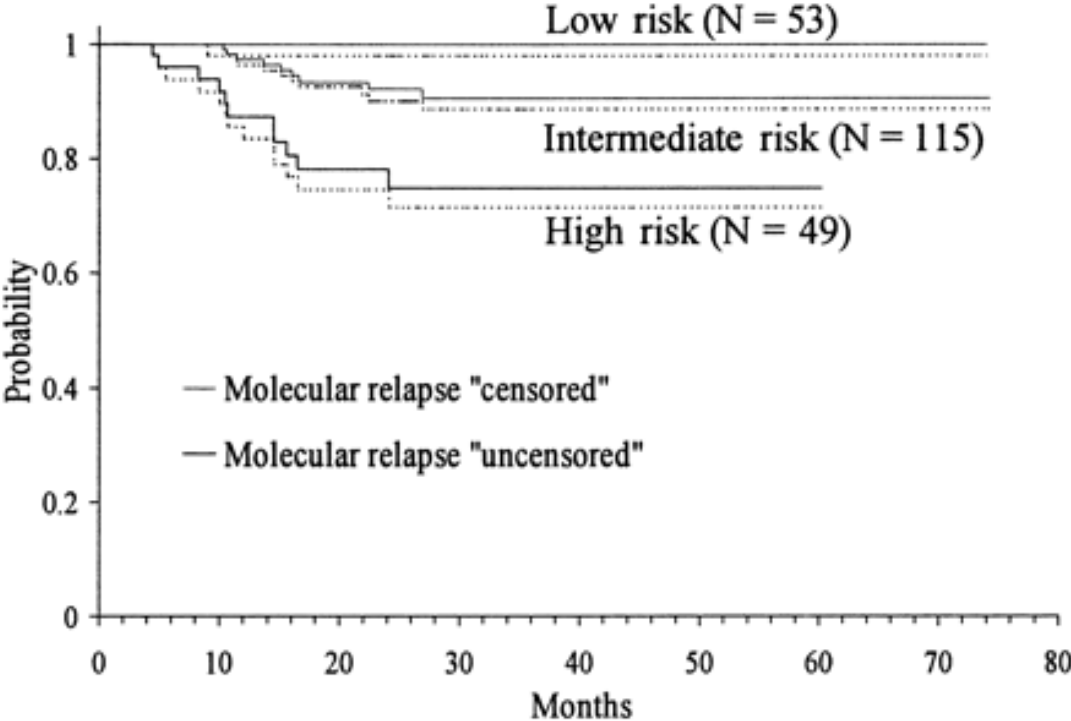
ATRA + ATO is at least not inferior and may be superior to ATRA + CHT in the treatment of patients with low-to-intermediate-risk APL

Advantage in terms of EFS, relapse rate and OS at 50 mo in final analysis (276 pts)

Risk-assessment, "Sanz-score"

➤ **High risk:**
WBC >10.000/mm³

➤ **Int risk:**
Concerns about higher possibility of induction mortality due to increased risk of fluid overload, differentiation syndrome, respiratory failure, disseminated intravascular coagulation (DIC), and severe bleeding.



All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4)

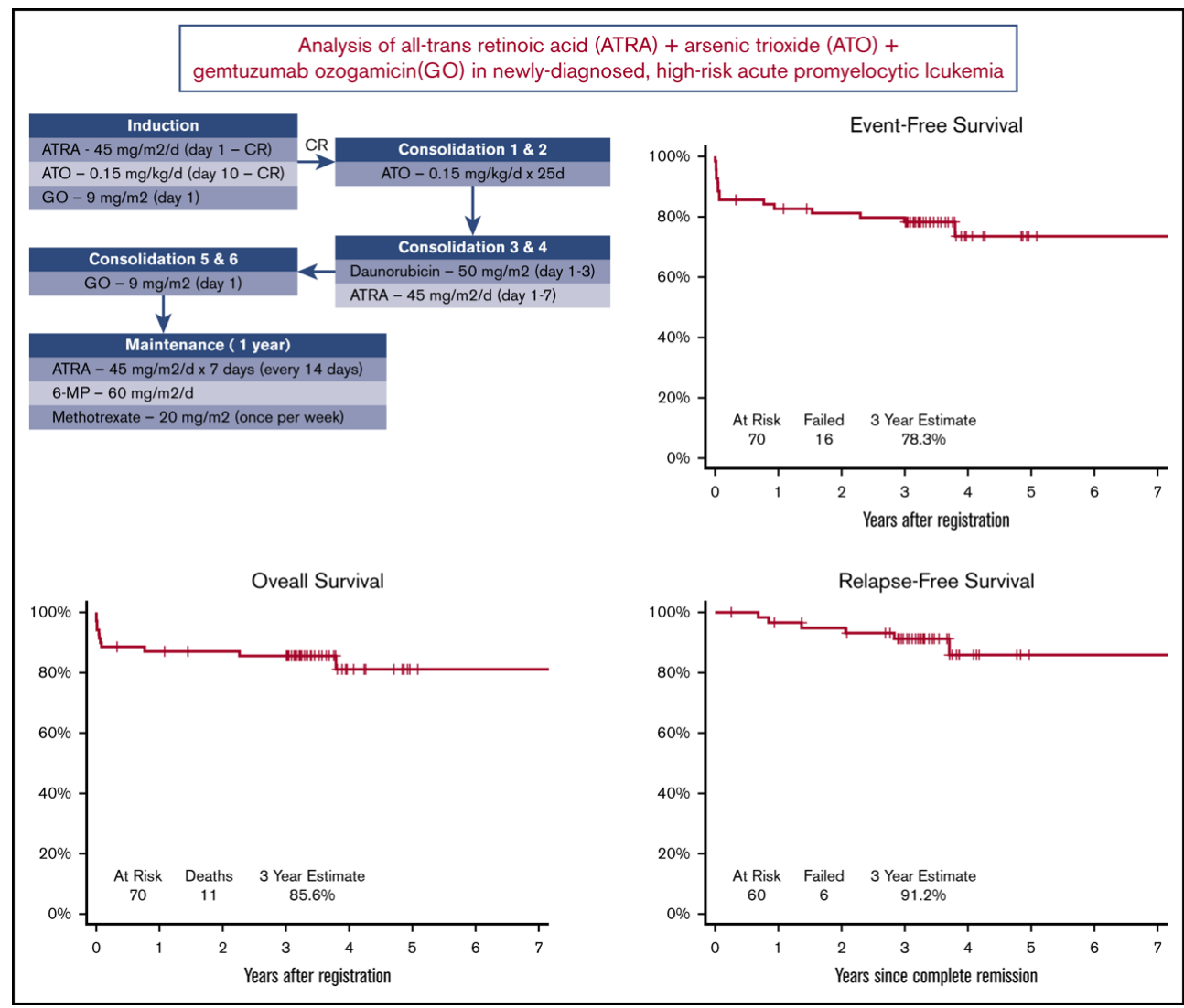
Harry J. Iland,^{1,2} Ken Bradstock,^{2,3} Shane G. Supple,¹ Alberto Catalano,¹ Marnie Collins,⁴ Mark Hertzberg,^{2,3} Peter Browett,⁵ Andrew Grigg,^{6,7} Frank Firkin,^{7,8} Amanda Hugman,¹ John Reynolds,⁴ Juliana Di Iulio,⁴ Campbell Tiley,^{9,10} Kerry Taylor,¹¹ Robin Filshie,^{7,8} Michael Seldon,^{10,12} John Taper,¹³ Jeff Szer,^{6,7} John Moore,^{14,15} John Bashford,¹⁶ and John F. Seymour,^{4,7} for the Australasian Leukaemia and Lymphoma Group

