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Long-term results of all-*trans* retinoic acid and arsenic trioxide in non-high risk acute promyelocytic leukemia: update of the APL0406 Italian-German randomized trial.

Laura Cicconi[1*], Uwe Platzbecker[2*], Giuseppe Avvisati[3], Francesca Paoloni[4], Christian Thiede[5], Marco Vignetti[4], Paola Fazi[4], Felicetto Ferrara[6], Mariadomenica Divona[7], Francesco Albano[8], Fabio Efficace[4], Marco Sborgia[9], Eros Di Bona[10], Massimo Breccia[11], Erika Borlenghi[12], Roberto Cairoli[13], Alessandro Rambaldi[14], Lorella Melillo[15], Giorgio La Nasa[16], Walter Fiedler[17], Peter Brossart[18], Bernd Hertenstein[19], Helmut R. Salih[20], Ombretta Annibali[3], Mohammed Wattad[21], Michael Lubbert[22], Christian H. Brandts[23], Mathias Hanel[24], Christoph Rollig[5], Norbert Schmitz[25], Hartmut Link[26], Chiara Frairia[27], Claudio Fozza[28], Alfonso Maria D'Arco[29], Nicola Di Renzo[30], Agostino Cortelezzi[31], Francesco Fabbiano[32], Konstanze Dohner[33], Arnold Ganser[34], Hartmut Dohner[33], Sergio Amadori[4], Franco Mandelli[4†], Maria Teresa Voso[1,35], Gerhard Ehninger[5], Richard F. Schlenk[36], and Francesco Lo-Coco[1,35†]

* The first two authors equally contributed to this work.

1. Department of Biomedicine and Prevention, University Tor Vergata, Rome, Italy
2. Universitätsklinikum Leipzig, Leipzig, Germany
3. Ematologia e Trapianto di cellule staminali, Università Campus Bio-Medico, Rome, Italy
4. GIMEMA Data Center, Rome, Italy
5. Universitätsklinikum Carl Gustav Carus der Technischen Universität, Dresden, Germany
6. Dipartimento di Ematologia e Trapianto di Cellule Staminali, Ospedale Cardarelli, Napoli, Italy
7. Laboratorio di Oncoematologia, Policlinico Tor Vergata, Rome, Italy
8. Dipartimento di Ematologia, Università di Bari, Bari, Italy
9. U.O. di Ematologia Clinica, Pescara
10. Dipartimento di Terapie cellulari ed Ematologia, Unità Operativa di Ematologia, Ospedale S. Bortolo, Vicenza, Italy
11. Dipartimento di Biotecnologie Cellulari ed Ematologia, Università La Sapienza, Rome, Italy
12. Dipartimento di Ematologia, Spedali Civili, Brescia, Italy
13. Grande Ospedale Metropolitano Niguarda, SC Ematologia, Milan, Italy
14. Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
15. Casa Sollievo della Sofferenza Hospital, IRCCS, San Giovanni Rotondo, Italy
16. Centro Trapianti Midollo Osseo, Ospedale R. Binaghi, Università di Cagliari, Cagliari, Italy
17. University Hospital Hamburg-Eppendorf, Hamburg, Germany
18. University Hospital Bonn, Department of Oncology, Hematology, Immuno-Oncology and Rheumatology, CIO Bonn, Germany
19. Klinikum Bremen Mitte, Bremen, Germany
20. University Hospital Tubingen, Germany
21. Kliniken Essen Süd, Essen, Germany
22. University Medical Center, Freiburg, Germany
23. Goethe University Frankfurt, Frankfurt, Germany
24. Klinikum Chemnitz gGmbH, Chemnitz, Germany
25. Asklepios Klinik St Georg Hamburg, Hamburg, Germany
26. Klinik für Innere Medizin I, Westpfalz-Klinikum, Kaiserslautern, Germany
27. Città della Salute e della Scienza, Hematology, Torino, Italy
28. University of Sassari, Sassari, Italy
29. U.O. Medicina Interna e Onco-Ematologica P.O. "Umberto I," Nocera Inferiore, Nocera Inferiore, Italy
30. Ospedale Vito Fazzi, Lecce, Italy
31. Foundation Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico and University of Milan, Milan, Italy
32. Divisione di Ematologia e Unità di Trapianti di Midollo Osseo, Ospedale Riuniti Villa Sofia-Cervello, Palermo
33. University Hospital Ulm, Ulm, Germany
34. Hannover Medical School, Hannover, Germany
35. Fondazione Santa Lucia, Laboratorio di Neuro-Oncoematologia, Roma, Italy
36. NCT Trial Center, National Center for Tumor Diseases Heidelberg, Germany

