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Retinoic Acid and Arsenic Trioxide with or without Chemotherapy for Acute Promyelocytic Leukemia with Different Risk Stratifications: An Interim Analysis of China APL 2012 Study

Milestones of Therapy in APL

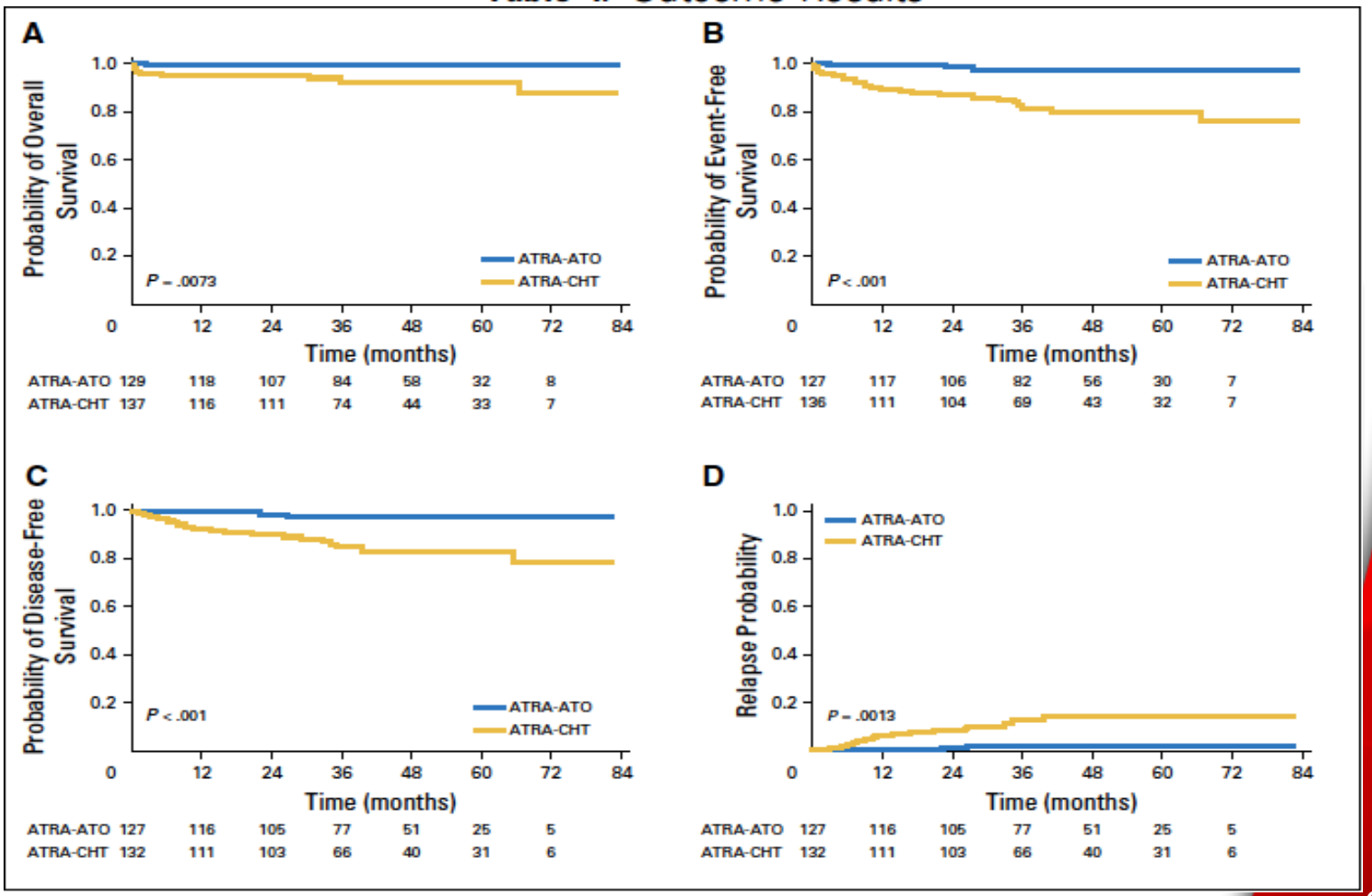
- First described by Hillestad in 1957
- Four periods in the treatment of APL
- At present, From highly fatal to highly curable
- In future, how to optimize the treatment of APL

Chemotherapy 1967~1982	ATRA 1982~1992	ATO 1992~2000	ATRA/ATO Since 2001
Bernard et al. Blood, 1973	*Huang et al. Blood, 1988*	*Shen et al. Blood, 1997*	*Shen et al. PNAS, 2004*

Low- and Intermediate-risk APL

APL 0406 updated data:

Table 4. Outcome Results



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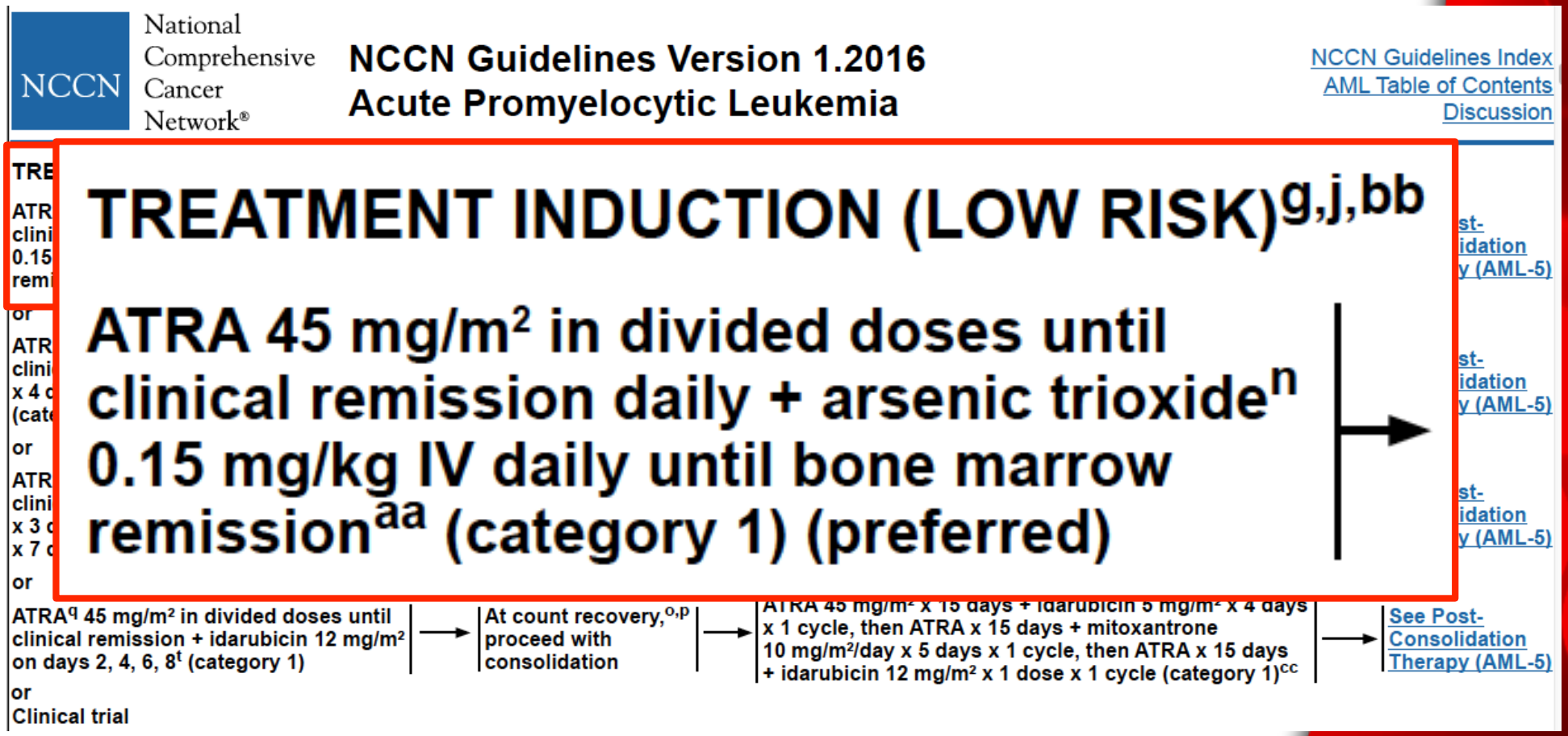
Low- and Intermediate-risk APL