Table 1. Components of the APML4 protocol

Induction		
ATRA	45 mg/m ² /d PO	Days 1-36 in divided doses
Idarubicin	12 mg/m ² /d IV (ages 1-60) 9 mg/m ² /d IV (ages 61-70) 6 mg/m ² /d IV (ages > 70)	Days 2, 4, 6, and 8
ATO	0.15 mg/kg/d IV	Days 9-36 as a 2-hour IV infusion Supplemental potassium and magnesium as required to maintain serum levels in the upper half of the respective normal ranges
Prednisone	1 mg/kg/d PO	Days 1-10 or until WBC count falls below 1 × 10 ⁹ /L or until resolution of differentiation syndrome (whichever occurs last)
Hemostatic support	Products administered once or twice daily as required to achieve specified targets	Platelets > 30 × 10 ⁹ /L Normal prothrombin time Normal activated partial thromboplastin time Fibrinogen > 1.5 g/L
Consolidation cycle 1 (3-4 wks after the end of induction)		
ATRA	45 mg/m ² /d PO	Days 1-28
ATO	0.15 mg/kg/d IV	Days 1-28
Consolidation cycle 2 (3-4 wks after the end of consolidation cycle 1)		
ATRA	45 mg/m ² /d PO	Days 1-7, 15-21, 29-35
ATO	0.15 mg/kg/d IV	Days 1-5, 8-12, 15-19, 22-26, 29-33
Maintenance: 8 cycles (3-4 wks after the end of consolidation cycle 2)		
ATRA	45 mg/m ² /d PO	Days 1-14
MTX	5-15 mg/m ² /wk PO	Days 15-90
6MP	50-90 mg/m ² /d PO	Days 15-90

PO indicates oral administration.

Excellent outcomes despite a substantial reduction in anthracycline exposure.



