

Update of the Italian-German study APL 0406

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7th International Symposium on Acute Promyelocytic Leukemia
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Background



Jean Bernard

BLOOD

The Journal of Hematology

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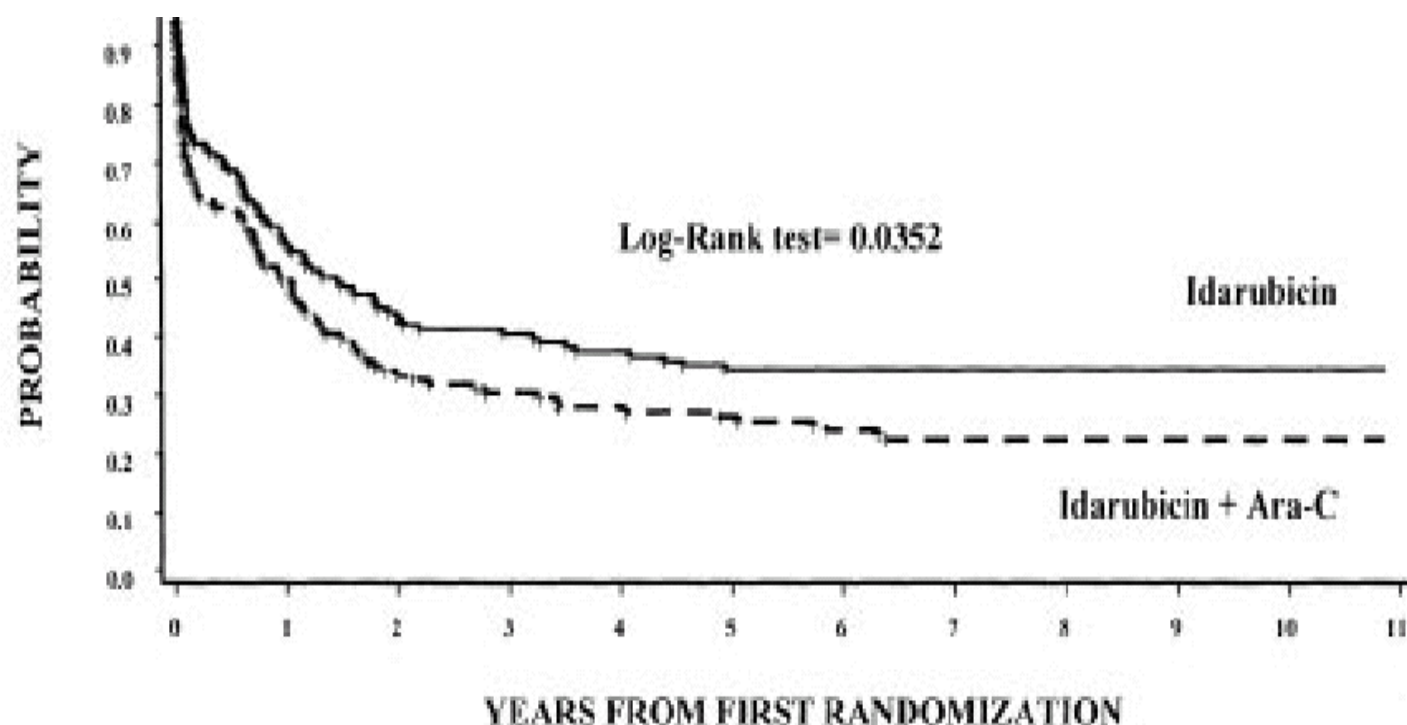
APRIL 1973

**Acute Promyelocytic Leukemia : Results of Treatment
by Daunorubicin**

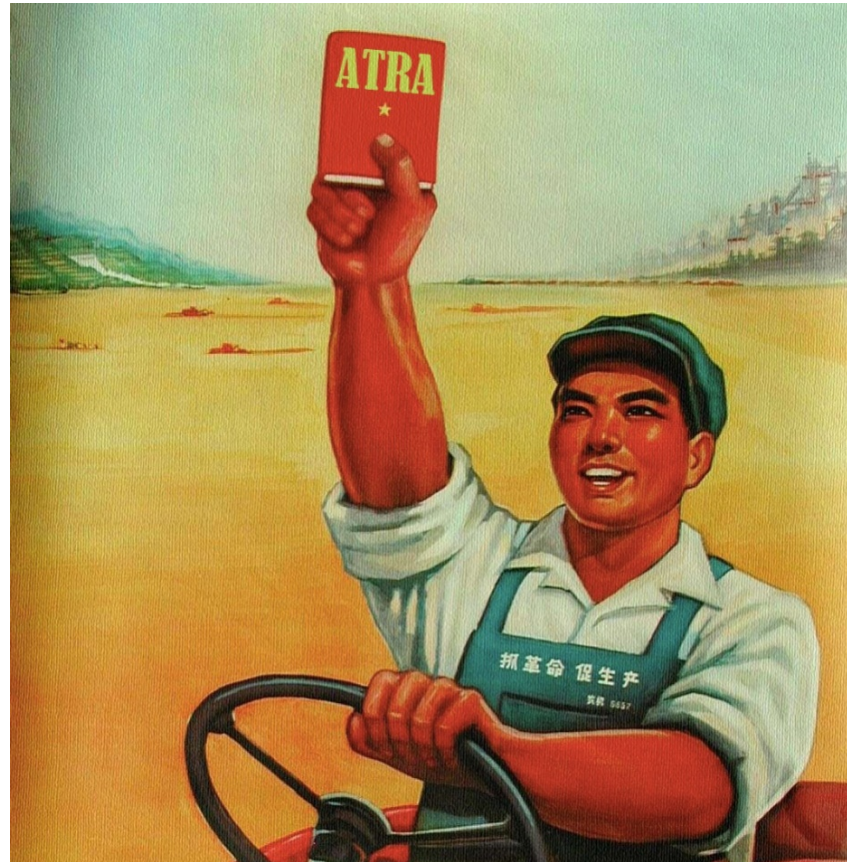
By Jean Bernard, Marise Weil, Michel Boiron, Claude Jacquillat,
Georges Flandrin, and Marie-François Gemon

Induction therapy with idarubicin alone significantly influences event-free survival duration in patients with newly diagnosed hypergranular acute promyelocytic leukemia: final results of the GIMEMA randomized study LAP 0389 with 7 years of minimal follow-up

Giuseppe Avvisati, Maria Concetta Petti, Francesco Lo-Coco, Maria Luce Vegna, Sergio Amadori, Michele Baccarani, Nicola Cantore, Eros Di Bona, Felicetto Ferrara, Giuseppe Fioritoni, Eugenio Gallo, Rosangela Invernizzi, Mario Lazzarino, Vincenzo Liso, Guglielmo Mariani, Francesco Ricciuti, Carmine Sileri, Simona Sica, Dino Veneri and Franco Mandelli



1988



blood

1988 72: 567-572

Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia

ME Huang, YC Ye, SR Chen, JR Chai, JX Lu, L Zhoa, LJ Gu and ZY Wang

1993 ATRA+Cht Higher Cure Rate



Laurent Degos



Pierre Fenaux

blood

1996 88: 1390-1398

AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study

G Awvisati, F Lo Coco, D Diverio, M Falda, F Ferrara, M Lazzarino, D Russo, MC Petti and F Mandelli

blood

2011 117: 4716-4725
Prepublished online March 8, 2011;
doi:10.1182/blood-2010-08-302950