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High-risk APL

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Acute Promyelocytic Leukemia

NCCN Guidelines Index
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Discussion

TREATMENT INDUCTION (HIGH RISK)[l,g,j]		CONSOLIDATION THERAPY[w]	
ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 50 mg/m² x 4 days + cytarabine 200 mg/m² x 7 days[r]	→ At count recovery,[o,aa] consider LP and proceed with consolidation[p] →	Arsenic trioxide[n] 0.15 mg/kg/d x 5 days for 5 wks x 2 cycles, then ATRA 45 mg/m² x 7 days + daunorubicin 50 mg/m² x 3 days for 2 cycles[r,bb]	→ See Post-Consolidation Therapy (AML-5)
or			
ATRA 45 mg/m² (days 1–36, divided) + age-adjusted idarubicin 6–12 mg/m² on days 2, 4, 6, 8 + arsenic trioxide 0.15 mg/kg (days 9–36 as 2 h IV infusion)[z]	→ At count recovery,[o,aa] consider LP and proceed with consolidation[p] →	ATRA 45 mg/m² x 28 days + arsenic trioxide[n] 0.15 mg/kg/d x 28 days x 1 cycle, then ATRA 45 mg/m² x 7 d every 2 wks x 3 + arsenic trioxide 0.15 mg/kg/d x 5 d for 5 wks x 1 cycle[z]	→ See Post-Consolidation Therapy (AML-5)
or			
ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[s]	→ At count recovery,[o,aa] consider LP and proceed with consolidation[p] →	Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine 2 g/m² (age <50) or 1.5 g/m² (age 50–60) every 12 h x 5 days[cc,dd] + daunorubicin 45 mg/m² x 3 days x 1 cycle 5 doses of IT chemotherapy[s]	→ See Post-Consolidation Therapy (AML-5)
or			
ATRA[q] 45 mg/m² in divided doses until clinical remission + idarubicin 12 mg/m² on days 2, 4, 6, 8[t]	→ At count recovery,[o,aa] consider LP and proceed with consolidation[p] →	ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² and cytarabine 1 g/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/d x 5 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 dose + cytarabine 150 mg/m²/8 h x 4 days x 1 cycle[t,bb]	→ See Post-Consolidation Therapy (AML-5)
or Clinical trial			

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APL 2012 Study

- A phase 4, prospective, randomized, open-label, multicenter trial.
- Objectives:
  - If CHT could be replaced by ATO in patients with low- and intermediate-risk APL in post-remission therapy?
  - If CHT could be minimized by ATO in patients with high-risk APL in post-remission therapy?

Criteria

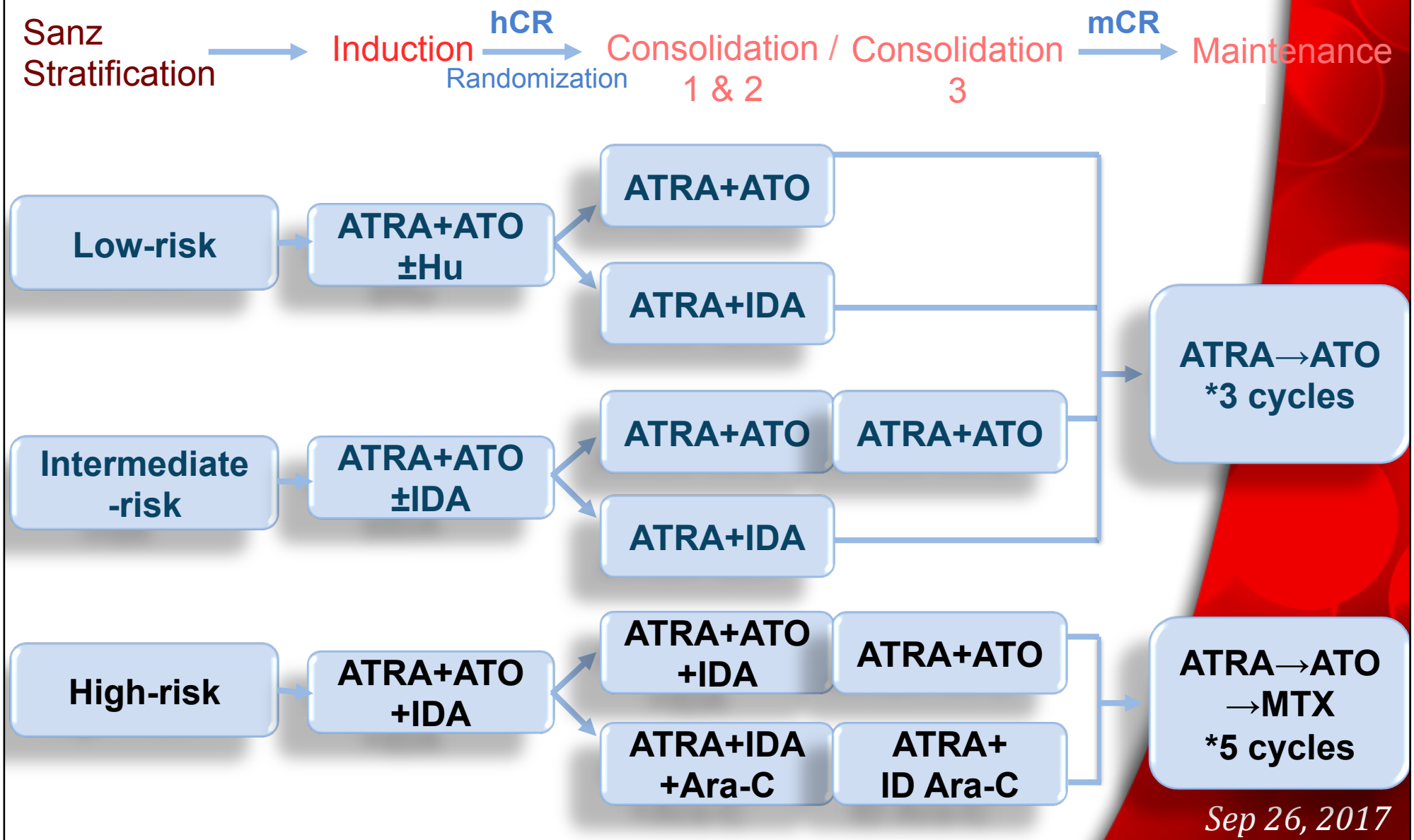
Inclusion criteria:

