Breakthroughs in the treatment of APL: role of arsenic in newly-diagnosed patients

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1. **Overview of APL treatment**
2. **Arsenic as first-line treatment in China**
2. **Optimization of Arsenic treatment**
3. **Ongoing clinical trial in the arsenic-based regimen for APL**

Overview of APL treatment in China

- Consensus and guideline for APL treatment by Chinese Society of Hematology, Chinese Medical Association

- ATRA + chemotherapy based regimen
  ATRA + arsenic based regimen

Chin J Hematol
2010;31:69

ATRA+chemotherapy

Group	Year	N	CR%	D(E)FS%	Strategy
European APL[33]	1999	99	94	84	ATRA/DA
GIMEMA[35]	1997	240	95	79	ATRA/Ida
North American[36]	1997	172	72	75	Maintenance
PETHEMA[54]	1999	123	89	92	No ara-C
GAMLCG[37]	2000	51	92	88	High-dose ara-C (High-risk)

Tallman M, Blood 2009;114:5126

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Arsenic: first-line treatment for APL

Rationale:

- Clinical data:
  relapsed pateints with previous ATRA/chemo: high CR rate and long-term survival
  newly-diagnosed APL: high CR rate and long-term survvial
- Laboratory study:
  degradation of PML-RAR□ induced by arsenic
  induction of aopotosis and differentiation
  inhibition of leukemia stem cell or leukemia initiate cells in mice model

Single-Institute analysis: RJH

- **ATRA + Arsenic as induction therapy**

	ATRA	Arsenic	ATRA+Arsenic
No of patients	20	20	21
Dose of ATRA(mg)	1230		810
Dose of arsenic(mg)		290	210
CR rate	19(95%)	18(90%)	20(95.2%)
Median Days to CR	40(25-65)	31(28-38)	26(18-35)