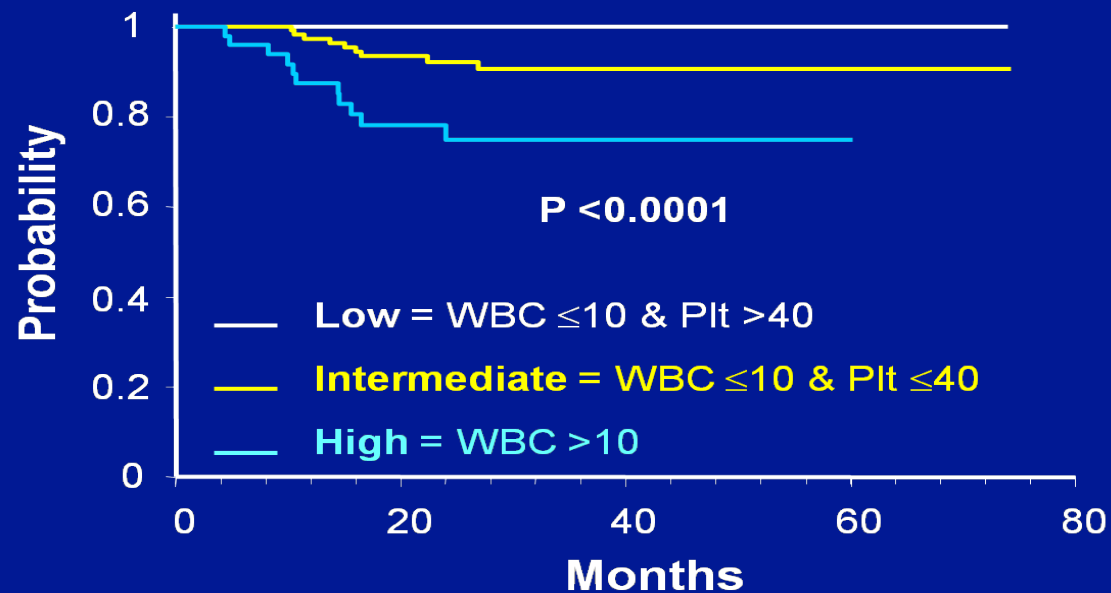
AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance

Giuseppe Awvisati, Francesco Lo-Coco, Francesca Paola Paoloni, Maria Concetta Petti, Daniela Diverio, Marco Vignetti, Roberto Latagliata, Giordina Specchia, Michele Baccarani, Eros Di Bona, Giuseppe Fioritoni, Filippo Marmont, Alessandro Rambaldi, Francesco Di Raimondo, Maria Grazia Kropp, Giovanni Pizzolo, Enrico M. Pogliani, Giuseppe Rossi, Nicola Cantore, Francesco Nobile, Attilio Gabbas, Felicetto Ferrara, Paola Fazi, Sergio Amadori, Franco Mandelli and for the GIMEMA, AIEOP, and EORTC Cooperative Groups

Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups

Miguel A. Sanz, Francesco Lo Coco, Guillermo Martín, Giuseppe Avvisati, Consuelo Rayón, Tiziano Barbui, Joaquín Díaz-Mediavilla, Giuseppe Fioritoni, José David González, Vincenzo Liso, Jordi Esteve, Felicetto Ferrara, Pascual Bolufer, Carlo Bemasconi, Marcos Gonzalez, Francesco Rodeghiero, Dolores Colomer, Maria C. Petti, José M. Ribera, and Franco Mandelli for the Spanish PETHEMA and the Italian GIMEMA Cooperative Groups

APL. GIMEMA & PETHEMA Study Relapse-free survival by relapse-risk group



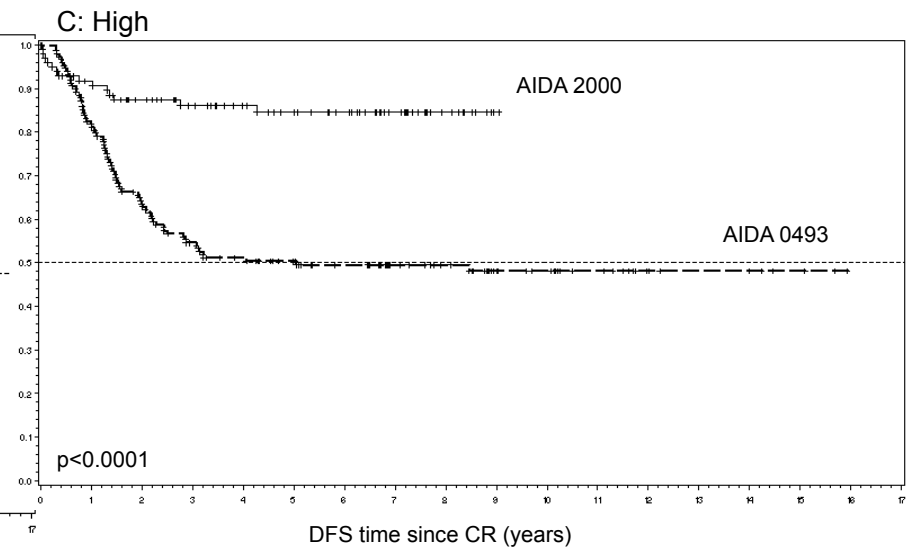
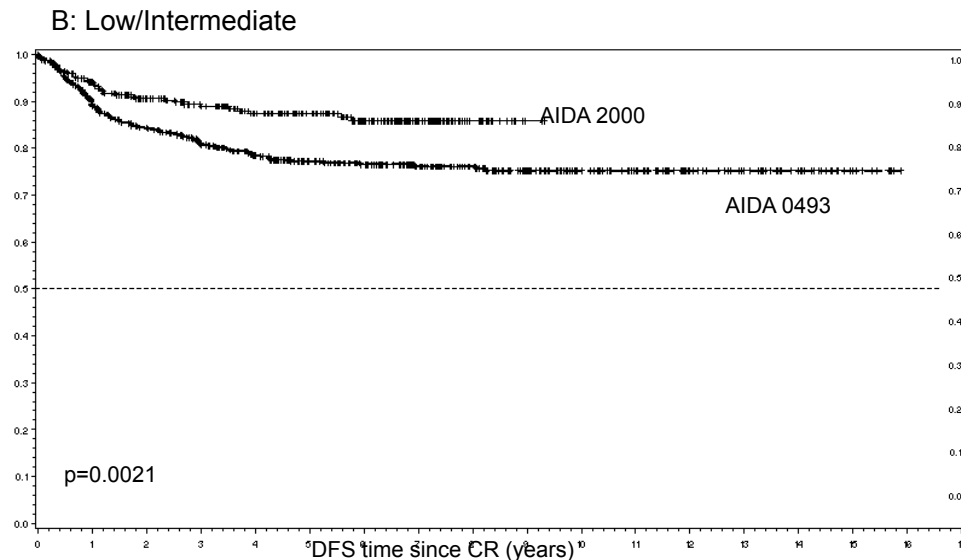
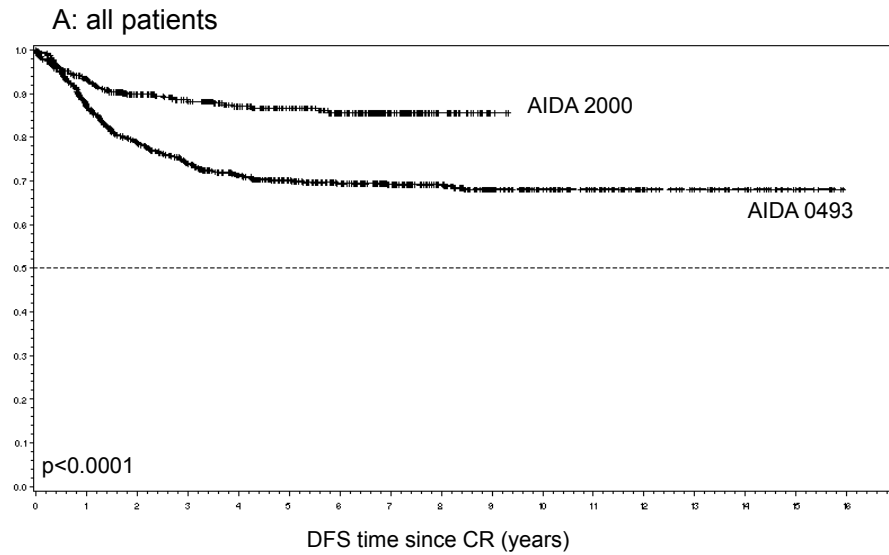
blood