- Newly diagnosed APL by cytogenetic or molecular test: t(15;17) and/or PML/RARα positive
- Age 18-65
- Normal liver and renal function
- Normal cardiac function
- ECOG 0-3
- Informed consent

Exclusion Criteria:

- Previously treated patient
- CNS infiltration
- Abnormal liver or renal function
- Severe hear disease, including AMI and heart failure
- QT interval > 450mm
- With other malignancy
- Active TB or HIV positive
- Do not obey the study
- <18 years old or >65 years old
- Pregnant or lactational period
- Contraindications to anthrycyclines
- Drug addiction or mental disorders
- Involved in other clinical trials simultaneously
- Other situations that against the trial

Protocol of Treatment



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Dosage of Treatment

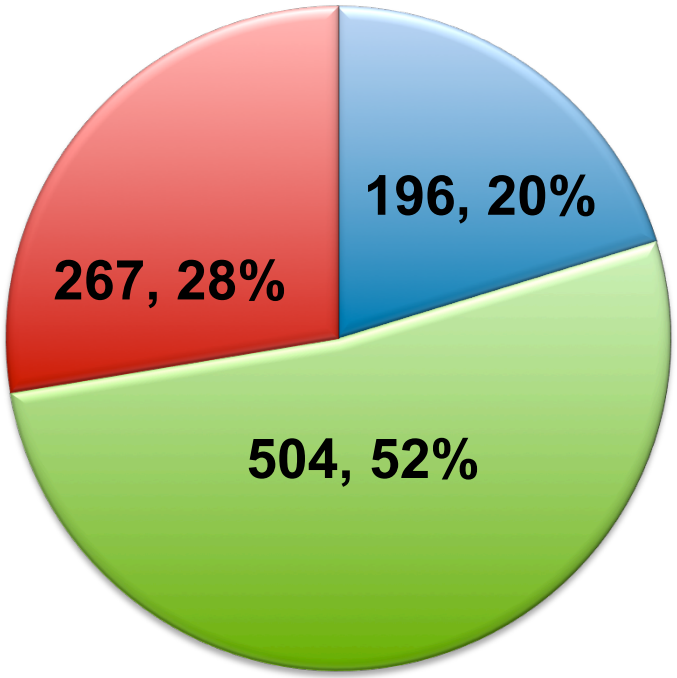
Induction:		
	ATRA	25mg/m^2/d, given orally, until CR
	ATO	0.16mg/kg/d, iv drip until CR
	IDA	8mg/m^2/d, D1-3 (in high- or most intermediate-risk)
Consolidation:		
Exp group:	ATRA	25mg/m^2/d, D1-14
	ATO	0.16mg/kg/d, D1-28
(high-risk)	IDA	8mg/m^2/d, D1-3
Ctrl group:	ATRA	25mg/m^2/d, D1-14
	IDA	8mg/m^2/d, D1-3
(high-risk)	Ara-C	150mg/m^2/d, D1-7 1st & 2nd course; 1g/m^2, Q12H, D1-3 3rd course
Maintenance:		
	ATRA	25mg/m^2/d, D1-14
	ATO	0.16mg/kg/d, D1-28
(high-risk)	MTX	15mg/m^2/wk, for 4 weeks

Enrollment

- 1039 cases screened from July 2012 to Jun 2017.
- 72 cases excluded before induction: unqualified or refused to the study.
- 967 cases enrolled, 18 cases withdrew due to intolerance, protocol violation during induction.
- 949 cases eligible for analysis.

Characteristics of Patients

- Risk stratification：



- Median age：38y（18-65）
- Male：513（53.1%）
  Female：454（46.9%）

Response

- CR rate：96.6% (910/942)
- Early death：3.4% (32/949)

Cause of early deaths:

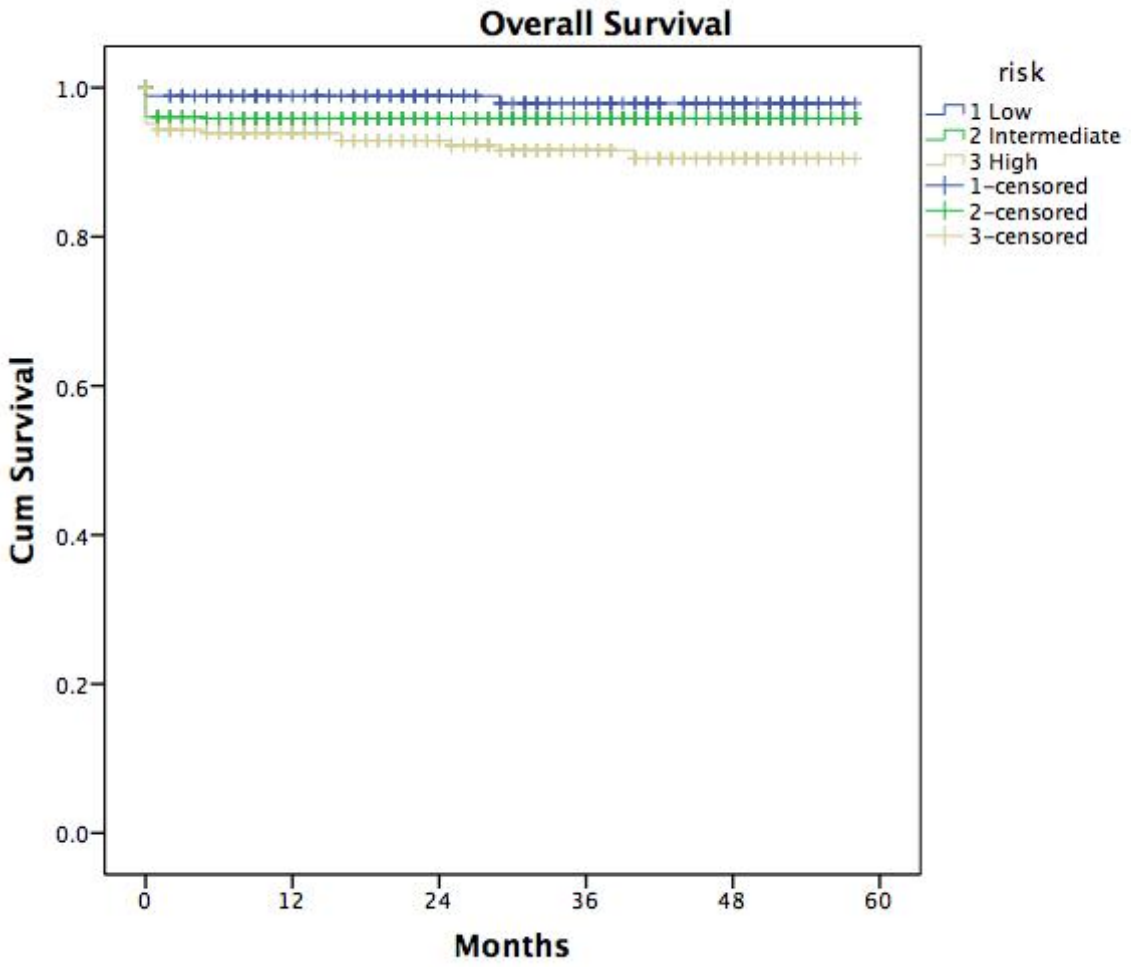
- Cerebral hemorrhage：15 cases
- Infection：7 cases
- Cerebral Infarction：2 cases
- Differentiation syndrome：1 case
- DIC：1 case
- MODS：2 case
- Pneumorrhagia：2 case
- Not quite clear：2 case