Shi Z, PNAS 2004;101:5328

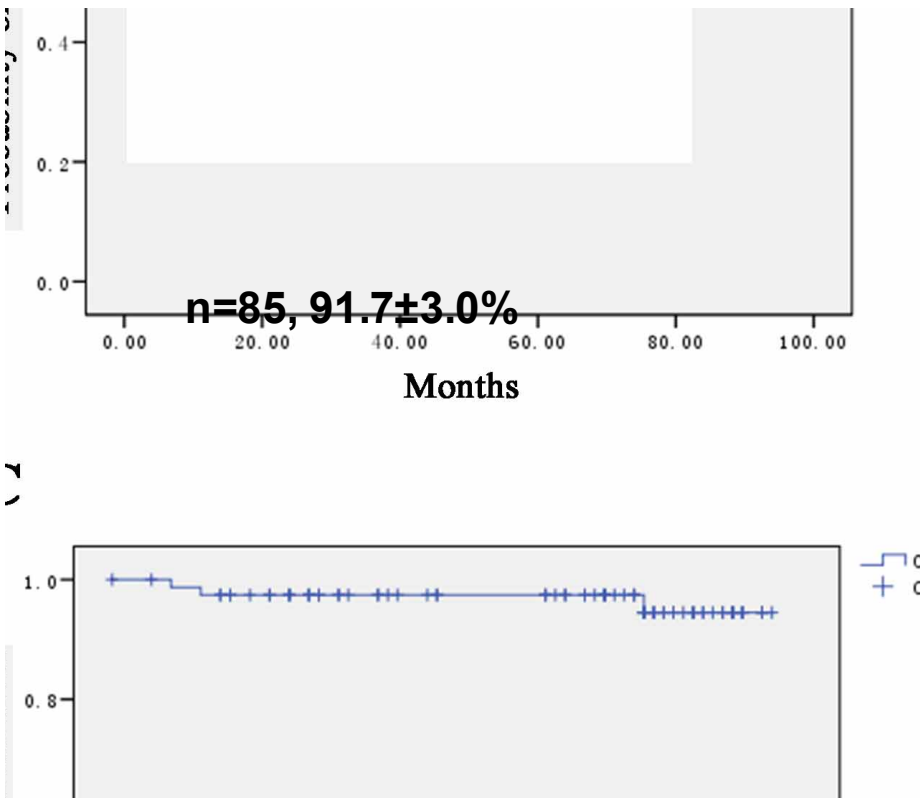
Single-Institute analysis: RJH

- **Arsenic as part of induction and maintenance:**

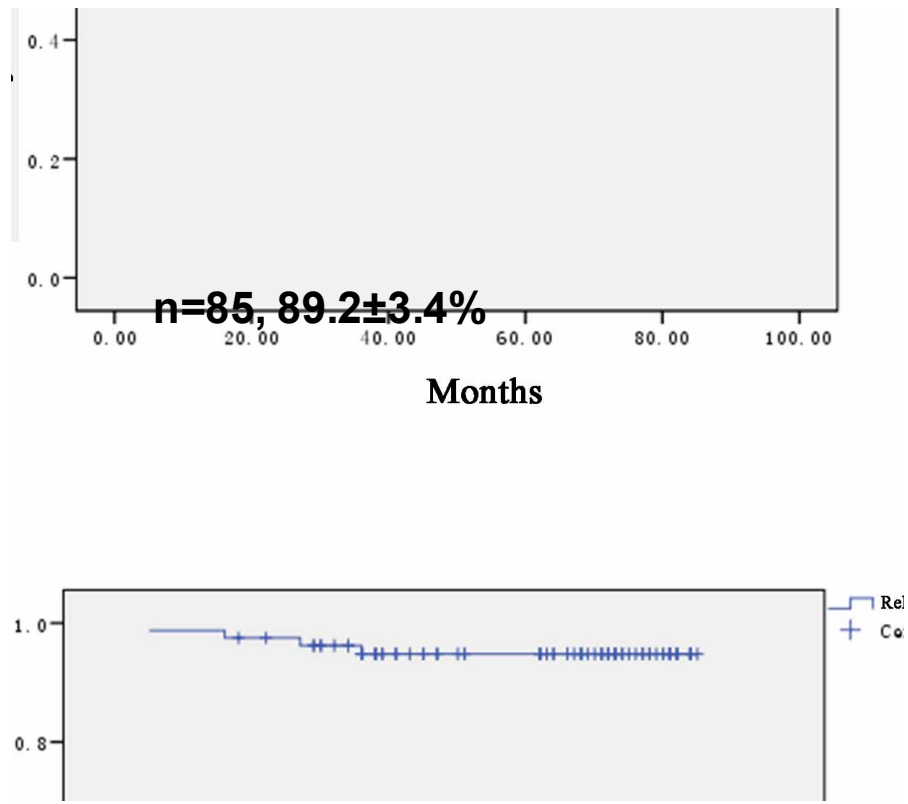
- induction: ATRA 25mg/m2/d + As2O3 0.16mg/kg/d
- consolidation: chemotherapy DA/ID-Ara-C/HA
- maintenance: 5 cycels of 3-month sequential maintenance
  ATRA:25mg/m2/d
  As2O3: 0.16mg/m2/d
  6-mercaptopurine (6-MP): 100mg/d □ Methotrexate 15mg/w