Corresponding author:
Maria Teresa Voso, MD
Tor Vergata University, Department of Biomedicine and prevention
Viale Oxford,81 00133 Rome
voso@med.uniroma2.it
Tel. 06/20903222
Fax 06/20903220

Dear Editor,

the combination of All-*trans* retinoic acid (ATRA) and chemotherapy has long since represented the standard of care for newly diagnosed acute promyelocytic leukemia (APL). This approach showed long-term cure rates exceeding 80% (1,2) but was associated with the risk of severe infections, deaths in remission and to the development of therapy-related leukemias and myelodysplastic syndromes (3-5).

More recently, based on the results of two randomized trials, the combination of arsenic trioxide (ATO) and All-*trans* retinoic acid (ATRA) has been established as the new standard of care for front-line therapy of non-high risk APL patients. The APL0406 study was designed by the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) as a prospective, randomized, multicenter, phase III non-inferiority trial comparing ATRA-ATO and ATRA-chemotherapy (AIDA) regimens in patients with low-intermediate risk APL (6). The study was conducted by the GIMEMA together with the German Acute Myeloid Leukemia Study Group (AMLSG) and Study Alliance Leukemia (SAL) group. This study has first shown that the chemotherapy-free approach with ATRA-ATO is at least equally effective to ATRA and chemotherapy-based regimens (6). The toxicity profile of ATRA-ATO combination appeared to be mild, with considerably reduced myelosuppression and infections as compared to ATRA-chemotherapy, and was associated with frequent but manageable side-effects [(i.e. leukocytosis, QTc prolongation, liver enzyme increase. The superior anti-leukemic efficacy of ATRA-ATO was later shown in an independent randomized trial (AML17) conducted in the UK by National Cancer Research Institute (7).

Albeit adopting a different ATO schedule as compared to the Italian-German study, Burnett and colleagues reported superior event-free survival (EFS), relapse free survival (RFS) and lower cumulative incidence of relapse (CIR) rates in ATRA-ATO treated patients as compared to those receiving ATRA-chemotherapy (7), supporting the feasibility and benefit of this chemotherapy-free strategy in APL all risk categories (including high-risk patients).

The survival benefit and the superior anti-leukemic efficacy of ATRA-ATO approach as compared to ATRA-chemotherapy, has been later confirmed in the extended series of the APL0406 trial, including 276 patients with low to intermediate risk disease with a median follow-up of 40.6 months (8). We hereby provide a long-term update of this patient series, with a prolonged median follow-up of 66.4 months, in order to verify the durability of the responses and to assess the potential occurrence of late adverse events.

The full trial design, the randomization procedure, inclusion criteria, and therapy schedules have been described elsewhere (6). Patients aged 18-71 years with newly diagnosed low-intermediate risk APL (WBC < $10x10^9$/L), were enrolled based on the morphologic suspect of APL and genetic diagnostic confirmation in a reference laboratory. Randomization to ATRA-ATO or ATRA-chemotherapy was centralized and stratified according to institution. The trial was conducted in accordance with the Declaration of Helsinki, received institutional review board approval by all participating Centers and was registered at Clinicaltrials.gov (NCT00482833).

Enrolment started in October 2007 and was completed in January 2013 and data analysis was performed on an intent-to-treat (ITT) principle. The primary objective of the study was EFS. Secondary objectives of the study included overall survival (OS), disease-free survival (DFS) and cumulative incidence of relapse (CIR), Quality-of-life (QoL) and molecular response (8,9). Outcome definitions are described in the Supplementary material section. Survival distributions were estimated using the Kaplan-Meier method,

while CIR was calculated using the proper nonparametric method. Differences in terms of OS, EFS, and DFS were evaluated using the log-rank test. The Gray test was applied to compare cumulative incidence curves. All tests were two-sided.