Disposition of Patients

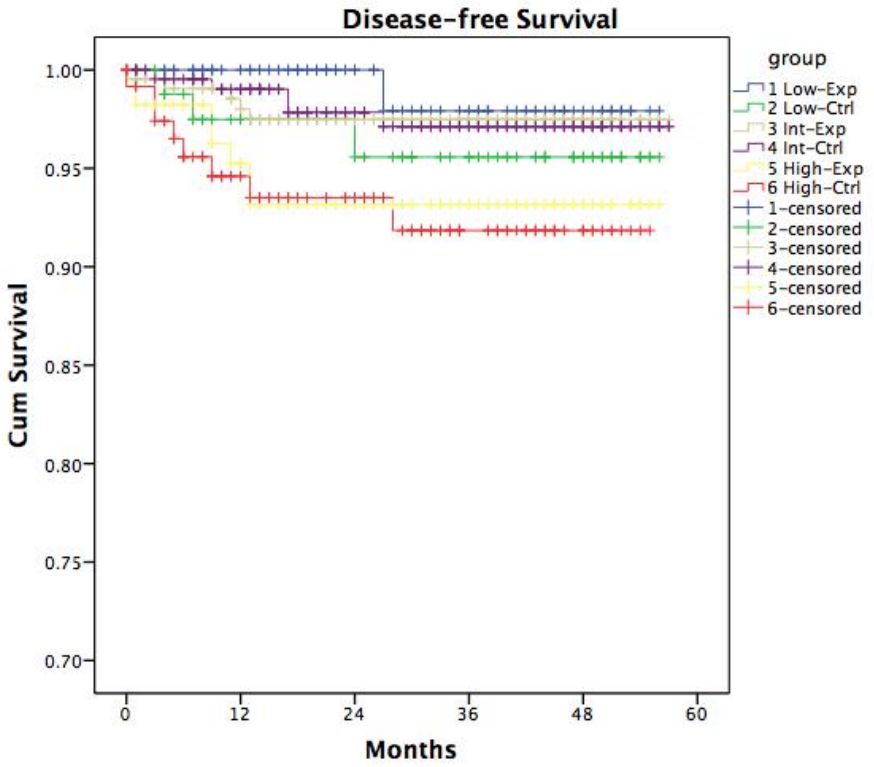
- In 949 eligible patients, 69 of them were withdrawn because of protocol violation, intolerance and loss to follow up in post-remission.
- The remaining 880 cases were adherent to protocol. Ten patients with protocol violation or intolerance could be evaluated for the primary end point. So a total of 890 patients were included in survival analysis.
- Patients with early death not included in the analysis of OS or DFS in experimental or control groups, because patients achieving CR entered into randomization.

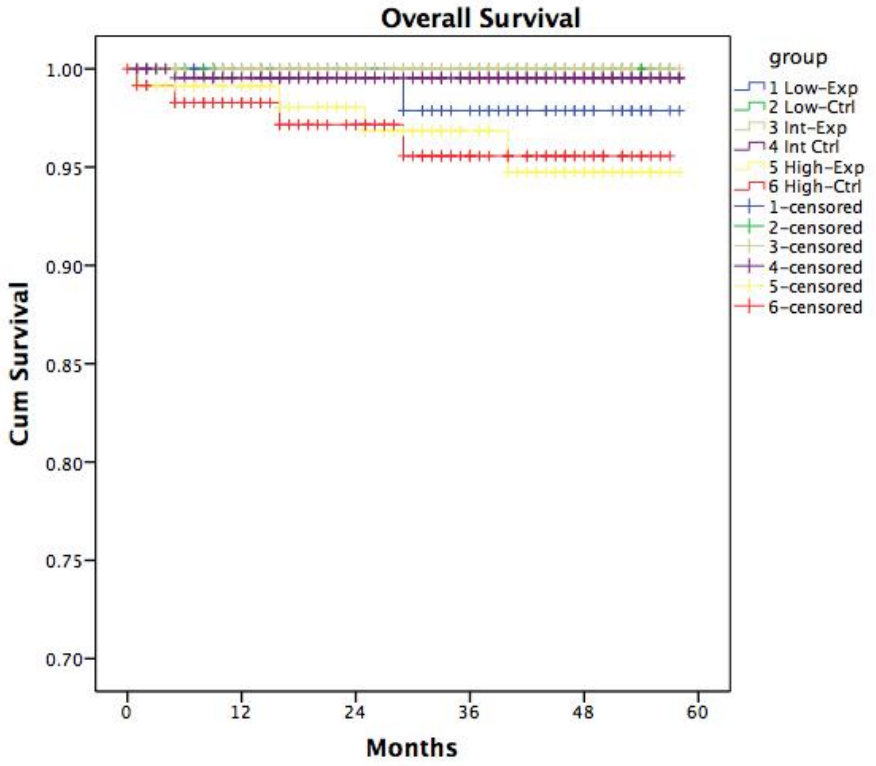
Overall Survival

- Median follow-up：32 months (0-58)
- 4-year OS:
  - Low-risk: 97.9%
  - Intermediate-risk: 95.9%
  - High-risk：90.5%
  - Low-Intermediate >High (*P*=0.006)