Hu J, PNAS 2009;106:3342

Follow-up：85 newly-diagnosed patients



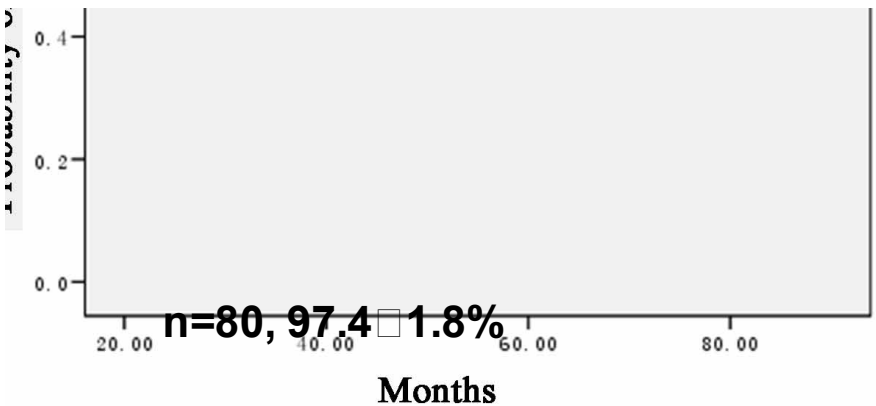
70月-OS

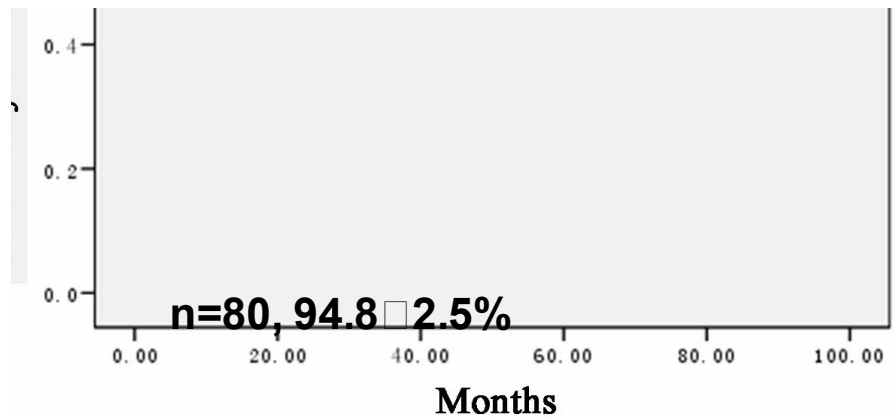


70月-EFS

Hu J, PNAS 2009;106:3342

Follow-up：80 patients in remission



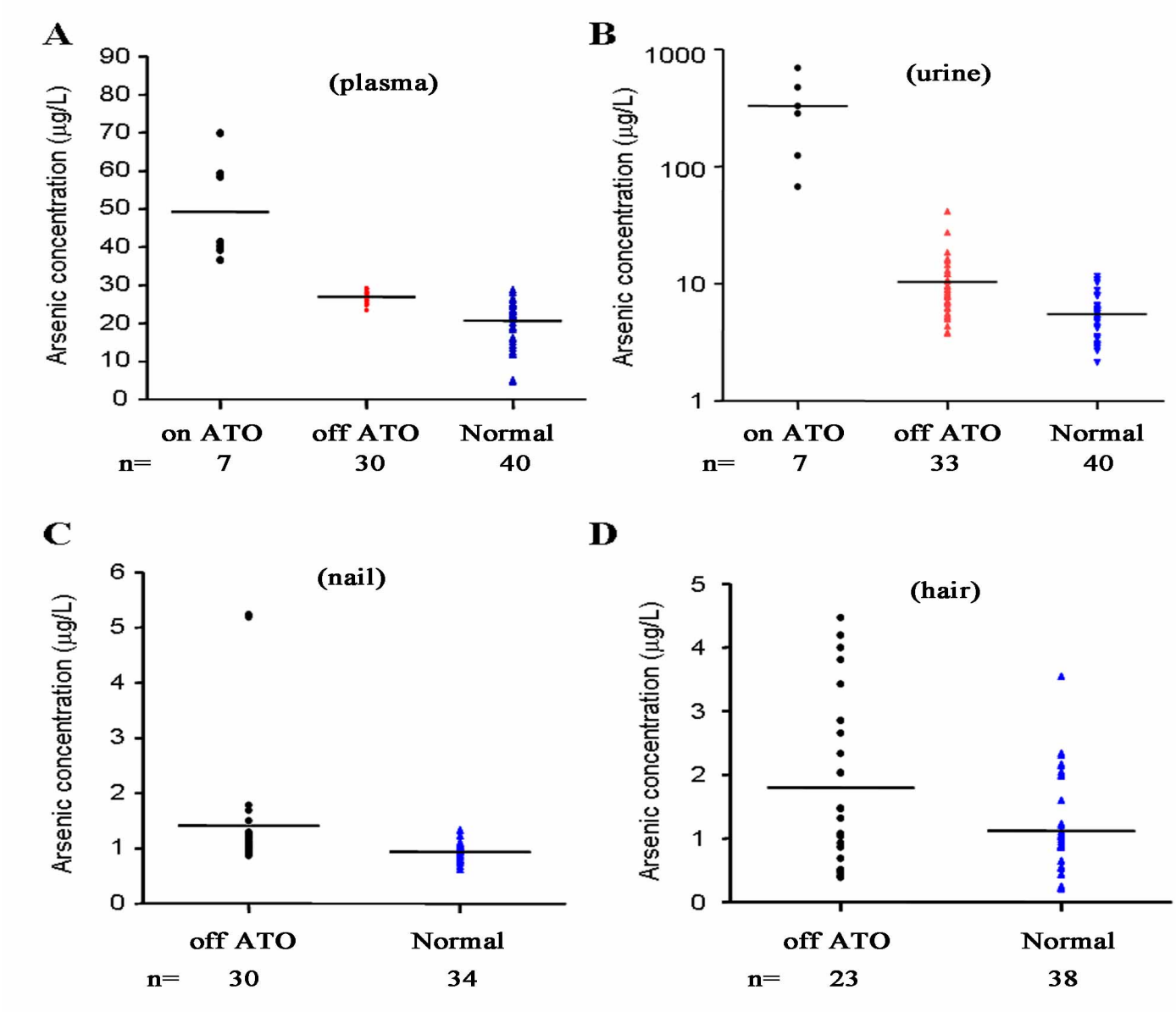


70月-OS

70月-EFS

Hu J, PNAS 2009;106:3342

Monitoring of arsenic during and after treatment



Hu J, PNAS 2009;106:3342

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Optimization of arsenic treatment

- Best timing of treatment: induction vs. consolidation vs. maintenance
- Montherapy vs combination
- Chemotherapy required?
- IV vs. oral
- Total dose of arsenic and safety issue

Optimization of arsenic treatment

	RuiJin*	MDACC*	North Am*	Hong Kong	Iran/India
Induction	+	+	-	-	+
Consolidation	-	+	+	-	+
Maintenance	+	-	-	+	+
Total cycles	6	5	2	12**	6-8***

* Arsenic combinaed with ATRA

** Oral arsenic 2 weeks every two months for 2 years

*** Arsenic as monotherapy. Maintenance: 10 day a months for 6 cycles

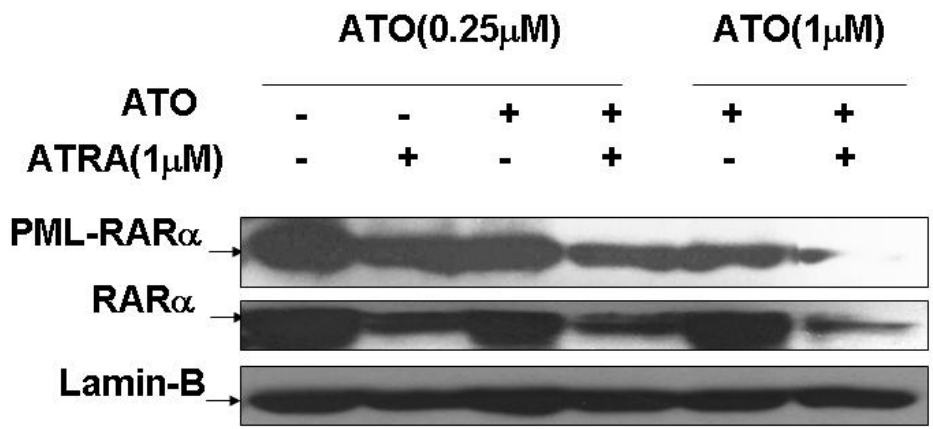
Hu J, PNAS 2009;106:3342; EsteyE, Blood 2006;107:3469
Powell B, Blood 2010;116:3751; Au W, Blood 2011;118:6535
Mathews V, JCO 2010;28:3866; Ghavamzadeh A, JCO 2011;29:2753