Anthracyclines

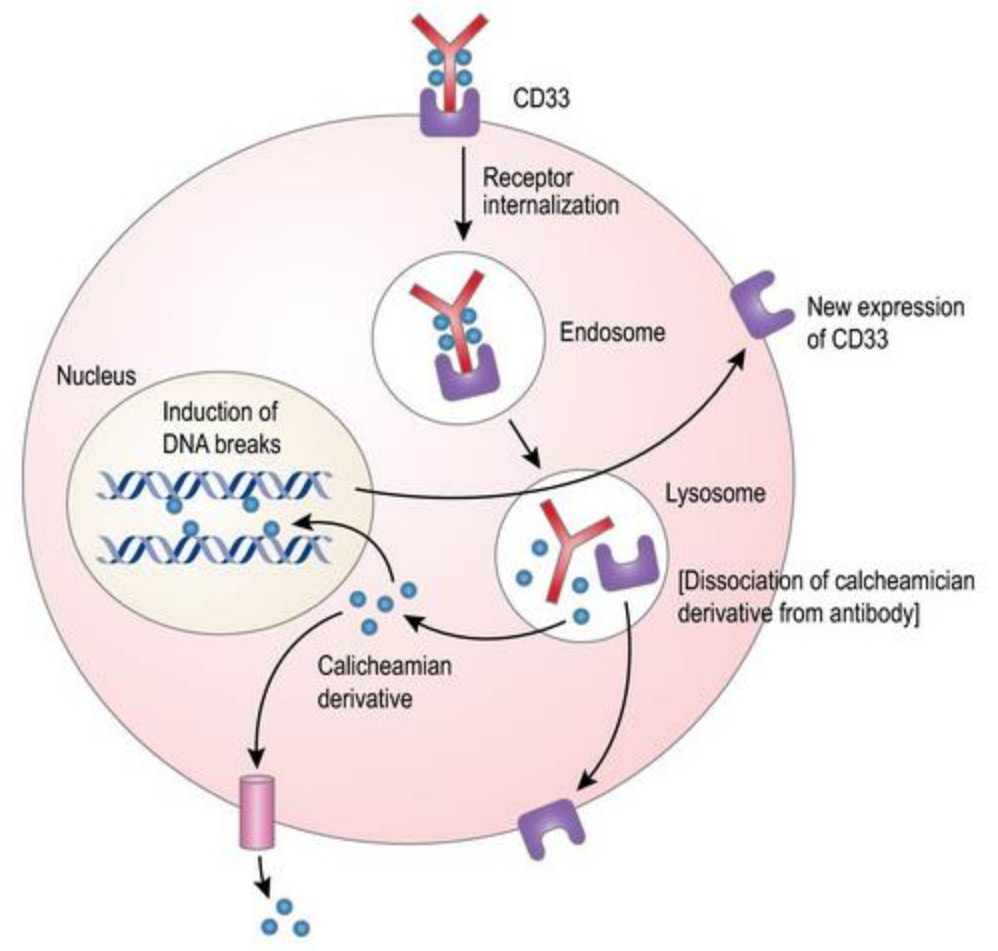
ATRA

ATRA + Chemo

ATO

ATRA-ATO in No HR APL

ATRA-ATO +/- chemo in HR APL



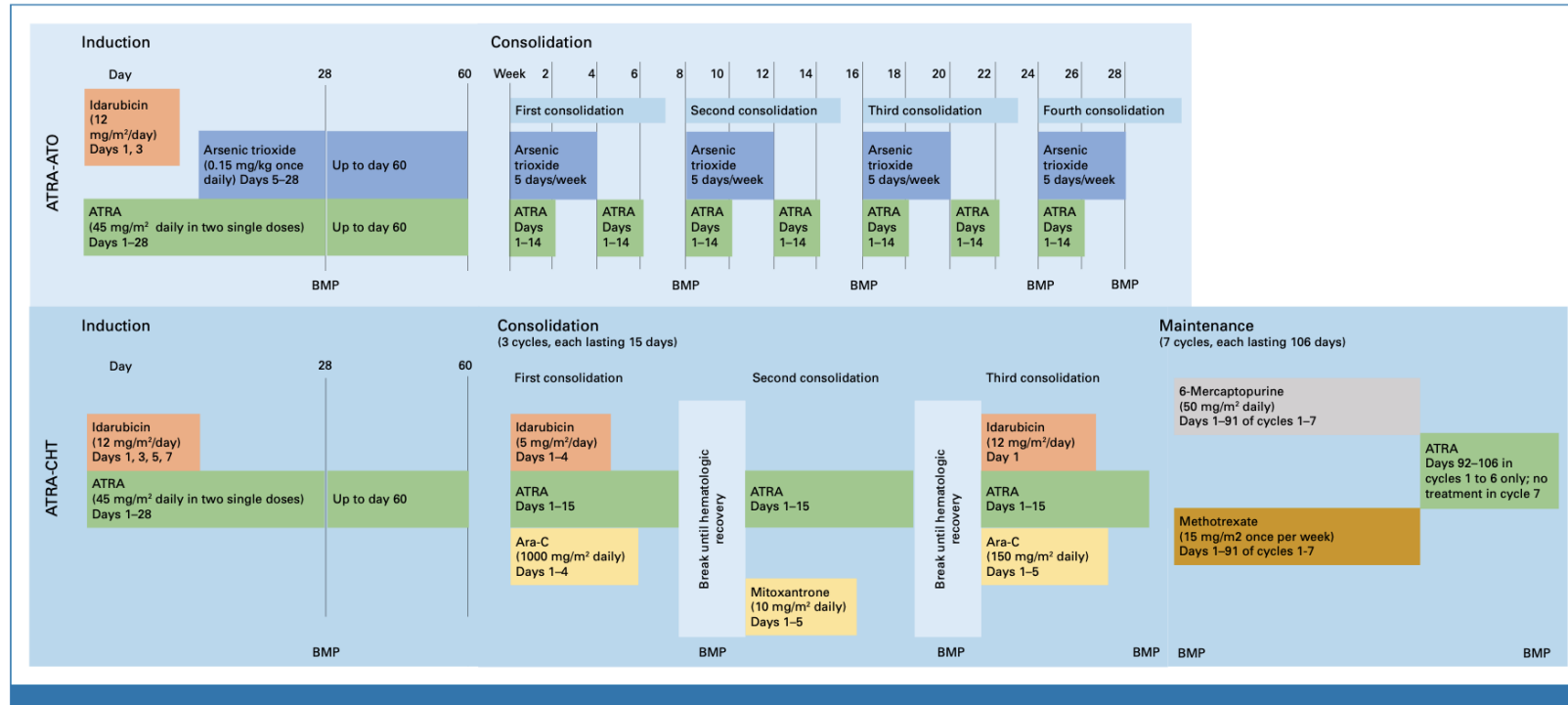
Gemtuzumab Ozogamicin

	Gemtuzumab ozogamicin		CD33
	Calicheamicin		P-gp (plasm glycoprotein efflux pump)