Post-remission Survival



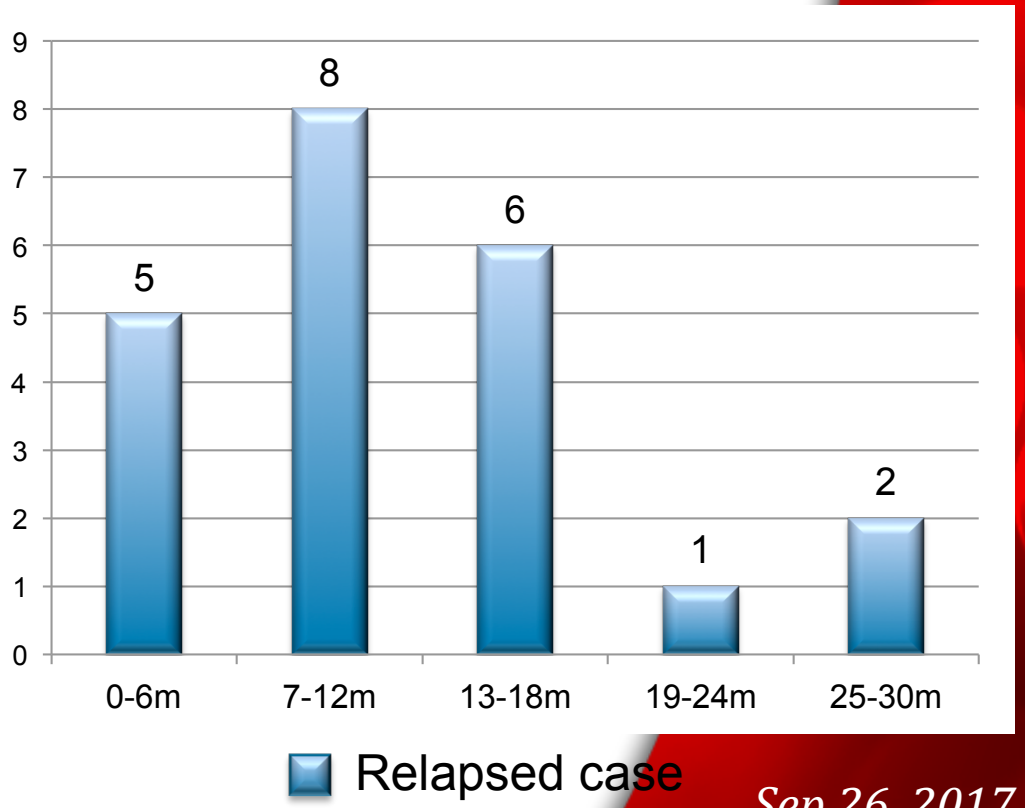


4y DFS	Low%	Int%	High%
Exp	97.9	97.5	93.2
Ctrl	95.6	97.1	91.8
P value	0.295	0.983	0.770

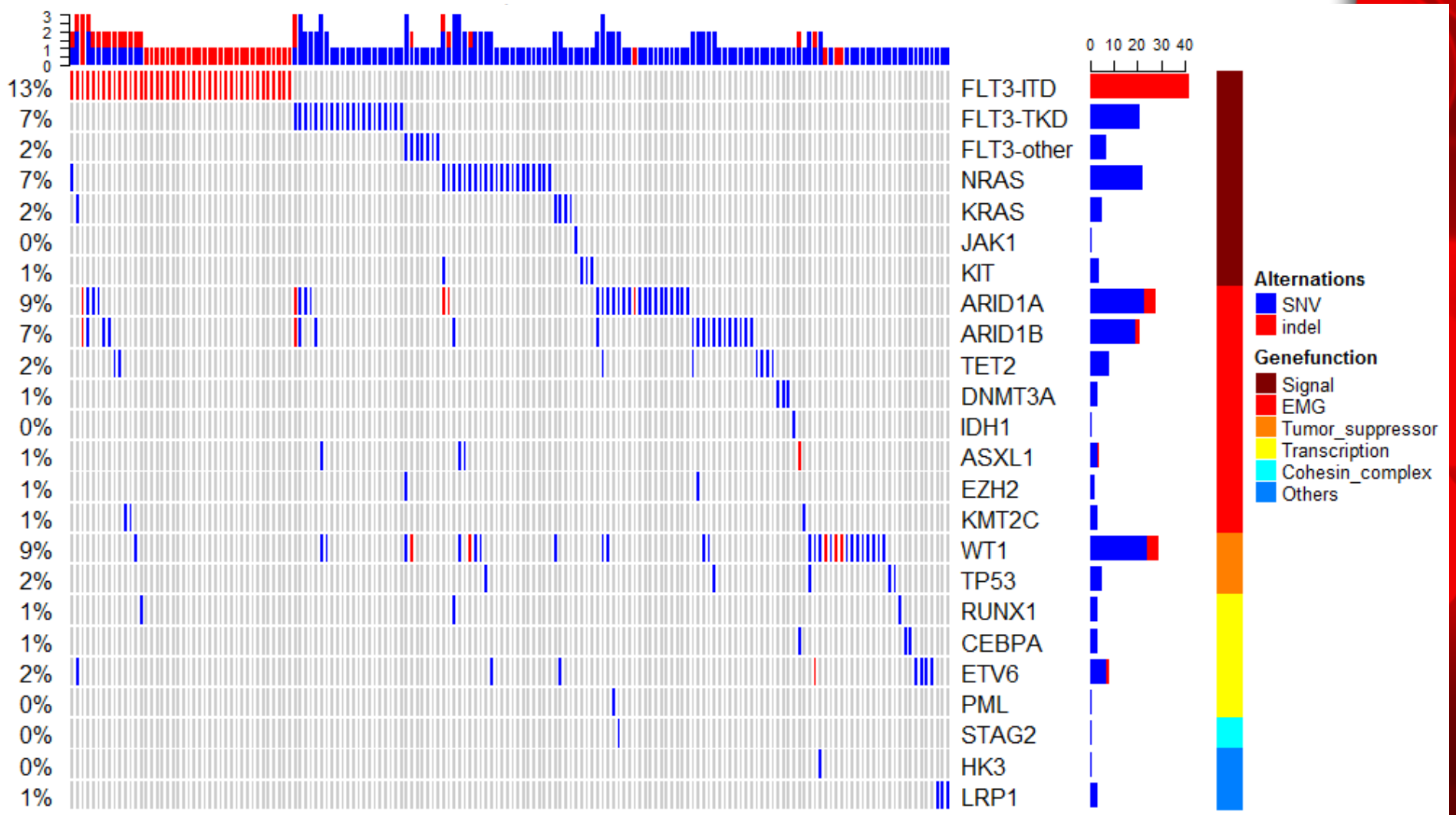
4y OS	Low%	Int%	High%
Exp	97. 9	100	94.7
Ctrl	100	99.5	95.6
P value	0.298	0.321	0.923