Optimization of arsenic treatment

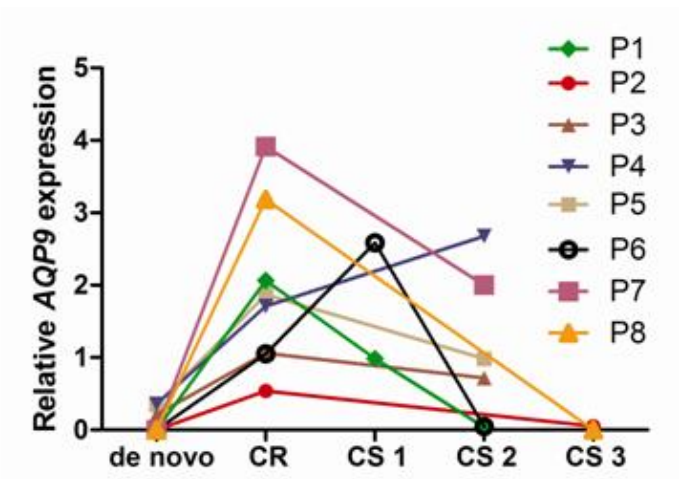
	RuiJin	MDACC	North Am	Hong Kong	Iran	India
No patients	85	82	-	76	197	72
CR	94%	91%	-	-	86%	86%
DFS/EFS	89%	-	80%	83.7%	67%	69%
OS	92%	85%	86%	90.6%	64%	74%

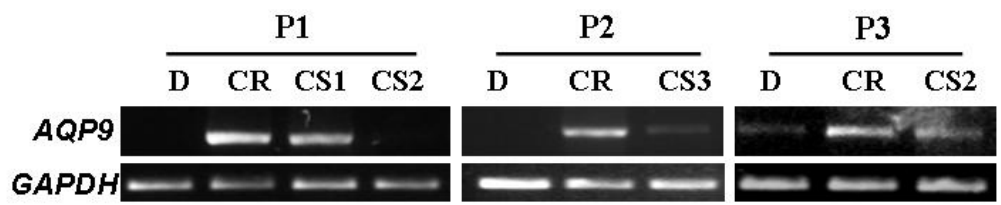
Hu J, PNAS 2009;106:3342; EsteyE, Blood 2006;107:3469
Powell B, Blood 2010;116:3751; Au W, Blood 2011;118:6535
Mathews V, JCO 2010;28:3866; Ghavamzadeh A, JCO 2011;29:2753

Combination of arsenic and ATRA



Synnergy in the degradation of PML-RAR□





ATRA induced AQP9 gene expression which increased the sensitivity of leukemia cell to arsenic

Hu J, PNAS 2009;106:3342

Combination of arsenic and ATRA

Treatment	Effect on PML-RARα	Effect on Promyelocytes	LIC Elimination	Outcome
RA	transactivation > degradation	differentiation	no	relapse
RA + arsenic	degradation > transactivation	differentiation	rapid	cure
Liposomal RA	transactivation and degradation	differentiation	slow	cure or relapse
RA + anthracycline		death and differentiation	slow	cure or relapse