2010 116: 3171-3179
Prepublished online July 19, 2010;
doi:10.1182/blood-2010-03-276196

Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group

Francesco Lo-Coco, Giuseppe Avvisati, Marco Vignetti, Massimo Breccia, Eugenio Gallo, Alessandro Rambaldi, Francesca Paoloni, Giuseppe Fioritoni, Felicetto Ferrara, Giorgina Specchia, Giuseppe Cimino, Daniela Diverio, Erika Borlenghi, Giovanni Martinelli, Francesco Di Raimondo, Eros Di Bona, Paola Fazi, Antonio Peta, Alberto Bosi, Angelo M. Carella, Francesco Fabbiano, Enrico M. Pogliani, Maria C. Petti, Sergio Amadori, Franco Mandelli and for the Italian GIMEMA Cooperative Group

AIDA 2000 Vs AIDA 0493 (historical)



1997



blood

1997 89: 3354-3360

Use of Arsenic Trioxide (As_2O_3) in the Treatment of Acute Promyelocytic Leukemia (APL): II. Clinical Efficacy and Pharmacokinetics in Relapsed Patients

Zhi-Xiang Shen, Guo-Qiang Chen, Jian-Hua Ni, Xiu-Shong Li, Shu-Min Xiong, Qian-Yao Qiu, Jun Zhu, Wei Tang, Guan-Lin Sun, Kan-Qi Yang, Yu Chen, Li Zhou, Zhi-Wen Fang, Yan-Ting Wang, Jun Ma, Peng Zhang, Ting-Dong Zhang, Sai-Juan Chen, Zhu Chen and Zhen-Yi Wang

blood

2006 107: 3469-3473
Prepublished online December 22, 2005;
doi:10.1182/blood-2005-10-4006

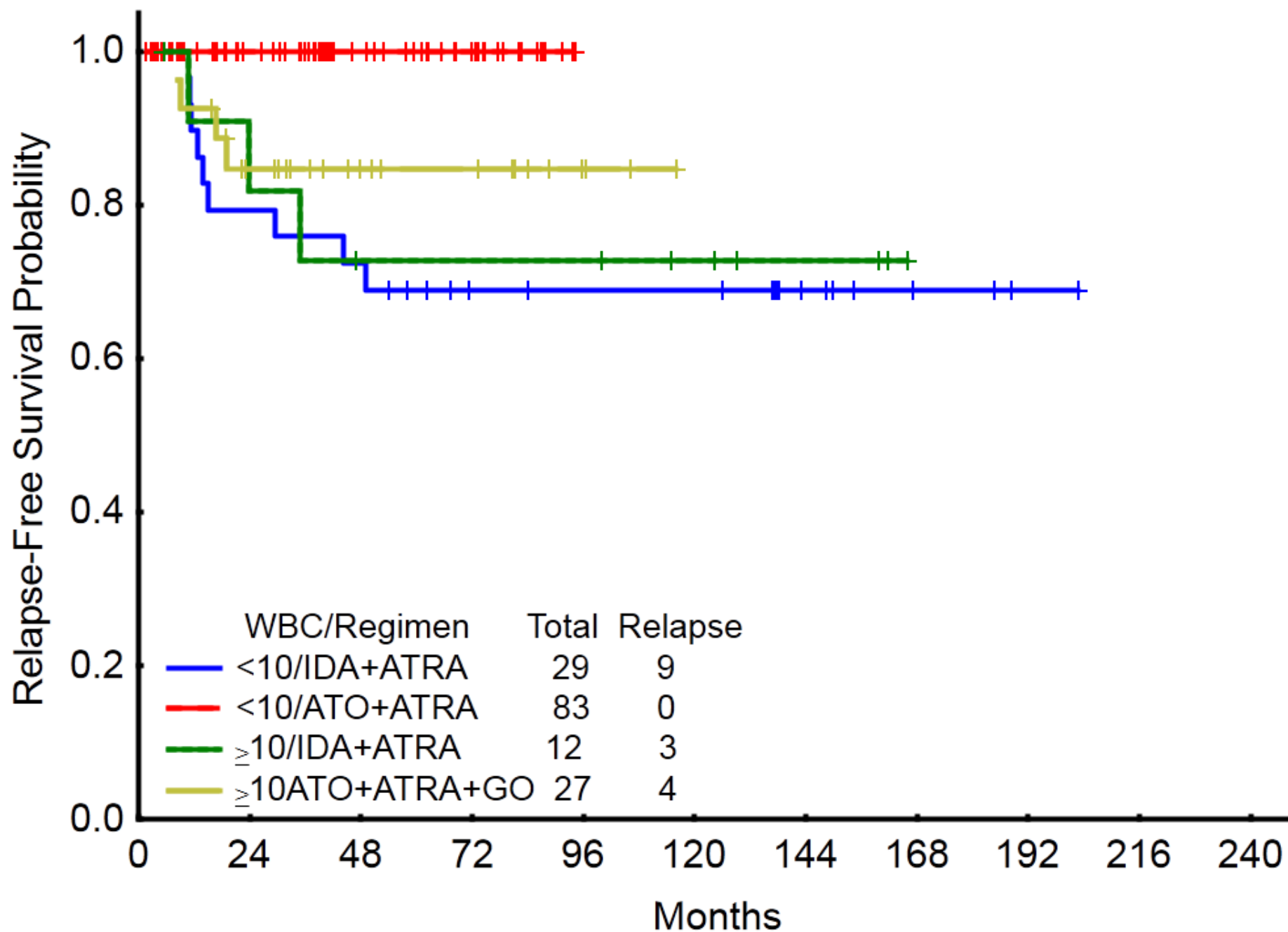
Use of all-*trans* retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia

Elihu Estey, Guillermo Garcia-Manero, Alessandra Ferrajoli, Stefan Faderl, Srdan Verstovsek, Dan Jones and Hagop Kantarjian



Elihu Estey

Experience with Arsenic in APL (Estey et al.)

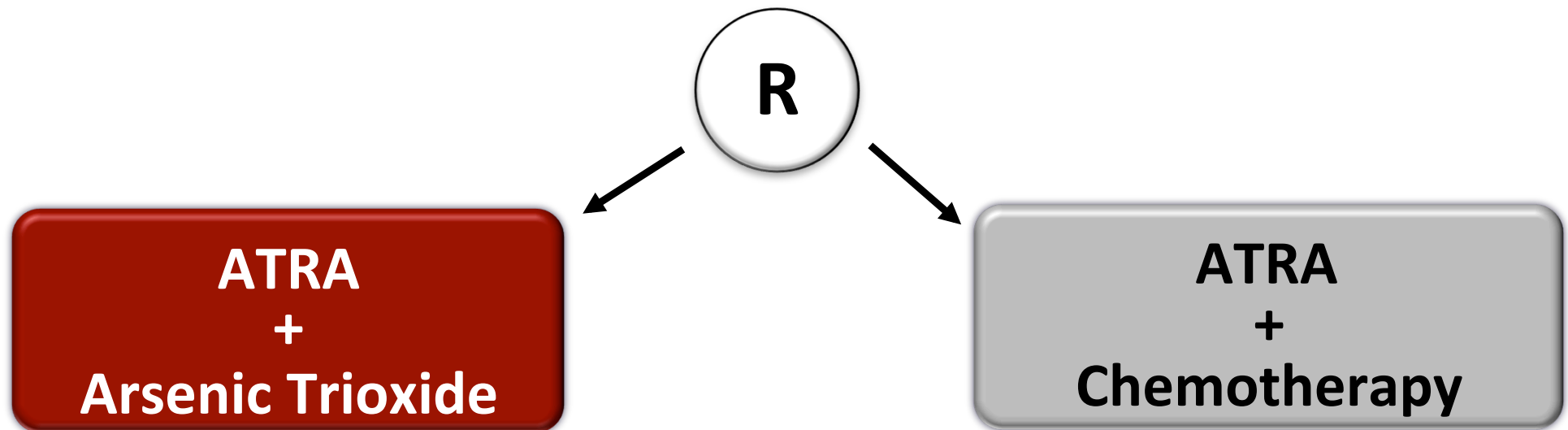


APL 0406 Italian-German

Phase III Study

Acute Promyelocytic Leukemia

Low-intermediate risk



APL-0406 Study in non-high risk (GIMEMA-AMLSG-SAL)