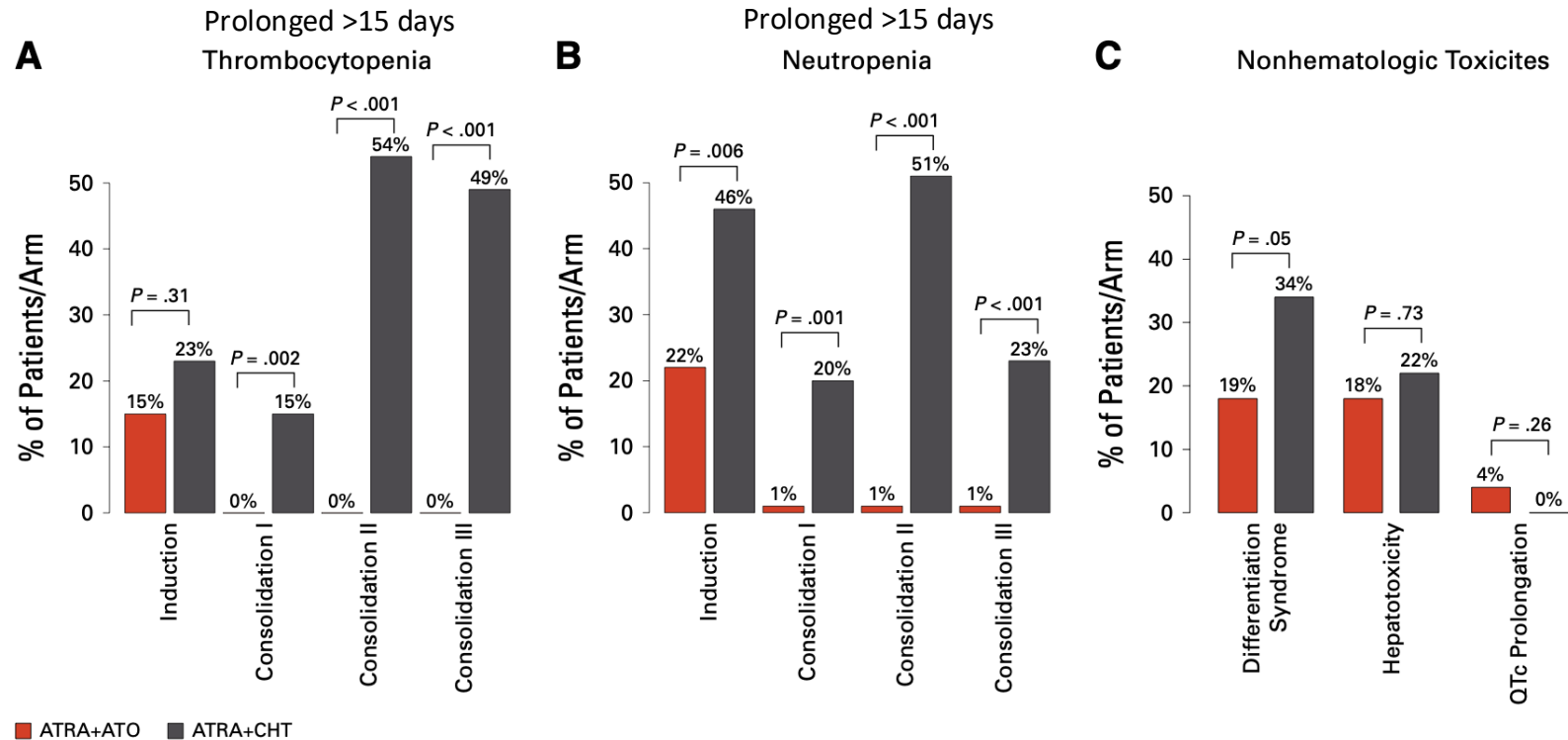
ADVANCES IN CELL AND GENE THERAPY

Boddu et Ravandi Adv Cell Gene Ther 2018

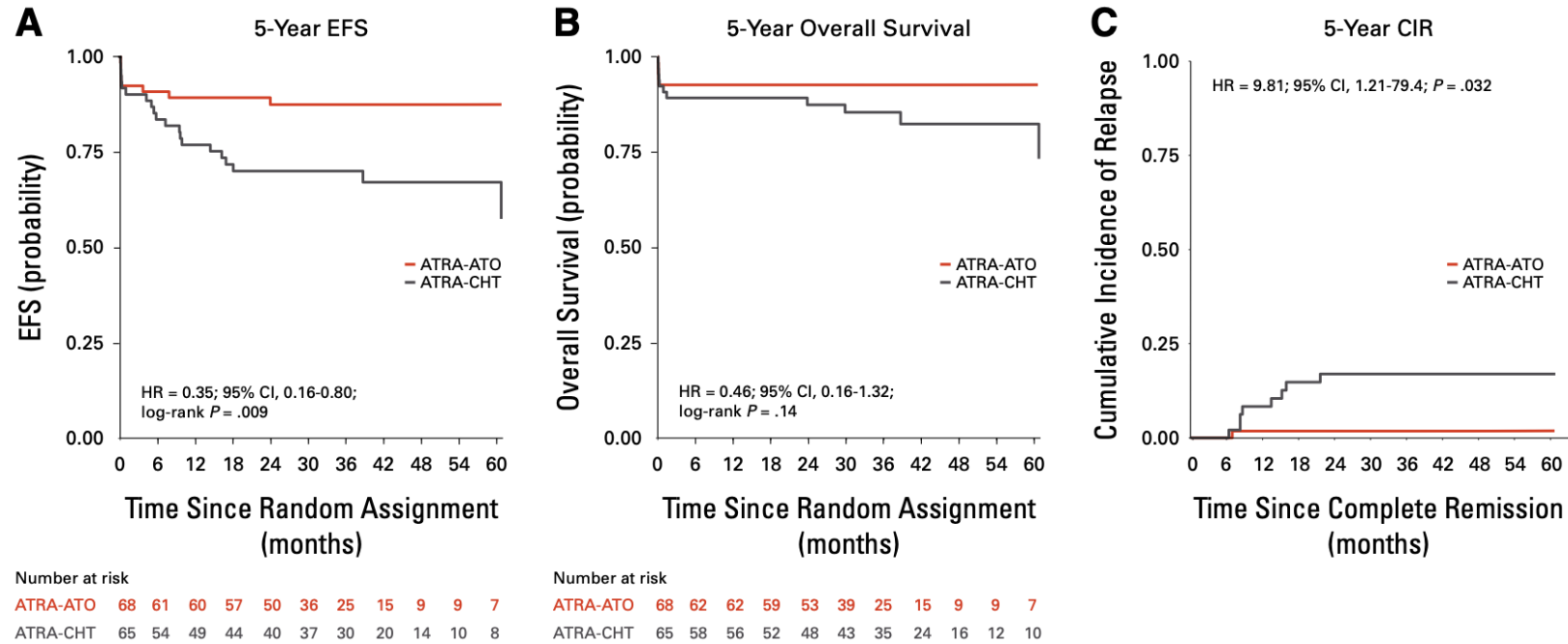
Ph3 Apollo Study : ATRA-ATO (+ 2 doses Ida) versus ATRA-CHT in high risk APL