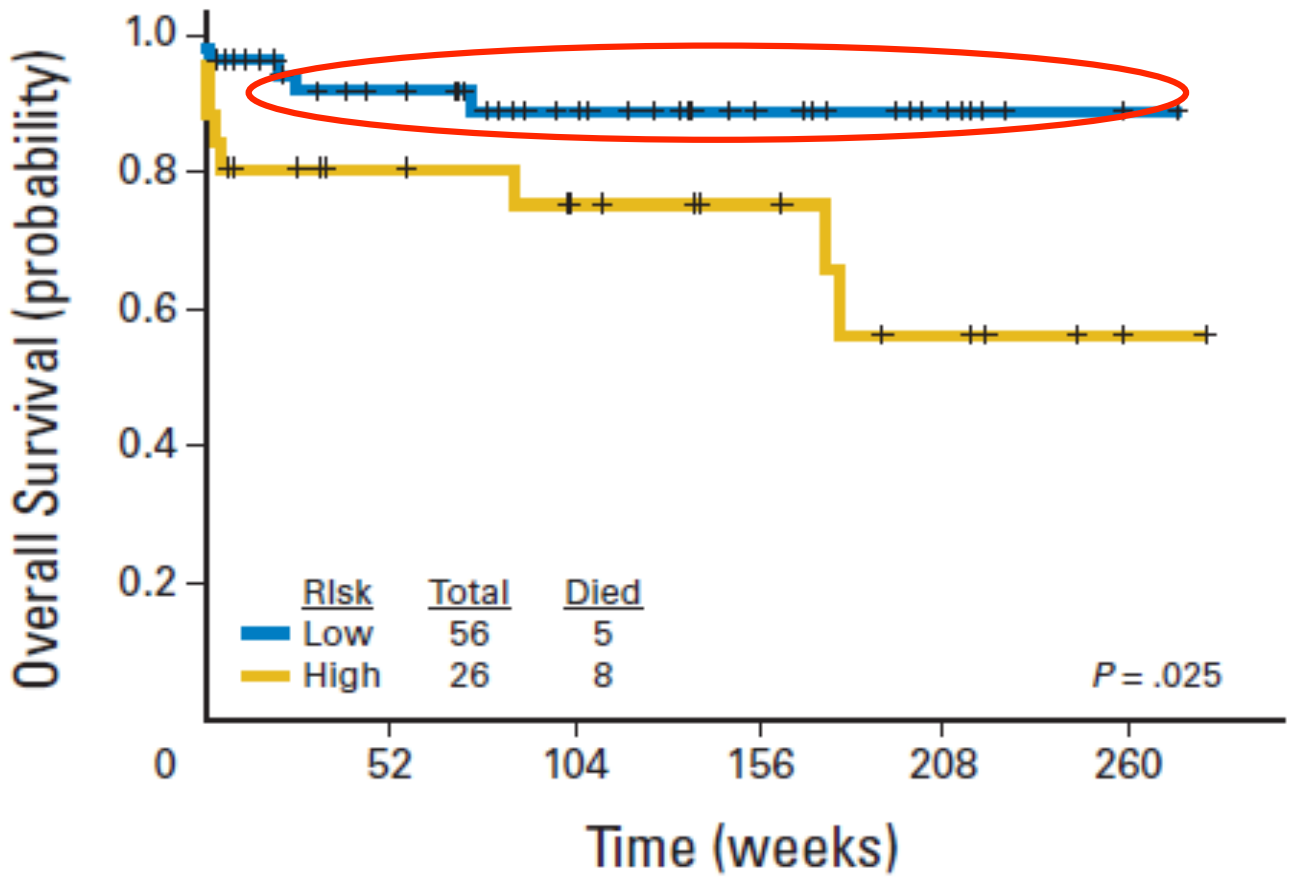
Scott Kogan, Cancer Cell 2009;15:7

Role of chemotherapy if arsenic is used as front-line therapy?

- Appealing concept to cure leukemia by non-chemotherapy agents: ATRA + As2O3
- Reduce the toxicity of chemotherapy
- Reduce the cost of treatment (China)

Ravandi F, J Clin Oncol 2009;27:504

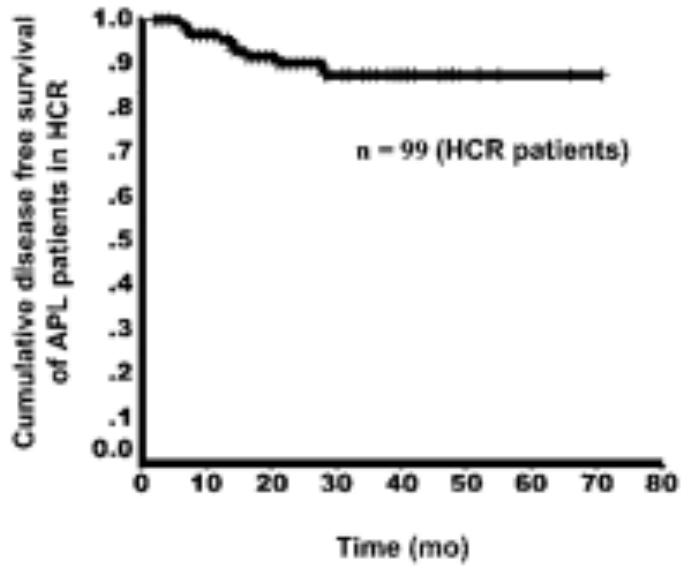
Chemotherapy required if arsenic is used as front-line therapy?