Lo-Coco *et al.* N Engl J Med 2013;369:111-21

Induction

Consolidation

weeks 0 4 8 12 16 20 24 28



4 weeks on / 4 weeks off



2 weeks on / 2 weeks off

Until CR
(max 60 days)

Estey *et al.* Blood 2006;107:3469-73

Induction

Consolidation

Maintenance



Until CR



3 monthly cycles



2 years

Lo-Coco *et al.* Blood 2010;116:3171-9

ATO
arm

R

Chemo
arm

Results

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JULY 11, 2013

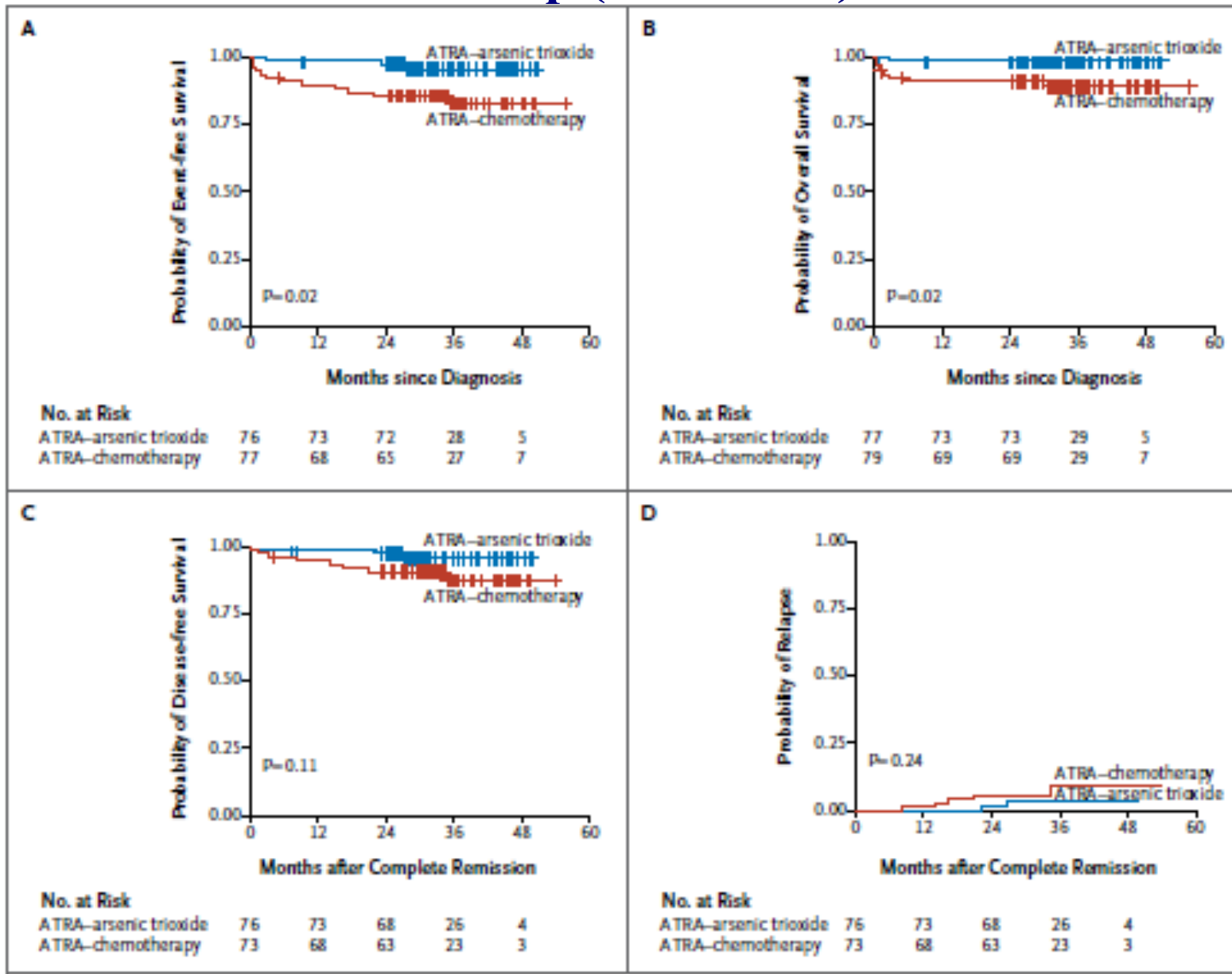
VOL. 369 NO. 2

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 trial original series

Follow-up (34 months)