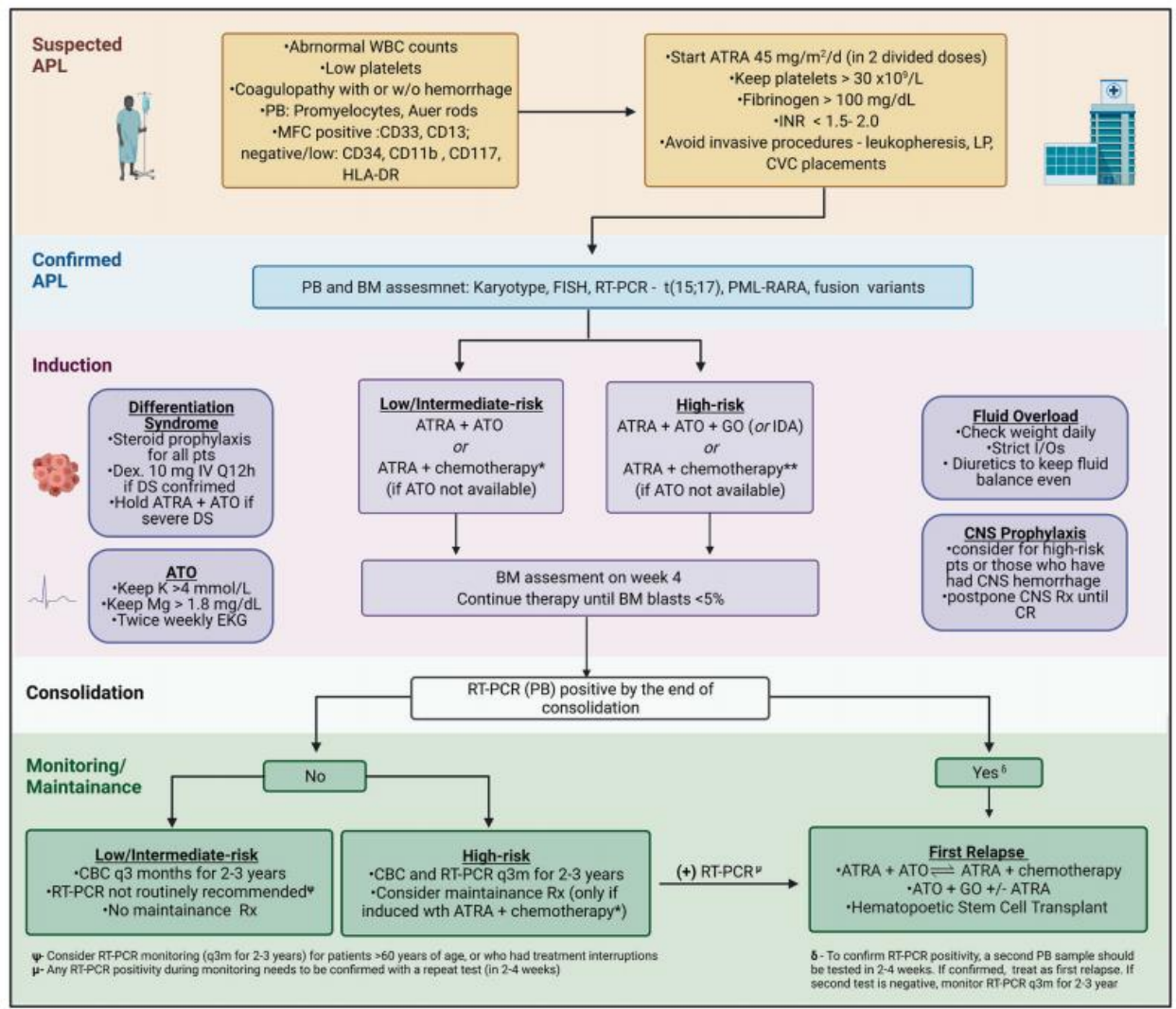
Ph3 Apollo Study : ATRA-ATO (+ 2 doses Ida) versus ATRA-CHT in high risk APL