Of a total of 276 patients with low-intermediate risk APL enrolled in the study in Italy and Germany, the presence of *PML/RARA* fusion gene was not confirmed in 6 patients (5 randomised to ATRA-ATO and 1 to ATRA-CHT arm). Of the remaining 270 patients, 4 did not start allocated treatment due to treatment refusal (n=2), and major protocol violation (n=2). Therefore, 266 patients (129 randomized to ATRA-ATO and 137 to ATRA-CHT, supplementary Table 1) were included in the present long-term ITT analysis, performed in March 2018, at a median follow-up of 66.4 months (range: 0.9-116.7 months).

As previously reported, with a median follow-up of 42 months, in 263 patients evaluable for response to induction therapy, complete remission (CR) was documented in 100% of patients randomized to ATRA/ATO and in 97% of patients treated with ATRA/CHT. Four deaths occurred during induction in patients included in the ATRA-CHT arm (7). Of the 259 patients who proceeded to consolidation therapy, 234 were evaluable for the assessment of molecular remission at the end of third consolidation cycle. Twelve patients in the ATRA-ATO arm and 13 in the ATRA-CHT arm were not evaluable for this analysis due to major protocol violations (n=3), loss to follow-up (n=6), toxicity (n=10), medical decision (n=1), missing data (n=3), hepatitis reactivation (n=1), consent withdrawal (n=1). All patients in the ATRA-ATO group achieved molecular complete remission, while 2 patients in the ATRA-CHT group tested PCR positive for PML/RARA (1.7%). Of these, 1 was rescued with ATO and subsequent allogeneic stem cell transplantation and is currently alive in second mCR, while for the other patient PCR positivity was not confirmed in a subsequent molecular test and the patient was continued on maintenance therapy.

In the present analysis, 263 patients are evaluable for the primary endpoint of the study. EFS at 72 months was 96.6% (95%CI: 93.4-99.9) in the ATRA-ATO group, and 77.4% (95%CI: 70.2-85.4) in the ATRA-chemotherapy group (HR:0.14, 95%CI:0.05-0.39, p=0.0002). The total number of events reported was 28 in the ATRA–chemotherapy group, versus 23 reported in the previous update (7). The post-induction events recorded in the ATRA-chemotherapy arm included 2 cases of molecular resistance after consolidation, 17 relapses occurring at a median time of 20 months (range: 2.4-55.7 months), and 5 deaths in CR. In the ATRA-ATO group, a total of 4 events were recorded including 2 relapses at 22 and 27 months, respectively, and 2 deaths in remission (1 due to H1N1-driven pneumonia and 1 due to an unrelated malignancy). Fatal events are reported in Table 1.

As to the secondary endpoints of the study, DFS at 72 months was 96.6% (95%CI: 93.4-99.9) in the ATRA-ATO group and 79.8% (95%CI: 72.7-87.6) in the ATRA-chemotherapy arm (HR: 0.16, 95%CI: 0.05-0.45, 0.0006) while CIR was 1.7% (95% CI: 0.0-4.0) and 15.5% (95% CI: 9.0-22.0) in the ATRA-ATO and in the ATRA-chemotherapy groups, (HR:0.102, 95%CI: 0.024-0.434, p=0.020). All comparative outcomes are reported in Figure 1.

This updated analysis of the APL0406 trial shows an increasing advantage over time of ATRA-ATO compared to ATRA-CHT in patients with newly diagnosed, low-intermediate risk APL. The improved results observed in the chemo-free group concern both efficacy and safety. Since our reports on the APL0406 initial and extended series (5,7), no additional relapses were reported in the ATRA-ATO group (n=2), while the relapse rate in the ATRA-CHT arm has increased over time, with 2 additional late relapses (50 and 55 months) being recorded after the last report. Moreover, no cases of secondary leukemias were observed in the ATRA-ATO compared to 2 cases developing in the ATRA-CHT group.

Recently, very long-term updates of single-arm studies employing ATRA and ATO based regimens with minimal chemotherapy have shown a durable benefit of these strategies, especially in reducing the relapse rate (10,11). Abaza and colleagues reported durability of responses in terms of EFS, DFS and OS in APL patients receiving ATRA, ATO +/- gemtuzumab ozogamycin (GO). In keeping with our findings, relapses beyond 12 months were only 3 in this study (10). In the long-term update of the APML4 study from the Australasian group, Iland and colleagues reported a 5-year freedom from relapse (FFR) and DFS rates of 95% using ATRA-ATO + Idarubicin (this latter given for induction only) for APL patients of all risk categories. These outcomes were stable with respect to the 2-year estimates reported in the first analysis (11).