Relapse/refractory

- 22 patients were relapsed and 3 patients with persistent positive PML/RARa after consolidation therapy (1 intermediate-risk and 2 high-risk, all in ctrl group)
  - Low-risk: 2.2%
    (4/182, 1 exp and 3 ctrl)
  - Intermediate-risk： 1.7%
    (8/460, 5 exp and 3 ctrl)
  - High-risk: 4.0%
    (10/248, 6 exp and 4 ctrl)
  - *P* >0.05



Mutation Pattern



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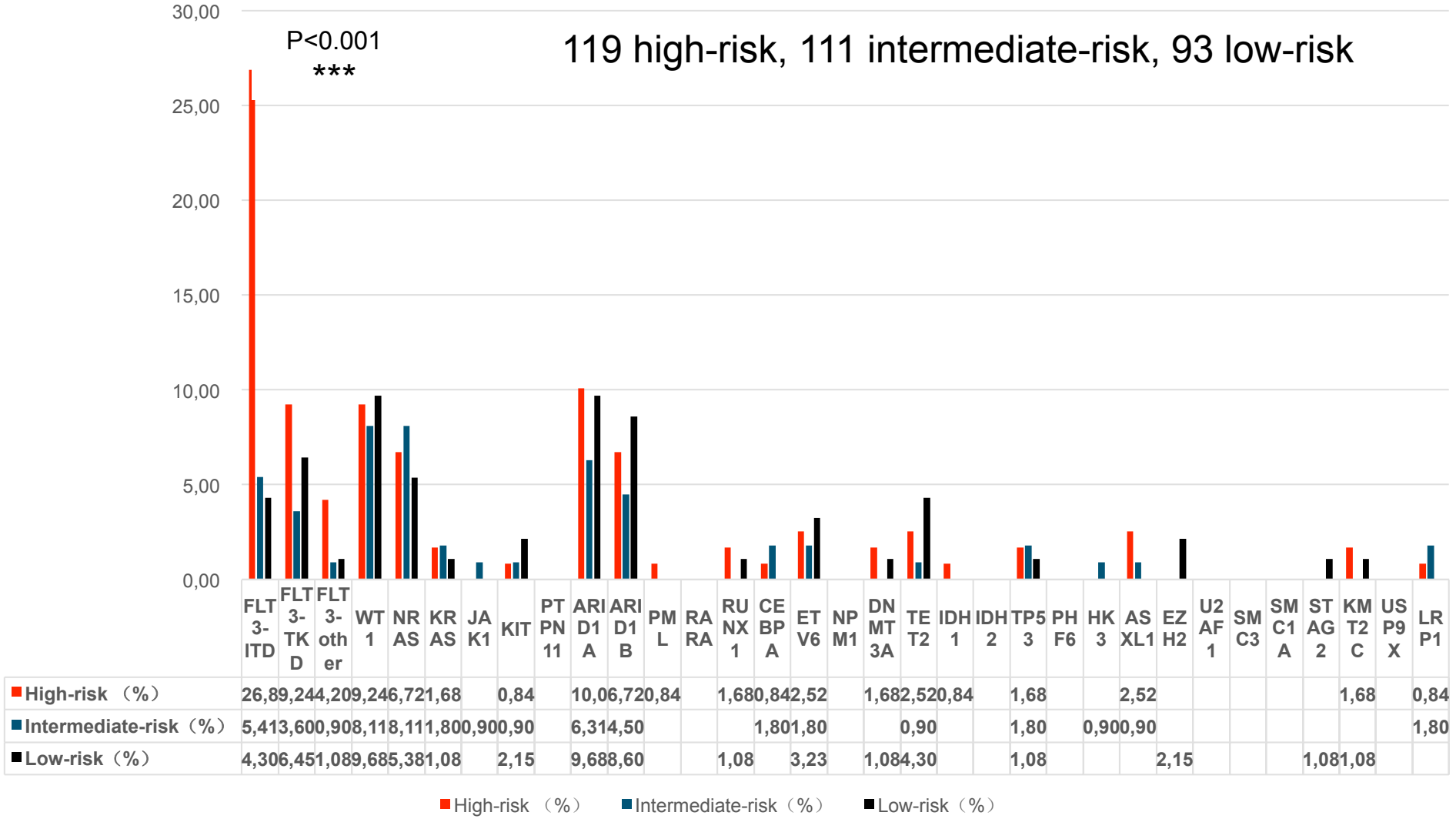
Mutation Pattern



	FLT3-ITD	FLT3-TKD	FLT3-other	WT1	NRAS	KRAS	JAK1	KIT	PTPN11	ARID1A	ARID1B	PML	RARA	RUNX1	CEBPA	ETV6	NPM1	DNMT3A	TET2	IDH1	IDH2	TP53	PHF6	HK3	ASXL1	EZH2	U2AF1	SMC3	SMC1A	STAG2	KMT2C	USP9X	LRP1
High-risk （%）	26,89	9,24	4,20	9,24	6,72	1,68		0,84		10,08	6,72	0,84		1,68	0,84	2,52		1,68	2,52	0,84		1,68			2,52						1,68		0,84
Intermediate-risk（%）	5,41	3,60	0,90	8,11	8,11	1,80	0,90	0,90		6,31	4,50				1,80	1,80			0,90			1,80		0,90	0,90								1,80
Low-risk（%）	4,30	6,45	1,08	9,68	5,38	1,08		2,15		9,68	8,60			1,08		3,23		1,08	4,30			1,08				2,15				1,08	1,08		

Conclusion

APL 2012 Trial

ATRA+ATO±CHT with High CR and reduced ED

For low-risk APL:

ATRA+ATO not inferior to ATRA+CHT

For intermediate-risk APL:

ATO replaced CHT in post-remission therapy

For high-risk APL:

ATO reduced CHT by replacing Ara-C

Acknowledgements

- Li Liu, Guohui Li, Department of Hematology, Tangdu Hospital, The Fourth Military Medical University, Shaanxi Xi'an 710038,China
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- Jianxiang Wang, Ying Wang, Institute of Hematology＆Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianfin 300020, China