Ph3 Apollo Study : ATRA-ATO (+ 2 doses Ida) versus ATRA-CHT in high risk APL

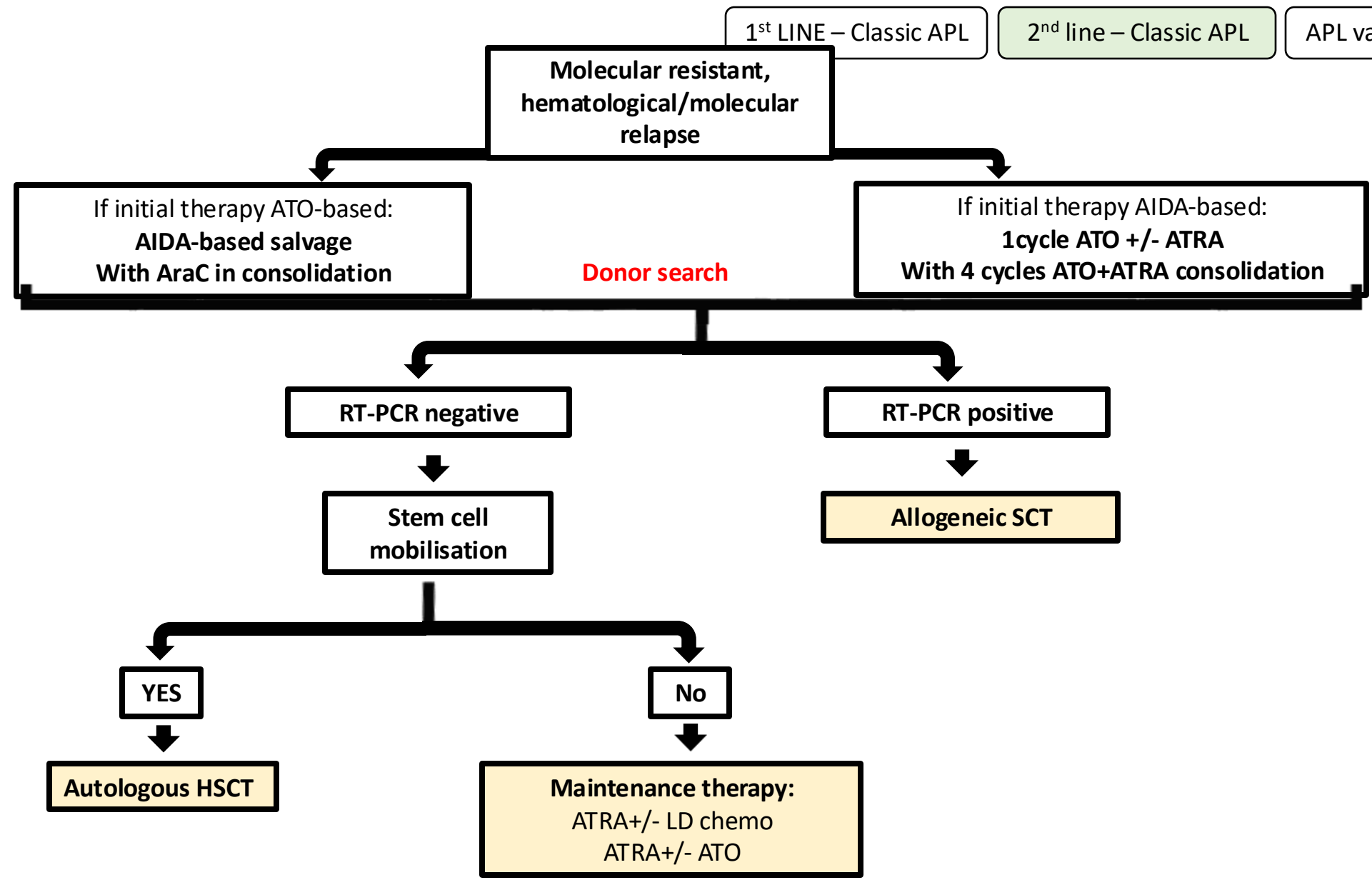


ATRA-ATO (+ 2 doses Ida) should be considered standard of care in high risk patients (but ATO is still not approved in Belgium for high risk APL)



- **ATRA should be started as soon as APL is suspected**
- Correct coagulation and avoid invasive procedures
- ATO or chemotherapy may be delayed until the genetic diagnosis is confirmed
- Confirm diagnosis with cytogenetic/molecular biology analysis
- CNS prophylaxis in selected patients, **after the achievement of CR**

1st LINE – Classic APL | 2nd line – Classic APL | APL variant X-RARa



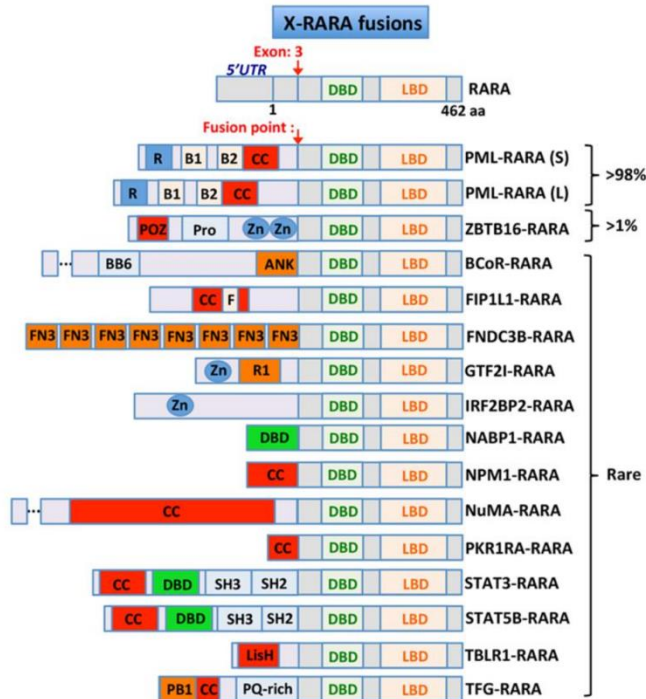
1st LINE – Classic APL

2nd line – Classic APL

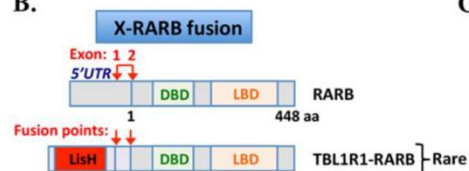
APL variant X-RARa

X-RARs fusions identified in APL: APL Variant

A.



B.



C.