The high anti-leukemic efficacy of ATRA-ATO was associated with a relatively safe profile in the short-term, particularly concerning hematologic toxicity and infections. However, both in our previous studies and in reports from other groups, ATRA-ATO was consistently associated with a higher incidence of transient AST/ALT increase, QTc prolongation and leukocytosis compared to ATRA-CHT. In our study, the omission of conventional chemotherapy and the mild side effects of the ATRA-ATO therapy seem to account for the reduced number of fatal events in remission (1 pneumonia and 1 apparently unrelated malignancy) as compared to those occurring in the ATRA-chemotherapy arm (n=13). The decreased incidence of relapse-related deaths and the absence of therapy-related myeloid neoplasms in the ATRA-ATO arm also accounted for the superior survival observed in this cohort, in line with results reported in the APML4 and MDACC studies (10,11).

In conclusion, the increased advantage over time of ATRA-ATO compared to ATRA-CHT or patients with newly diagnosed, low intermediate risk APL further supports this chemotherapy-free regimen as the new standard of care.

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Conflict of interest statement

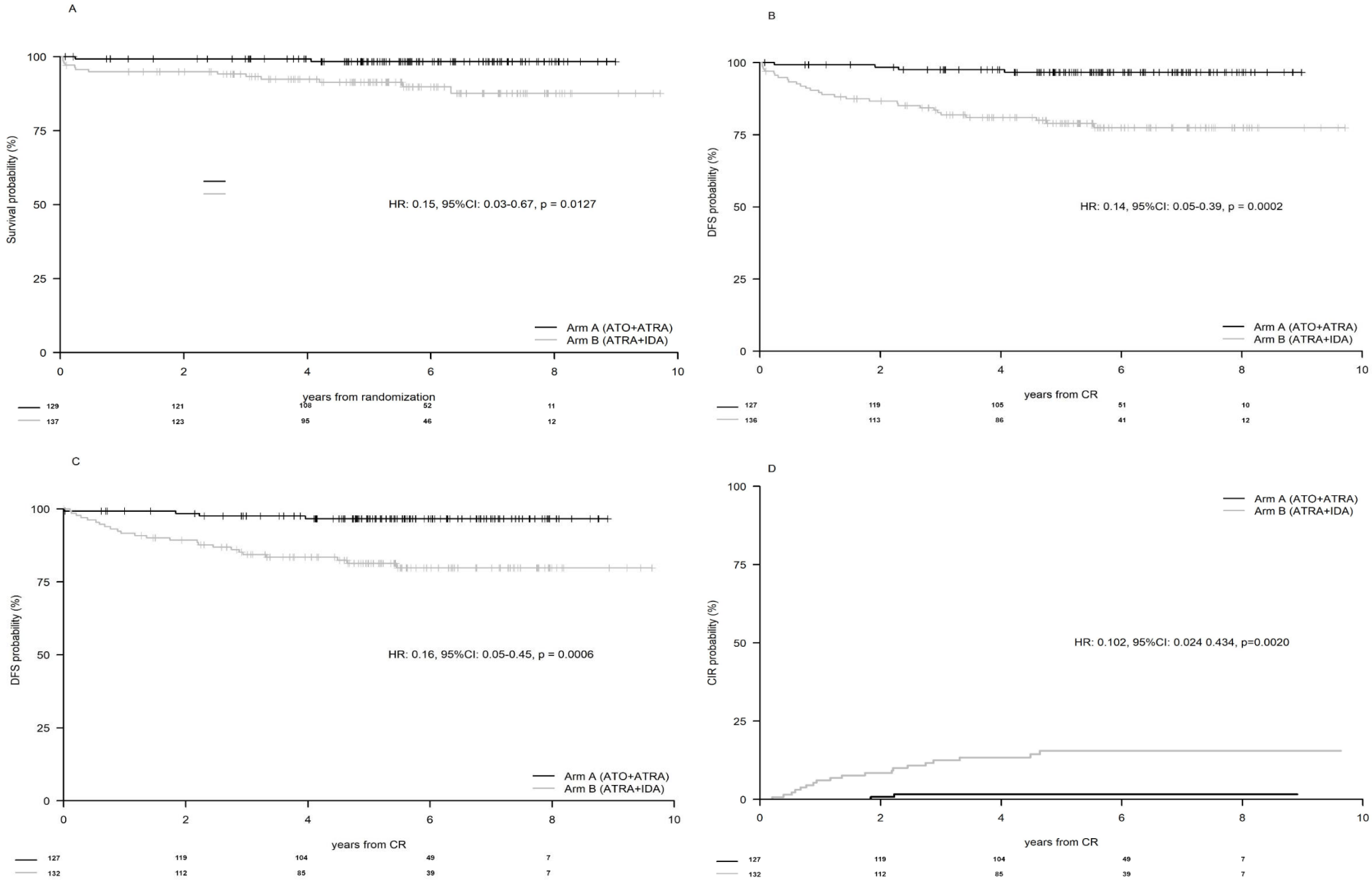
The following Authors declared potential conflicts of interest:

L. Cicconi, Speakers' Bureau: Teva Pharmaceutical Industries; Uwe Platzbecker, Honoraria and Research Funding: Teva Pharmaceutical Industries; C. Thiede, Employment: AgenDix; F. Efficace, Advisory Role: Teva Pharmaceutical Industries, Research Funding: Lundbeck (Inst); H. Link, Honoraria and Research Funding: Teva Pharmaceutical Industries; R. F. Schlenk, Honoraria and Research Funding: Teva Pharmaceutical Industries; F. Lo-Coco, Honoraria: Teva Pharmaceutical Industries, Lundbeck, Consulting or Advisory Role: Teva Pharmaceutical Industries, Lundbeck. Other authors declared no relevant conflicts of interests.

Table 1. Fatal events in APL0406 trial by treatment arm.

UPN (n=15)	Age*	Treatment Arm	Phase of therapy	APL status	Time from diagnosis (months)	Cause of death
1	60	ATRA-CHT^	Induction	-	0.5	ARDS°
2	26	ATRA-CHT	Induction	-	0.7	Cardiovascular disease
3	46	ATRA-CHT	Induction	-	0.5	Ischemic stroke
4	51	ATRA-CHT	Induction	-	0.9	Respiratory disease
5	55	ATRA-CHT	Off-therapy	CR	3.0	Haemorrhagic shock
6	67	ATRA-CHT	Off-therapy	CR	5.5	Pneumonia
7	70	ATRA-CHT	Off-therapy	CR	2.8	Pulmonary embolism
8	62	ATRA-CHT	Off-therapy	CR	66.6	t-AML[#]
9	60	ATRA-CHT	Off-therapy	CR	36.1	t-MDS evolved in AML
10	30	ATRA-CHT	Off-therapy	Relapse	7.3	Progressive disease
11	44	ATRA-CHT	Off-therapy	Relapse	34.7	Progressive disease
12	52	ATRA-CHT	Off-therapy	Relapse	55.2	Progressive disease
13	50	ATRA-CHT	Off-therapy	Relapse	9.2	Transplant related death
14	48	ATRA-ATO[§]	Off-therapy	CR	2.9	Pneumonia
15	64	ATRA-ATO	Off-therapy	CR	48.8	Colon carcinoma

Figure legend. *Age at diagnosis; ^all-trans retinoic acid and chemotherapy; [§] all-transretinoic acid and arsenic trioxide;°Acute respiratory distress syndrome;[#]therapy-related acute myeloid leukemia


A
Survival probability (%)
100
75
50
25
0
0
2
4
6
8
10
years from randomization
HR: 0.15, 95%CI: 0.03-0.67, p = 0.0127
Arm A (ATO+ATRA)
Arm B (ATRA+IDA)
129 121 108 52 11
137 123 95 46 12
B
DFS probability (%)
HR: 0.14, 95%CI: 0.05-0.39, p = 0.0002
years from CR
127 119 105 51 10
136 113 86 41 12
C
DFS probability (%)
HR: 0.16, 95%CI: 0.05-0.45, p = 0.0006
years from CR
127 119 104 49 7
132 112 85 39 7
D
CIR probability (%)
HR: 0.102, 95%CI: 0.024 0.434, p=0.0020
years from CR
127 119 104 49 7
132 112 85 39 7