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Acknowledgements

- Jianda Hu, Zhengjun Wu, Fujian Institute of Hematology, Fujian Provincial Key Laboratory of Hematology, Fufian Medical University Union Hospital, Fuzhou, Fujian 350001, China
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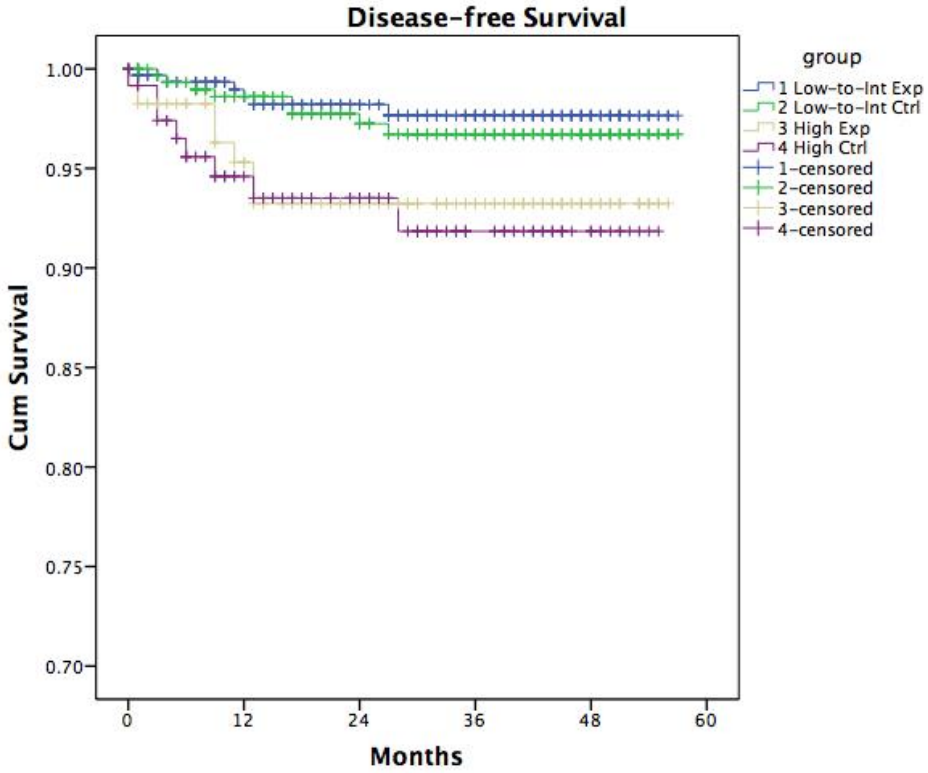
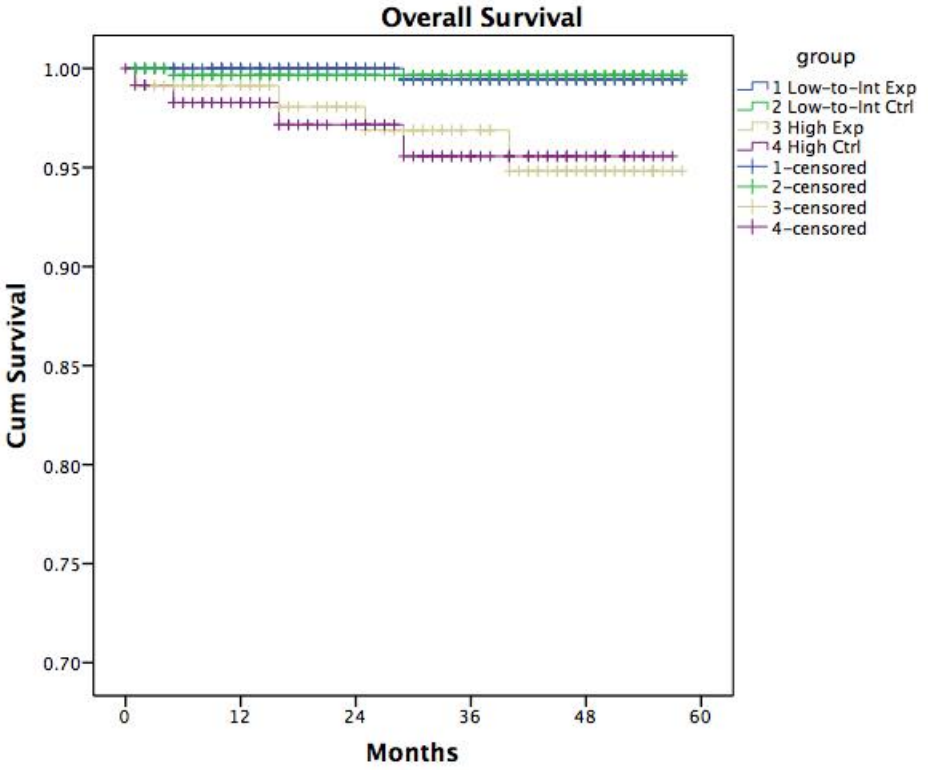
Sep 26, 2017

Funded by the National High-tech Research and Development Program [863 Program] of China 2012AA02A505 and others; ClinicalTrials.gov identifier: NCT01987297.

Li Chen, Hongming Zhu, Jiong Hu, Bing Chen, Xiaoyang Li, Lining Wang, Yunxiang Zhang, Yuhong Ren, Huijin Zhao, Yu Chen, Huiping Sun, Qiusheng Chen, Yu Chen, Weili Zhao, Jianqing Mi, Zhixiang Shen, Zhenyi Wang, Zhu Chen, Saijuan Chen of the Shanghai Institute of Hematology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine.

Post-remission Survival





4y DFS	Low-to-Int%	High%	*P* value
Exp	97.6	93.2	0.027
Ctrl	96.7	91.8	0.032
P value	0.591	0.770	

4y OS	Low-to-Int%	High%	*P* value
Exp	99.4	94.7	0.011
Ctrl	99.7	95.6	0.007
P value	0.990	0.923	