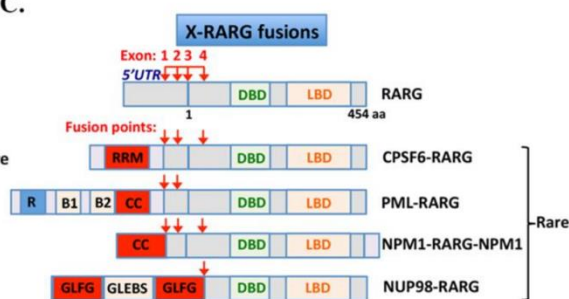


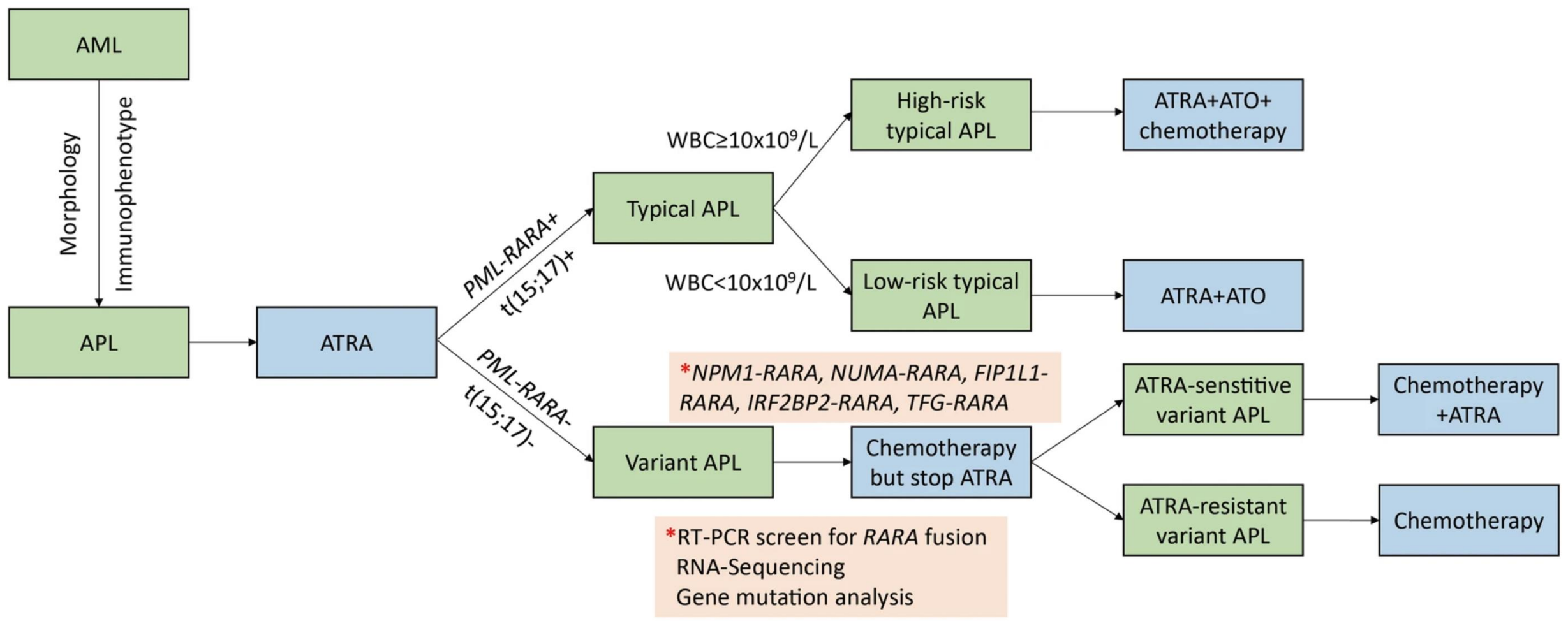
Table 2. ATRA/ATO therapy response for X-RARs fusions.

Fusion Protein	ATRA Response	ATO Response	Blast Decrease	Blast Differentiation	Self-Renewal of Bone Marrow
X-RARA					
PML-RARA	Sensitive	Sensitive	Yes	Yes	Yes
ZBTB16-RARA *	Resistant	Resistant	Yes	Yes	No
BCoR-RARA	Resistant	Resistant	ND	Yes ^a	ND
FIP1L1-RARA	Sensitive ^a	ND	Yes ^a	Yes ^a	Yes ^a
FNDC3B-RARA	Uncertain	ND	No	Yes ^a	No
GTF2I-RARA	Resistant	Resistant	No	No	No
IRF2BP2-RARA	Likely	Resistant	No	Yes ^a	Yes ^a
NABP1-RARA *	Uncertain	ND	No	Yes	ND
NPM1-RARA	Sensitive	ND	Yes	Yes	Yes
NuMA-RARA	Likely	ND	ND	Yes	ND
PRKAR1A-RARA	Uncertain	Uncertain	ND	Yes	ND
STAT3-RARA	Resistant	Resistant	No	No	ND
STAT5b-RARA	Resistant	Resistant	No	No	No
TBLR1-RARA	Resistant	Resistant	No	No	No
TFG-RARA	Sensitive	ND	Yes	ND	Yes
X-RARB					
TBLR1-RARB	Resistant	ND	No	No	No
X-RARG					
CPSF6-RARG	Resistant	Resistant	No	No	No
NPM1-RARG-NPM1	Resistant	Resistant	No	No	No
NUP98-RARG	Resistant	Resistant	No	No	No
PML-RARG	Resistant	ND	ND	No	ND

* ZBTB16-RARA (PLZF-RARA); NABP1-RARA (OBFC2A/RARA). ND: Non-determined; ^a (in 1 case). Uncertain: ATRA treatment combined with additional chemotherapy and/or stem cell transplantation.



1st LINE – Classic APL 2nd line – Classic APL APL variant X-RARa



ATRA

ATO

Coagulopathy

Leukocytosis

Differentiation Syndrome

Practical considerations

1. ATRA
2. ATO
3. Coagulopathy
4. Leukocytosis
5. Differentiation syndrome

ATRA

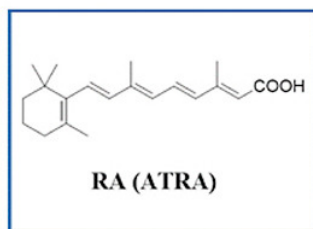
ATO

Coagulopathy

Leukocytosis

Differentiation Syndrome

ATRA



- Vitamine A- metabolite
- 45 mg/m² in two equally divided doses.
- FAT soluble - ORAL administration with meals.

Side effects:

- Leukocytosis, Differentiation syndrome, pseudotumor cerebri
- Fatigue, headache, fever, dermatitis, nasal stuffiness, hepatitis.
- Teratogenic
- Interactions: i.e. posaconazole – increases ATRA side effects



ATRA administration through nasogastric tube



Figure 1 – Process to manipulate all-trans retinoic acid (ATRA). (A) Materials: gown, gloves, class II-B2 biological safety cabinet, thermometer, 20-mL syringe, luer lock or other available syringe/lock system, light protection (e.g.: aluminum foil or other effective system), distilled water heated to 40 °C and ATRA. (B) Syringe filled with 5-10 mL of heated distilled water with ATRA and air space for effective mixing. (C) Final product after vigorous shaking. (D) ATRA protected from the light.

Pseudotumor cerebri (ATRA)

Idiopathic intracranial hypertension

More common in children than adults

ATRA can induce the production of cerebrospinal fluid and inhibits its reabsorption

15% of pediatric patients



Clinical feature

Headache, papilledema, and/or vision loss.

Elevated ICP

Normal CSF composition.