Ravandi F, JCO 2009;27:504

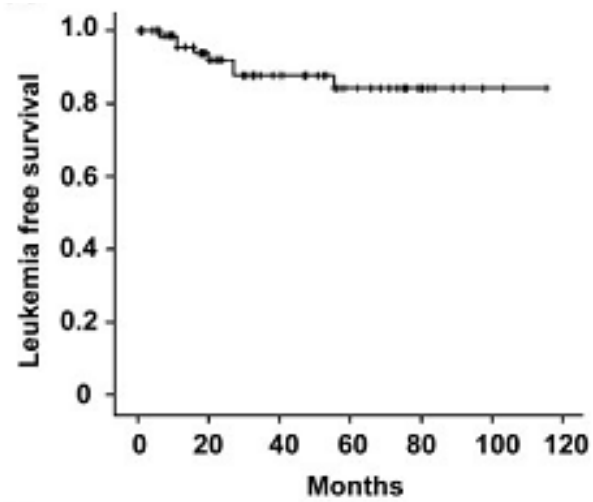
Ravandi F, J Clin Oncol 2009;27:504

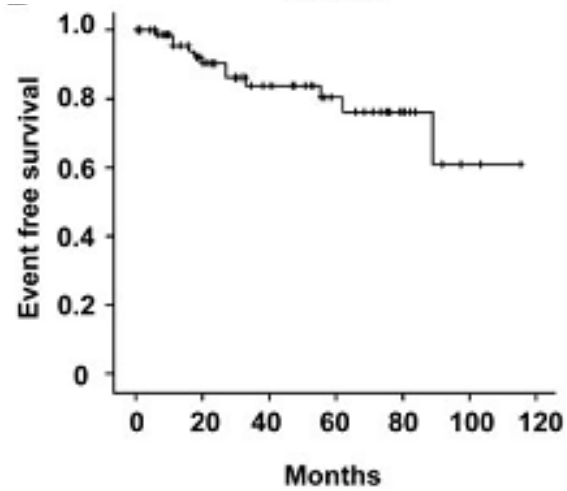
Oral arsenic



99 patients with oral As4S4 as post-remission therapy: DFS

Lu Blood. 2002;99:3136
Au W, Blood 2011;118:6535





76 patients with oral As2O3 as maintenance therapy: OS/EFS

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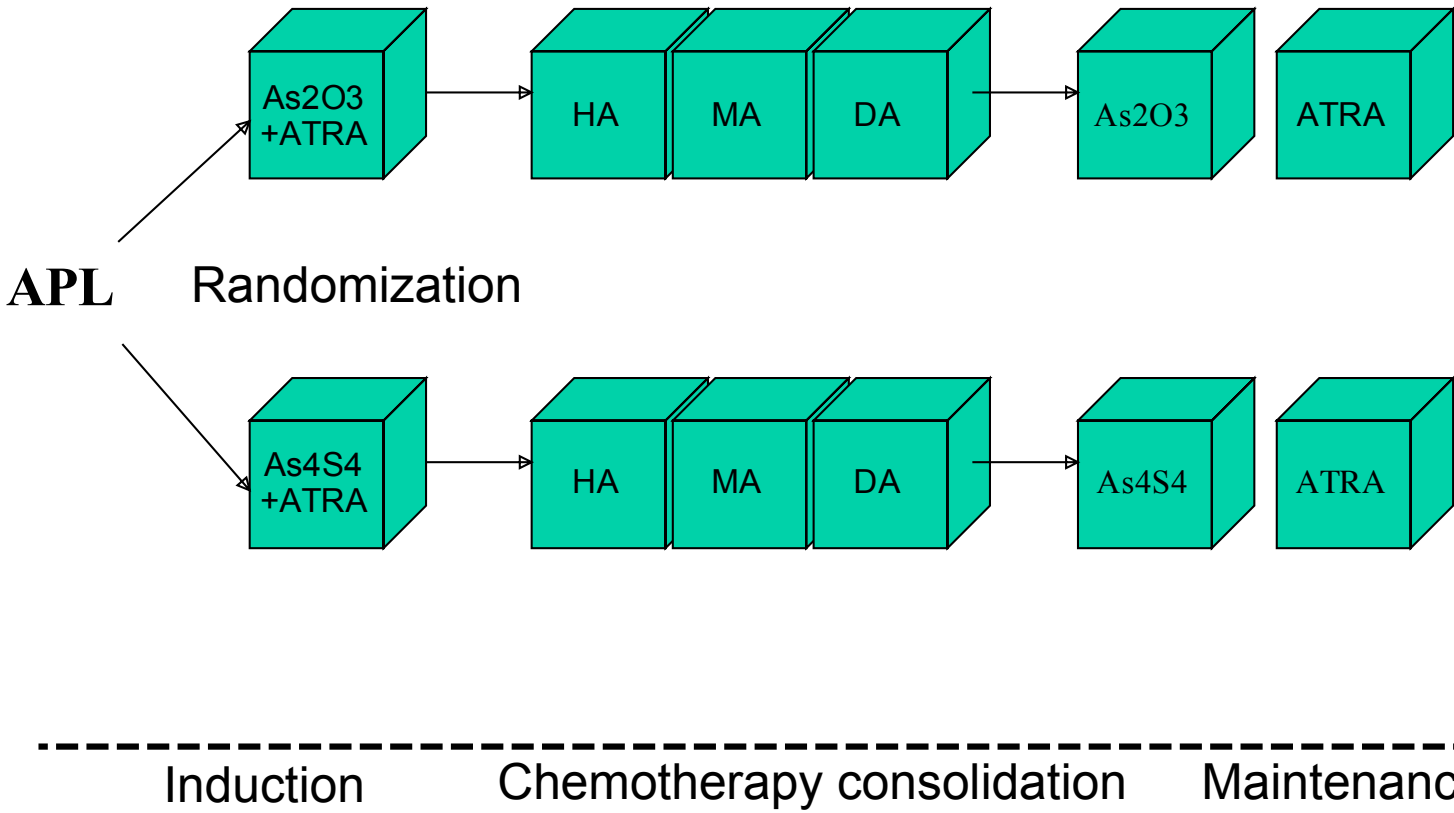
Randomized study compare iv As2O3 and oral As4S4