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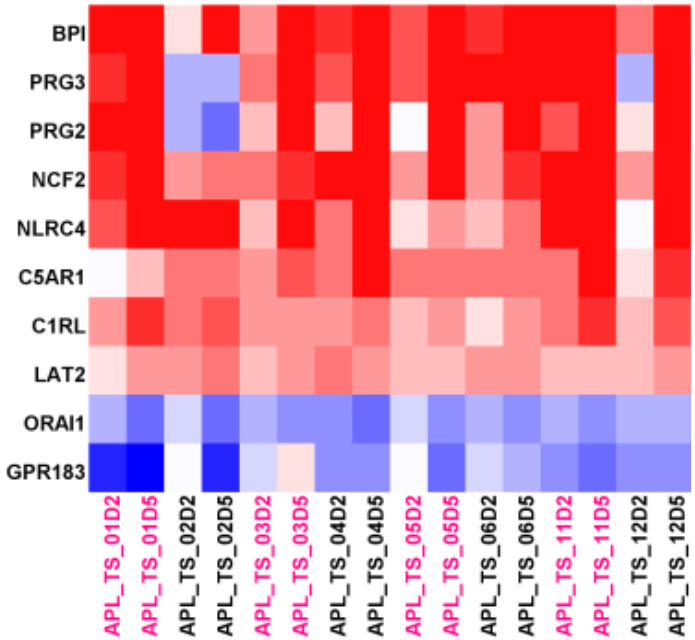
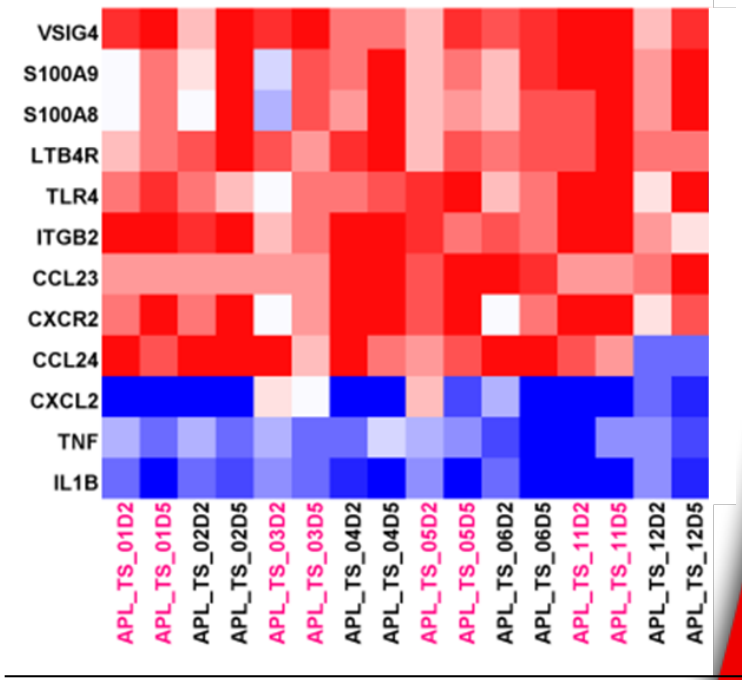
Regulation of Signaling Pathways upon ATRA and ATO

Immune response



Inflammatory response



- Innate immune response (NLRC4/BPI/ C1RL)
- Adaptive immune response (GPR183/ ORAI1/PAG1)
- Intrinsic (TLR4/MYD88/ TNF)
- Extrinsic (CCL23/CXCL2/ IL1B)

Data unpublished

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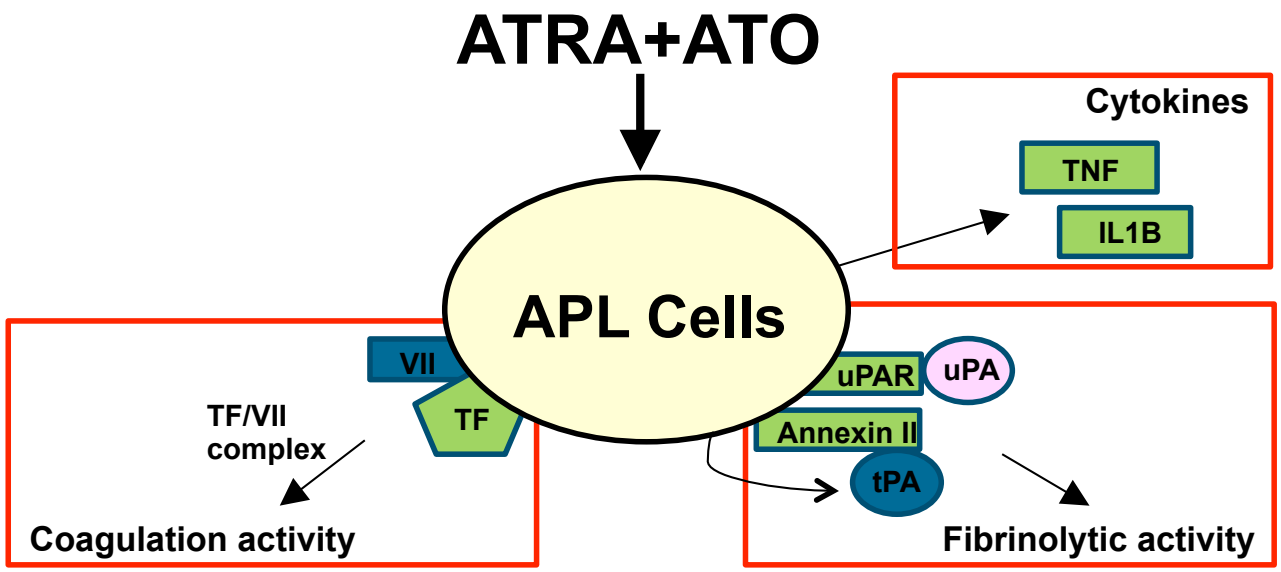
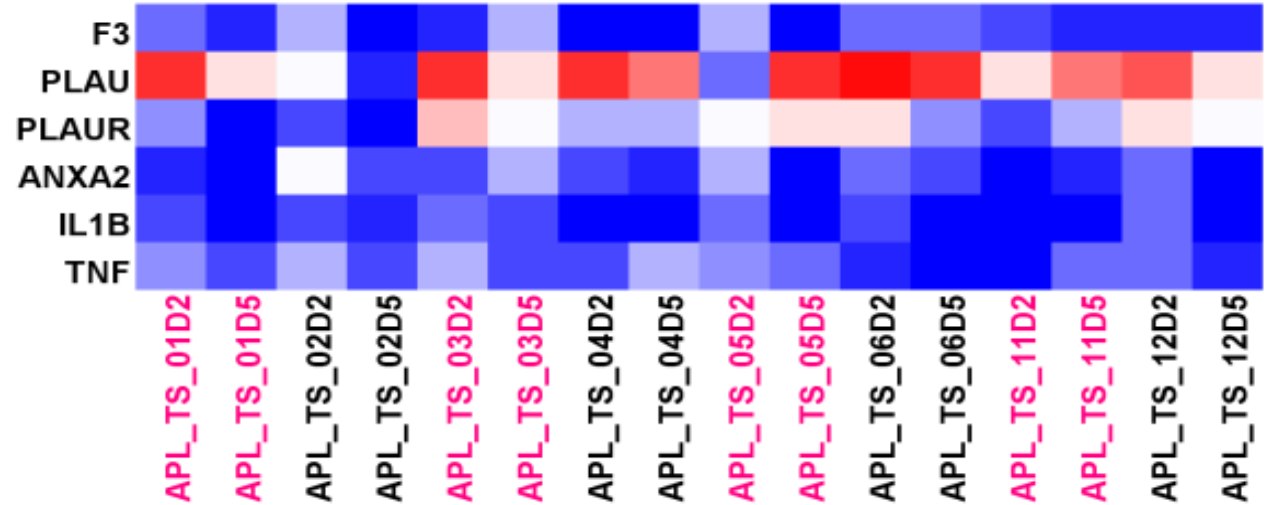
Regulation of Signaling Pathways upon ATRA and ATO





Data unpublished

Sep 26, 2017