Haematological Toxicity

Grade 3-4 thrombocytopenia >15 days

Grade 3-4 neutropenia >15 days

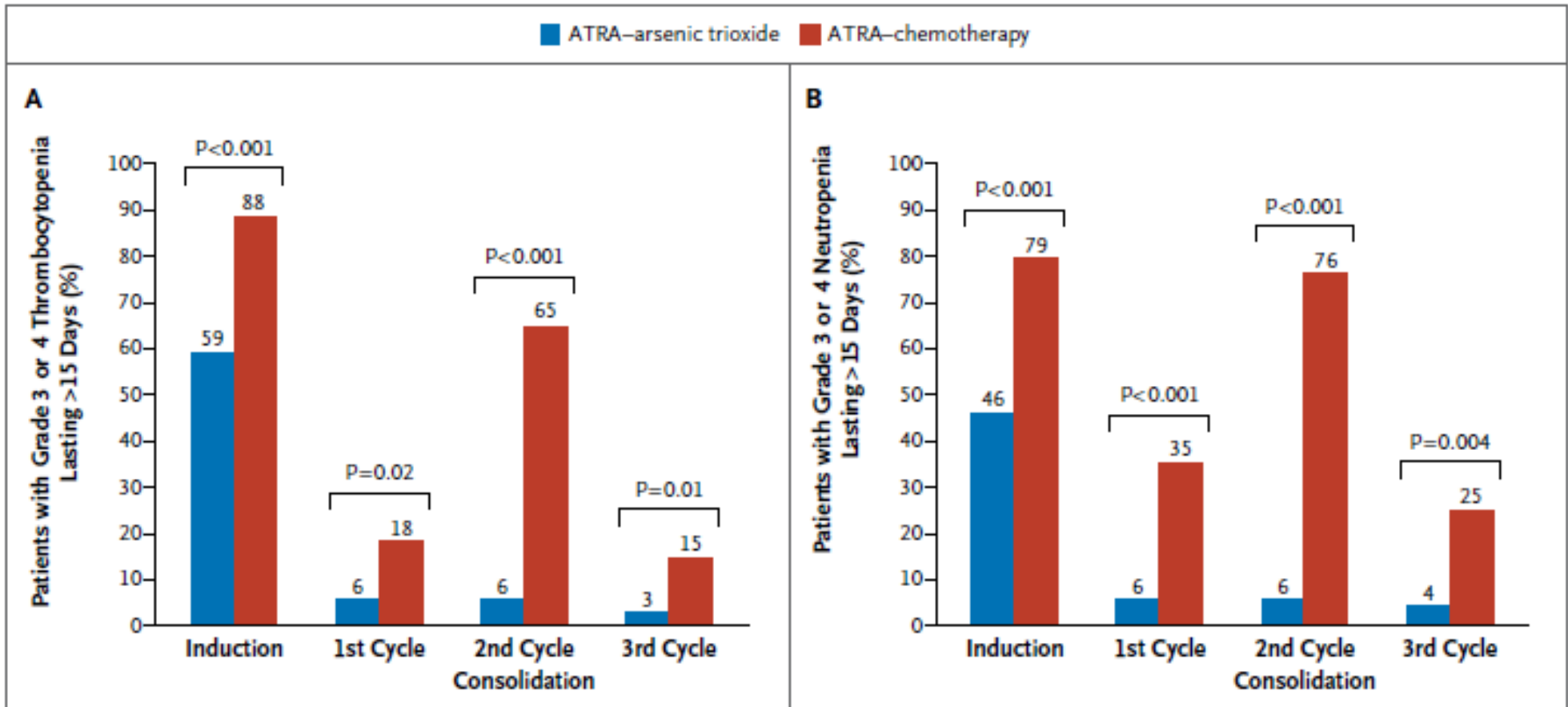


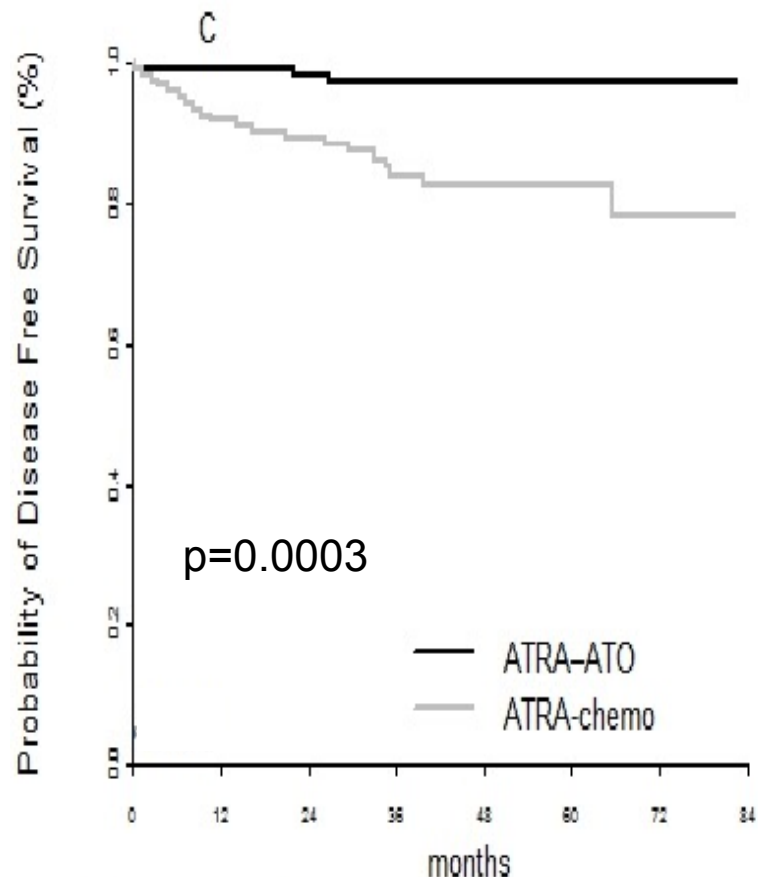
Figure 4. Hematologic Toxic Effects.

Improved Outcomes With Retinoic Acid and Arsenic Trioxide Compared With Retinoic Acid and Chemotherapy in Non–High-Risk Acute Promyelocytic Leukemia: Final Results of the Randomized Italian-German APL0406 Trial

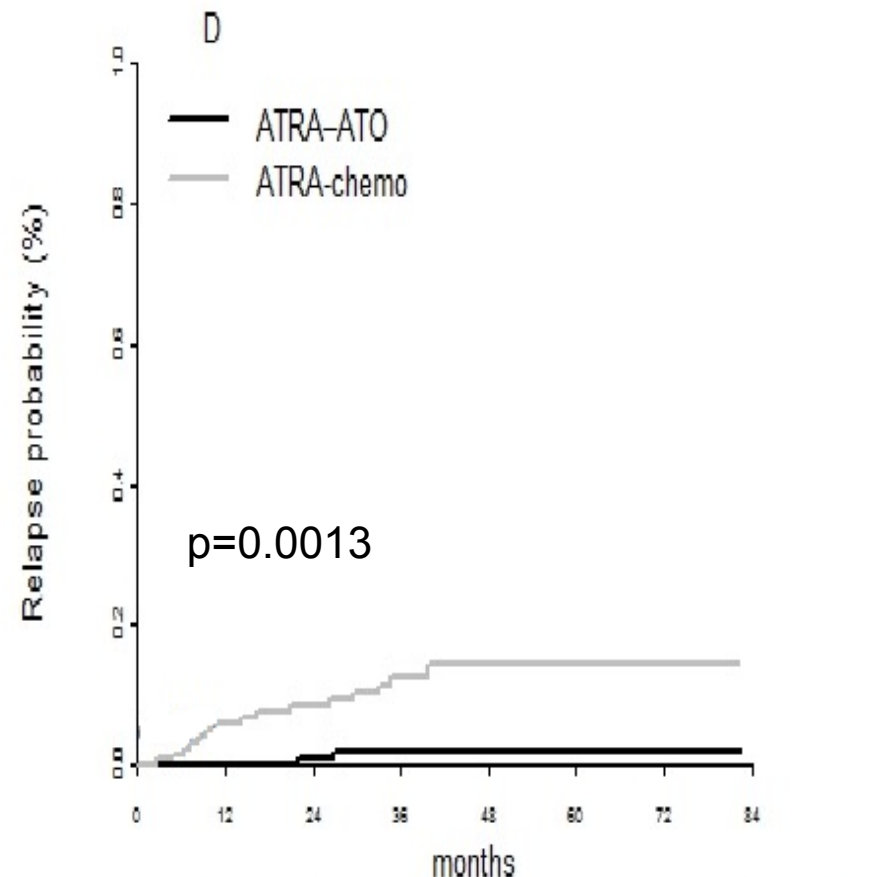
Uwe Platzbecker, Giuseppe Avvisati, Laura Cicconi, Christian Thiede, Francesca Paoloni, Marco Vignetti, Felicetto Ferrara, Mariadomenica Divona, Francesco Albano, Fabio Efficace, Paola Fazi, Marco Sborgia, Eros Di Bona, Massimo Breccia, Erika Borlenghi, Roberto Cairoli, Alessandro Rambaldi, Lorella Melillo, Giorgio La Nasa, Walter Fiedler, Peter Brossart, Bernd Hertenstein, Helmut R. Salih, Mohammed Wattad, Michael Lübbert, Christian H. Brandts, Mathias Hänel, Christoph Röllig, Norbert Schmitz, Hartmut Link, Chiara Frairia, Enrico Maria Pogliani, † Claudio Fozza, Alfonso Maria D'Arco, Nicola Di Renzo, Agostino Cortelezzi, Francesco Fabbiano, Konstanze Döhner, Arnold Ganser, Hartmut Döhner, Sergio Amadori, Franco Mandelli, Gerhard Ehninger, Richard F. Schlenk, and Francesco Lo-Coco

APL 0406: Updated and extended series

Follow-up (41.9 mos)