Negative CT/MRI

Papilledema is common

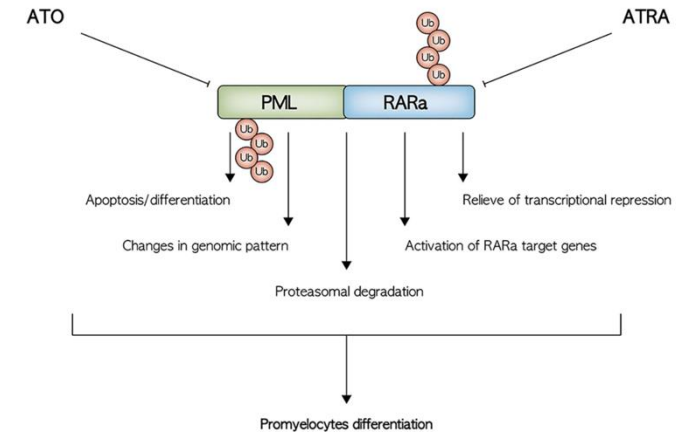
Treatment

Lumbar puncture

Temporary discontinuation ATRA, steroids, Acetazolamide

Arsenic trioxide (ATO)

- 0.15 mg/Kg IV
- Peripheral line
- Oral formulation available in China
- ATO should be restricted to cases confirmed to be PML/RARA
- Adverse events: QT prolongation, Leukocytosis, Differentiation Syndrome, hepatitis, neuropathy



ATO

- QTc monitoring and adaptation according to protocol

>450 msec for men and >460 msec for women : stop ATO and other QT prolonging drugs.

Once QTc normalized, resume ATO at 50% dose for the first 7 days, and then if no further prolongation occurred progressively escalate to standard dose in two weeks.

DON'T USE BAZETT FORMULA

Bazett correction tends to overestimate true corrected QT

- Electrolytic disturbances: keep the serum potassium > 4.0 mEq/L and serum magnesium > 0.8 mmol/l
- Pay attention to drugs that can prolong QT- posaconazole; ondansetron; fluoroquinolones.....

Coagulopathy

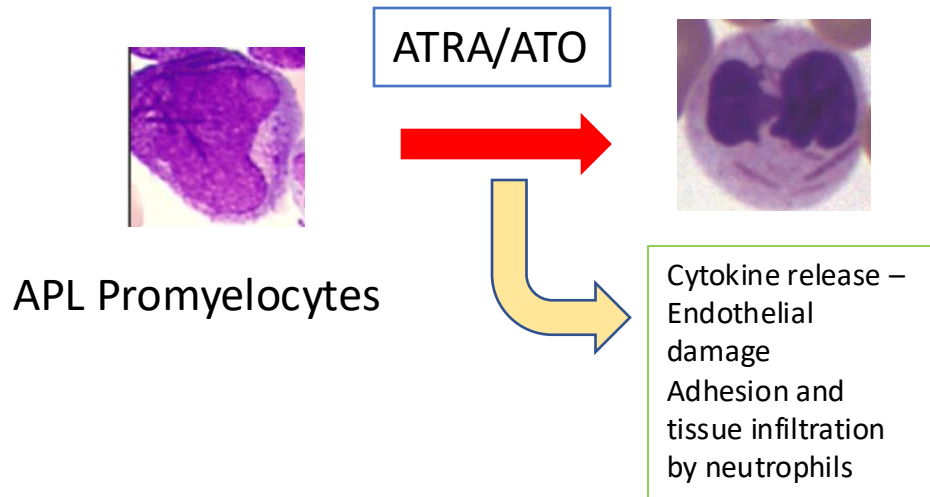
- Start ATRA (coagulopathy is sustained by APL blasts)
- Fibrinogen/platelets/fresh frozen plasma to maintain:
 - Fibrinogen > 100-150 mg/dl
 - Platelets > 30000-50000/mcl
 - INR < 1.5
- Heparin, tranexamic acid → No benefit
- Avoid invasive procedures due to bleeding risk (lumbar puncture, central venous line placement...)
- Monitor coagulation until normalisation

Leukocytosis

- Cytoreductive chemotherapy should be started without delay
- Possibilities:
 - idarubicin or daunorubicin alone or combined with cytarabine
 - GO
 - Hydroxycarbamide
- Leukapheresis should be avoided due to risk of precipitating fatal hemorrhage
- Prophylactic corticosteroids can be given, which may reduce the risk of APL differentiation syndrome

Methylprednisolone 0.5 mg/kg

Differentiation syndrome



Clinical features

- Fever $\geq 38^\circ\text{C}$
- Weight gain $> 5\text{ kg}$
- Hypotension
- Dyspnoea
- Radiographic opacities
- Pleural or pericardial effusion
- Acute renal failure

Grading of DS severity:

- Severe:** ≥ 4 features
- Moderate:** 3 features
- Indeterminate:** 1–2 features

Treatment of presumed APL DS:
<p>Start empiric treatment</p> <p>Dexamethasone 10 mg every 12 h</p> <p>If no improvement within 24 h: increase frequency to every 6 h</p> <p>Stop/taper once complete relief of signs/symptoms</p>
+
<p>What to do with ATRA/ATO?</p> <p>Hold: if severe DS OR no response to dexamethasone OR organ failure present and admission to ICU needed</p> <p>Restart: once severe DS AND any organ failure resolved</p>
+
<p>Aggressive supportive care measures</p> <p>(based on clinical features present)</p> <p>Oxygenation/mechanical ventilation</p> <p>Fluid management/renal replacement therapy</p> <p>Management of coagulopathy</p>
+
<p>Rule out “mimickers” AND consider empiric treatment</p> <p>(based on clinical features present)</p> <p>Infection/Sepsis</p> <p>Pulmonary embolus</p> <p>Diffuse alveolar haemorrhage</p> <p>Congestive heart failure</p> <p>Anaphylactic reaction to drugs</p> <p>Other causes of acute renal failure</p>

- 25% of patients
- Associated with high white blood cells, poor PS and hypoalbuminemia
- An increase of WBC levels above 10000 /mcl after treatment initiation with ATRA and/or ATO should be interpreted as a sign of ATRA/ATO-induced differentiation and **should not lead to reclassification of the patient as having high-risk disease**

Take Home Messages

- APL is a medical emergency
- If you suspect APL, ask for PML/RAR α FISH/PCR and START ATRA
- Treat coagulopathy aggressively and avoid invasive procedures
- Chemo-free approach SOC in non high risk patients and in high risk?
- Morphological variant (macro versus microgranular) \neq Molecular variant (X-RAR α)
- Special adverse events with ATRA ATO to be aware of

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