Coutersy from Prof Xiao-Jun Huang, Hong-hu Zhu

	共计		As4S4组		As2O3组		
	n=233	range	n=112	range	n=121	range	p
年龄	37	15-60	33	15-60	39	15-60	0.034
男/女	131/105		59/53		67/54		NS
WBC	2.18	0.3-50	2.26	0.3-54	2.2	0.3-54.3	NS
HGB	82	38-154	82	38-144	82	40-154	NS
PLT	30	5-333	29	5-133	31	5-164	NS
APL-PB%	32%	0-96	30	0-92	30	0-96	NS
APL-BM%	81%	19-96	82	35-96	81	19-96	NS
PML/RARA	45%	9.4-141.7	43.1	11.3-141.7	42.9	8.0-132.3	NS
PT	13.8	10.5-76	13.7	10.5-120	13.9	10.9-71.2	NS
APTT	29.1	2.5-180	29	2.5-180	28.9	20.5-62.5	NS
INR	1.15	0.85-2.39	1.13	0.88-2.25	1.16	0.87-2.39	NS
FDP	25.8	1.78-3422	20	1.78-3422	20	1.84-5201	NS
FIB	150	100-324	175	50-418	137	20-400	NS
D-D	1102	380-9999	1154	82-9999	1008	380-9999	NS
AST	21	8-212	20	6-164	21	7.4-212	NS
ALT	18	5-166	19	7-166	18	5-114	NS
BUN	4.7	1.6-148	4.8	1.6-148	4.5	1.88-82	NS
Cr	61	27-203	61	28-104	60	27-203	NS

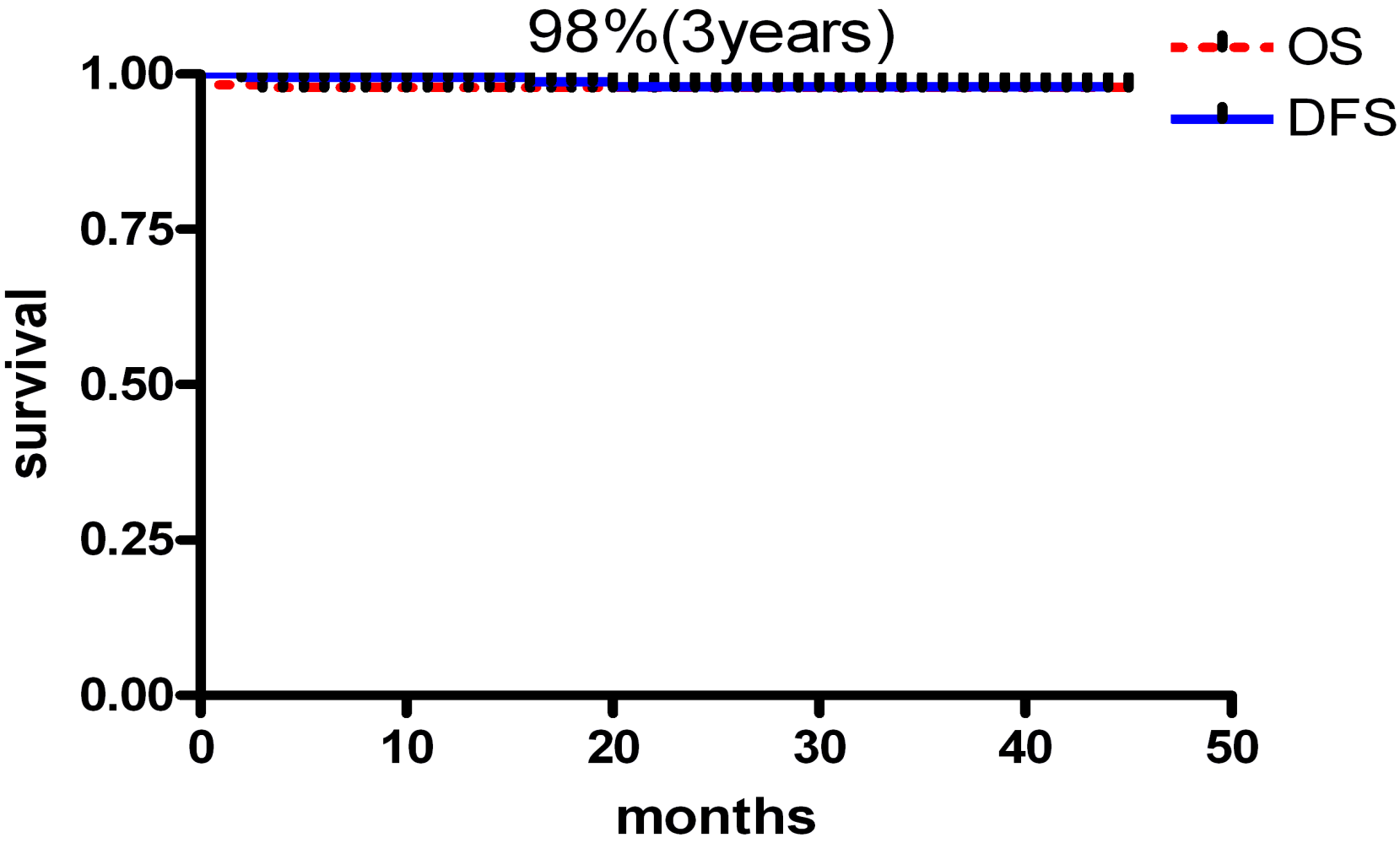
Coutersy from Prof Xiao-Jun Huang, Hong-hu