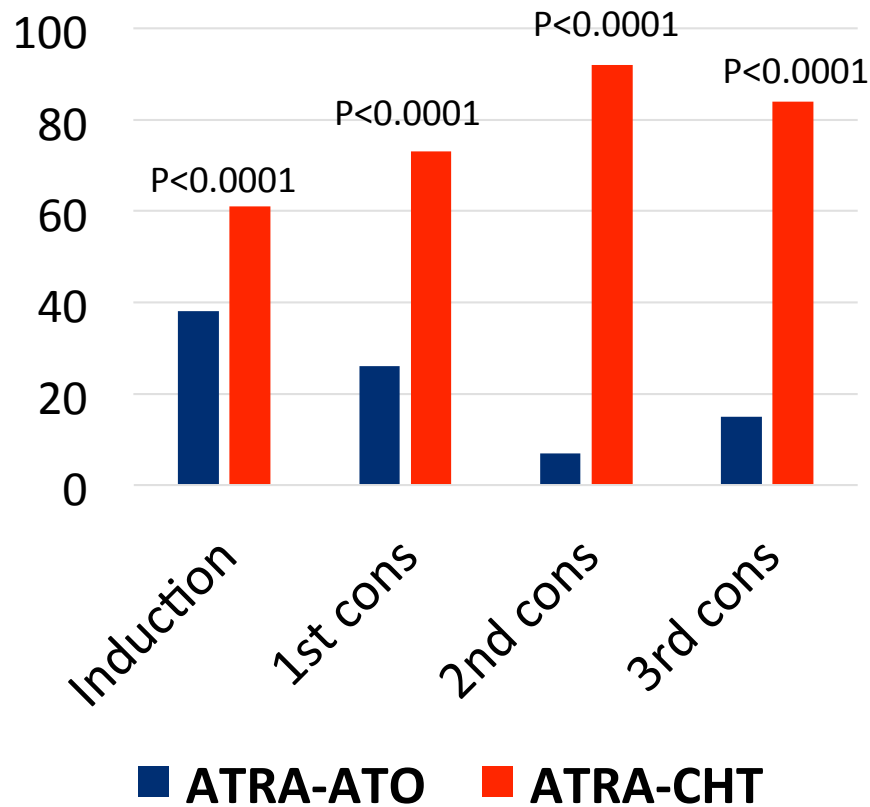
127	116	105	77	51	25	5	ATRA-ATO
132	111	103	68	40	31	6	ATRA-chemo



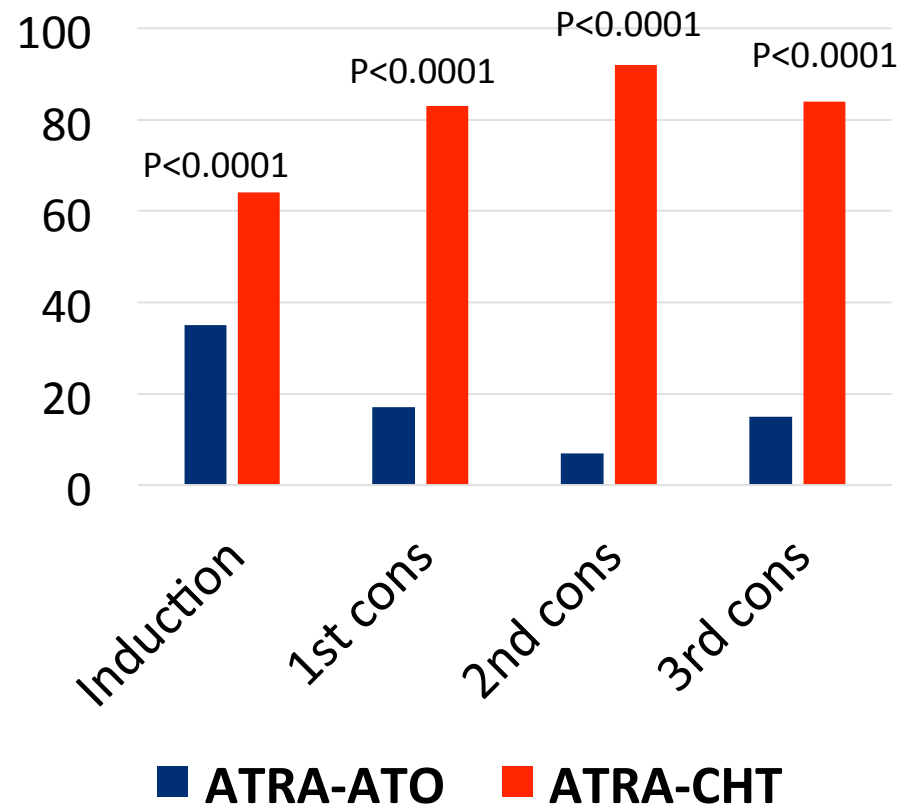
127	116	105	77	51	25	5	ATRA-ATO
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Haematological Toxicity

Grade 3-4 thrombocytopenia >15 days



Grade 3-4 neutropenia >15 days



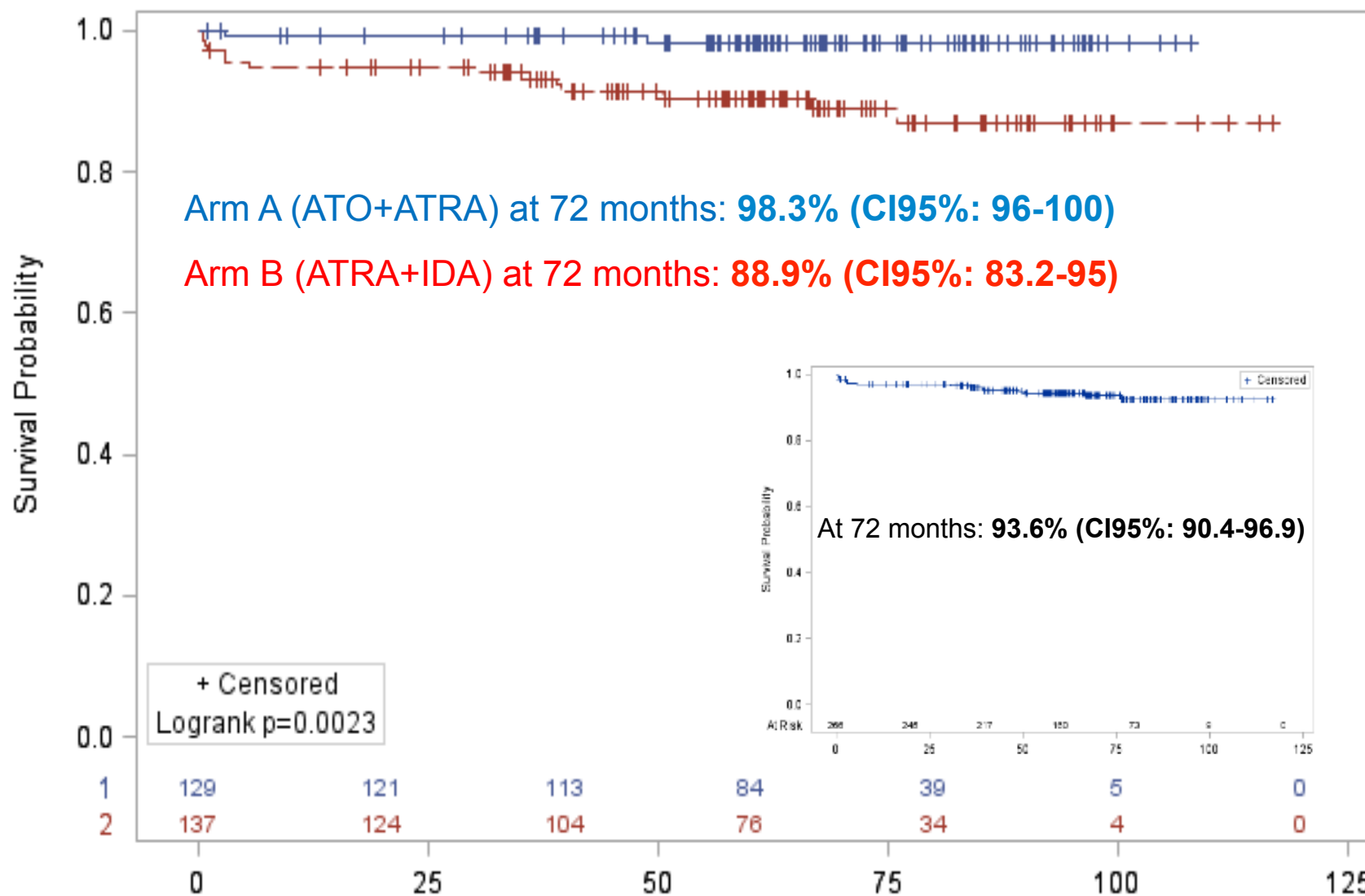
APL0406. Non-haematologic toxicities

Side effect	ATRA+ATO	ATRA+CHT	P-value
QTc prolongation	15.6%	0%	P<0.001
Hyperleukocytosis	47%	24%	P=0.007
Hepatic toxicity (grade 3-4)	63.2%	5.8%	P<0.001
Gastrointestinal toxicity (grade 3-4)	4.4%	9.9%	P=0.33
Oral toxicity (grade 3-4)	0%	19.4%	P<0.001

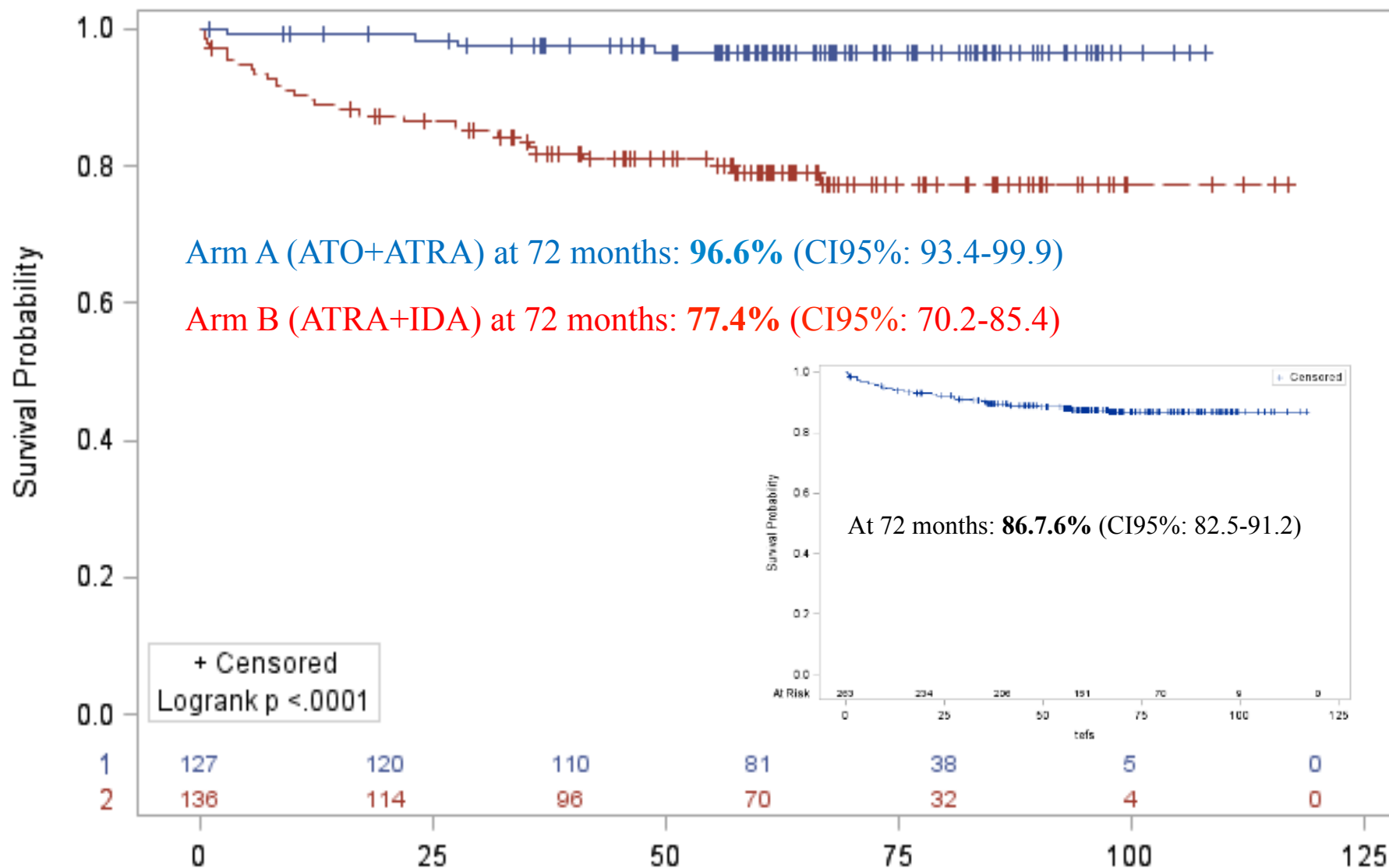
**Update of the Italian-German study
APL 0406
as of September 20 – 2017**

Median follow-up : 66.2 months (0.9-116.7)