Induction therapy

	As4S4 n=112	As2O3 n=121	p
CR	98%	98%	>0.05
Time to CR	30days	29days	>0.05
PML/RAR□			
CR	15.0%	2.1%	<0.05
Consolidation	0	0	>0.05
Mol CR	100%	100%	>0.05
Follow-up(mths)	22	22	>0.05

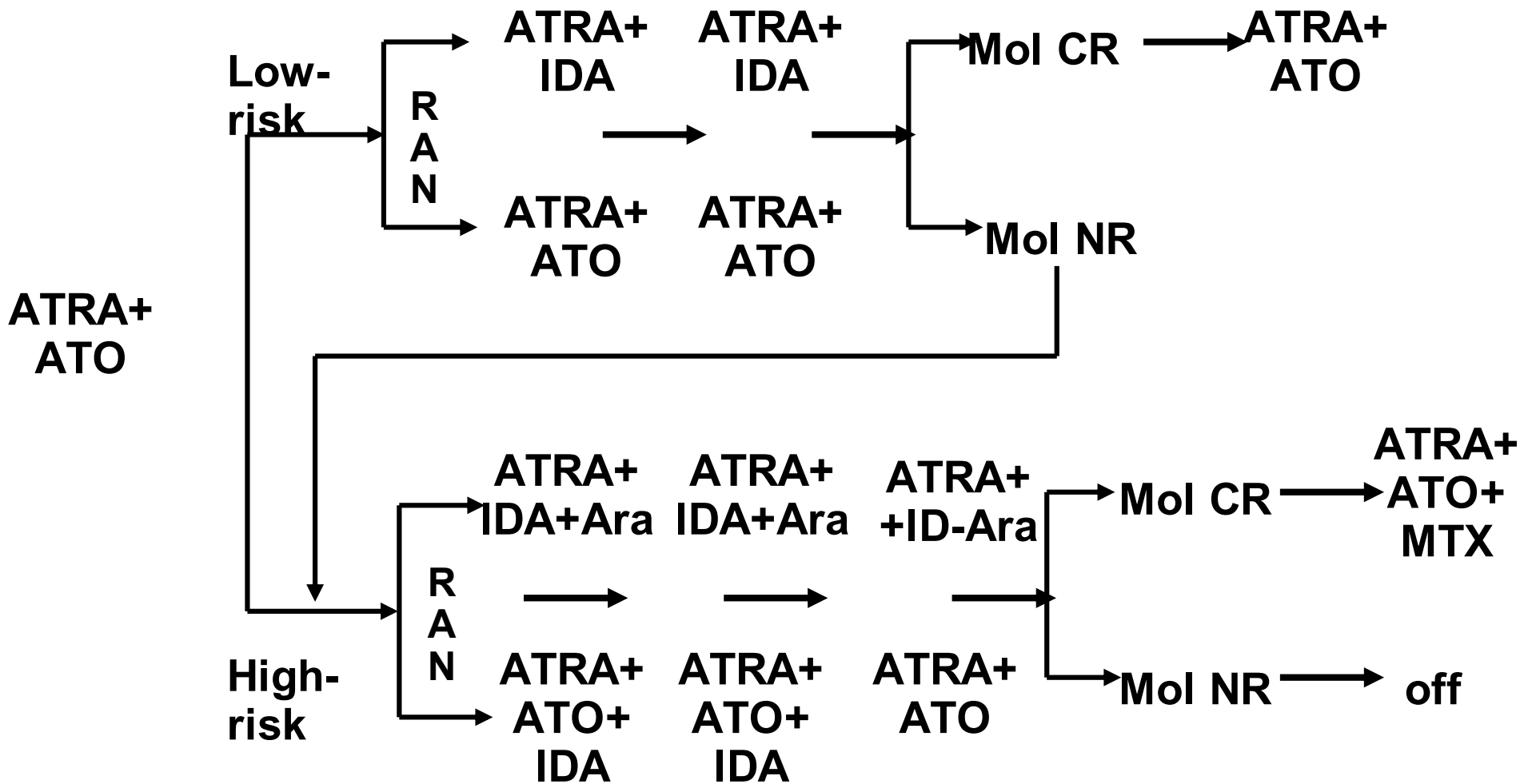
Coutersy from Prof Xiao-Jun Huang, Hong-hu

DFS/OS



Coutersy from Prof Xiao-Jun Huang, Hong-hu

Study design



Summary

- **Arsenic as front-line therapy: improved long-term DFS/EFS/OS**
- **Optimization of arsenic:**

- Oral arsenic: promising primary data and may replacing iv arsenic in future

- high-adapt strategy:

ATRA+Arsenic for low-risk patients

ATRA+Arsenic+chemo for high-risk patients

- long-term toxicity of arsenic

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