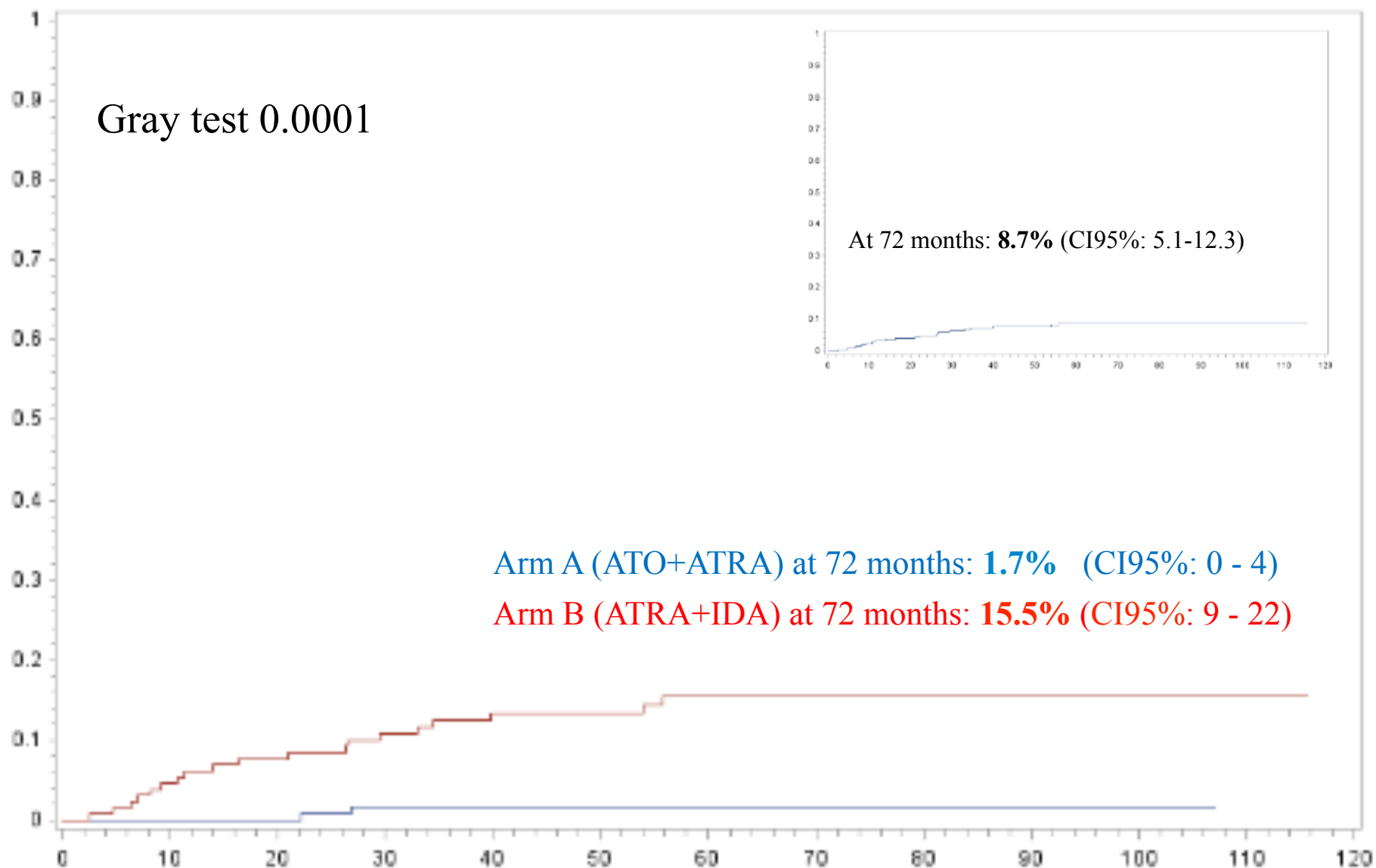
OVERALL SURVIVAL



EVENT FREE SURVIVAL



CUMULATIVE INCIDENCE of RELAPSE



EVENTS as of September 20, 2017

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

Causes of Death as of September 20, 2017

	#	ATRA-ATO	AIDA
Induction Deaths	4	-	2 ARDS 1 Cardiac 1 Ischemic stroke
Deaths in CR	7	1 Unknown 1 Pneumonia	1 Unknown 1 Hemorrhagic 1 Infection 1 ARDS 1 TE (Lung)
Deaths in Relapse	5	-	4 Unknown 1 M.O.C post Haplo BMT
Total	16	2	14

APL0406 Study Outcomes as of September 20,2017

		Survival probability (95% CI)			P-value
		24 months	50 months	72 months	
OS	ATRA-ATO	99.2% (97.7-100)	99.2% (97.7-100)	98.3% (96-100)	0.0023
	ATRA-CHT	94.8% (91.1-98.6)	92.6% (87.9-97.5)	88.9% (83.2-95)	
EFS	ATRA-ATO	98.3% (95.9-100)	97.3% (94.3-100)	96.6% (93.4-99.9)	<0.0001
	ATRA-CHT	86.8% (81-92.5)	80% (72.9-88.3)	77.4% (70.2-85.4)	
CIR	ATRA-ATO	0.9% (0-2.7)	1.9% (0.0-4.5)	1.7% (0-4)	0.0001
	ATRA-CHT	8.2% (3.3-13.1)	13.9% (7.1-20.6)	15.5% (9-22)	

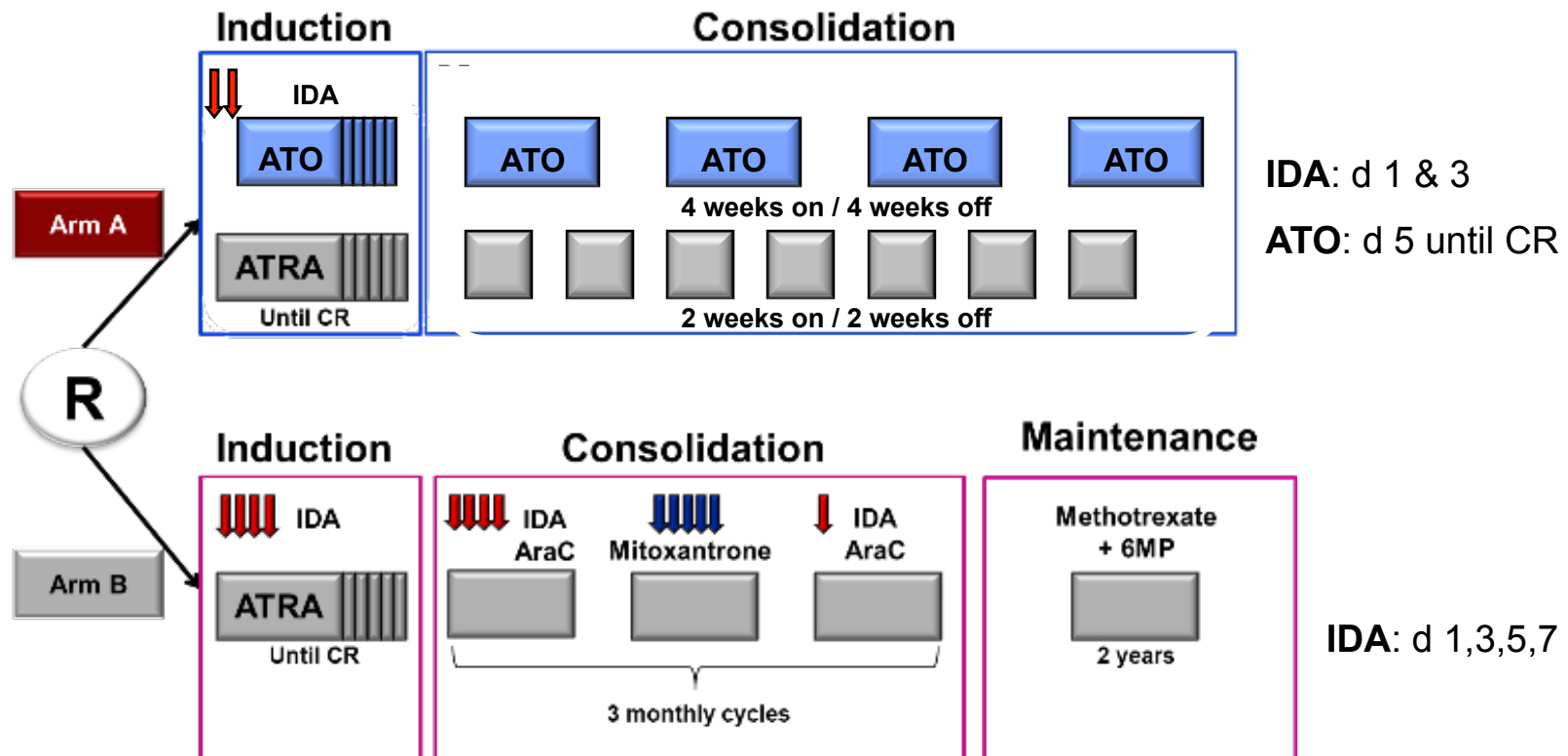
CONCLUSION

ATRA+ATO must be considered the standard
Treatment of newly diagnosed non high risk
APL patients.

Next Step

Phase III European trial for high-risk APL (APOLLO started on January 2017)

(Treatment Arms)



Aknowledgements (1)

- **APL patients**
- **All Nurses and Colleagues involved in the treatment of these patients**
- **All Cooperative groups in the world which contributed with GIMEMA to cure these Pts**

Aknowledgements (2)

- Francesco Lo Coco
- Francesca Paoloni
- Marco Vignetti

- Gerhard Ehninger
- Christian Thiede
- Uwe Platzbecker

- Hartmut Döhner
- Arnold Ganser
- Richard Schlenk

GIMEMA
Italy

SAL
Germany

AMLSG
Germany

Franco Mandelli