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# 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

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## ABSTRACT

### Purpose
The initial results of the APL0406 trial showed that the combination of all-*trans*-retinoic acid (ATRA) and arsenic trioxide (ATO) is at least not inferior to standard ATRA and chemotherapy (CHT) in first-line therapy of low- or intermediate-risk acute promyelocytic leukemia (APL). We herein report the final analysis on the complete series of patients enrolled onto this trial.

### Patients and Methods
The APL0406 study was a prospective, randomized, multicenter, open-label, phase III noninferiority trial. Eligible patients were adults between 18 and 71 years of age with newly diagnosed, low- or intermediate-risk APL (WBC at diagnosis $\leq 10 \times 10^9$/L). Overall, 276 patients were randomly assigned to receive ATRA-ATO or ATRA-CHT between October 2007 and January 2013.

### Results
Of 263 patients evaluable for response to induction, 127 (100%) of 127 patients and 132 (97%) of 136 patients achieved complete remission (CR) in the ATRA-ATO and ATRA-CHT arms, respectively ($P = .12$). After a median follow-up of 40.6 months, the event-free survival, cumulative incidence of relapse, and overall survival at 50 months for patients in the ATRA-ATO versus ATRA-CHT arms were 97.3% *v* 80%, 1.9% *v* 13.9%, and 99.2% *v* 92.6%, respectively ($P < .001$, $P = .0013$, and $P = .0073$, respectively). Postinduction events included two relapses and one death in CR in the ATRA-ATO arm and two instances of molecular resistance after third consolidation, 15 relapses, and five deaths in CR in the ATRA-CHT arm. Two patients in the ATRA-CHT arm developed a therapy-related myeloid neoplasm.

### Conclusion
These results show that the advantages of ATRA-ATO over ATRA-CHT increase over time and that there is significantly greater and more sustained antileukemic efficacy of ATO-ATRA compared with ATRA-CHT in low- and intermediate-risk APL.

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## INTRODUCTION

Standard therapy of acute promyelocytic leukemia (APL) has long since relied on the combination of all-*trans*-retinoic acid (ATRA) and chemotherapy (CHT). Despite providing high cure rates, this approach is associated with frequent severe hematologic toxicity and development of secondary myeloid neoplasms in approximately 2% of patients.[1-11] The introduction of arsenic trioxide (ATO) in APL treatment has resulted in similarly high remission and survival rates coupled with significantly reduced myelosuppression. ATO is currently regarded as the most effective single agent in APL and is licensed for the treatment of relapsed and refractory APL.[12-15]

Recently, CHT-free regimens based on ATO with or without ATRA have proven highly effective in newly diagnosed APL.[16-19] After pilot studies suggesting that ATRA plus ATO could substitute the standard approach in the treatment of newly diagnosed disease,[18,19] two large independent randomized trials reported significantly improved outcomes for patients treated with ATRA-ATO compared with those receiving ATRA-CHT.[20,21] On the basis of these data, expert panels from the United States and Canada have indicated ATRA-ATO as the favored option in first-line therapy of non–high-risk APL.[22,23]

The APL0406 randomized trial reported by the Gruppo Italiano per le Malattie Ematologiche dell'Adulto (GIMEMA), Acute Myeloid Leukemia Study Group (AMLSG), and Study Alliance Leukemia (SAL) showed in the initial series of 156 patients that ATO-ATRA is at least not inferior, and probably superior, to standard ATRA-CHT for patients with newly diagnosed, non–high-risk APL.[20] We herein report the results of this study after a more prolonged follow-up and including the extended and final series of patients who were randomly assigned to receive ATRA-ATO or ATRA-CHT.

## PATIENTS AND METHODS

### Study Design and Patients

The APL0406 study was a prospective, randomized, multicenter, open-label, phase III noninferiority trial. The study was designed by GIMEMA in April 2006 (APL0406); it was started in Italy in October 2007 and was joined in 2008 by the German SAL and AMLSG groups. The study was designed to show that the ATRA-ATO regimen is not inferior to the ATRA-CHT regimen in terms of event-free survival (EFS) rate at 2 years. The full trial design and the results obtained in the initial series of 156 patients were reported in 2013.[20] Briefly, eligible patients were adults age 18 to 71 years with newly diagnosed, low- or intermediate-risk APL (WBC at diagnosis $\leq 10 \times 10^9$/L). Initial patient enrollment and random assignment were based on the sole morphologic diagnosis of APL according to the French-American-British criteria. Random assignment was stratified by institutions; random block size was four.

Genetic diagnostic confirmation was mandatory for eligibility and was carried out through centralized reference laboratories in Italy and Germany (F.L.-C., Università Tor Vergata in Rome, Italy, for GIMEMA and C.T., Carl Gustav Carus Universitätsklinikum in Dresden, Germany, for SAL and AMLSG). 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 (identifier: NCT00482833).

In September 2010, the study reached the initially programmed accrual of 162 patients and enrollment was suspended. At the time of inclusion of the last patient, however, compliance with quality-of-life (QoL) questionnaires was lower than initially anticipated. Therefore, considering QoL was a key secondary objective of the trial, the study was amended and restarted in March 2011 in an effort to maximize information obtained regarding burden of disease and treatment effects over time from patients themselves. The new target accrual to meet the QoL objective was set to 276 patients. The amendment was approved by all ethical committees of participating centers, and all patients provided written informed consent. A list of authors and centers that contributed to the APL0406 trial can be found in the Appendix (online only).

### Treatment Arms, Supportive Measures, and Management of Complications

The treatment schedules for the ATRA-ATO and ATRA-CHT regimens, the recommended supportive measures to prevent and treat the APL-associated coagulopathy and differentiation syndrome (DS), and the management of major expected therapy-related complications (QTc prolongation, hyperleukocytosis, and hepatotoxicity) have been reported in detail.[20] In particular, prednisone prophylaxis (0.5 mg/kg daily) was administered during the entire remission induction phase to prevent DS. Hydroxyurea was the only cytotoxic agent allowed to control hyperleukocytosis. Finally, temporary discontinuation and dose adjustments were recommended to manage ATO nonhematologic toxicity, as detailed elsewhere.[20]

### Laboratory Studies

Genetic studies, including reverse transcriptase polymerase chain reaction (RT-PCR) amplification of the *PML-RARA* hybrid using standardized protocols, were mandatory at diagnosis and after the third consolidation for all patients enrolled onto the study. Furthermore, longitudinal prospective monitoring of minimal residual disease was assessed by nested RT-PCR and quantitative RT-PCR in marrow samples for patients in both arms after induction therapy (for investigational purposes only) and during follow-up. Molecular studies also included fms-like tyrosine kinase 3 (*FLT3*) mutational status for the presence of the internal tandem duplication.

### Outcomes

The primary study objective was to compare EFS at 2 years from diagnosis between the two treatment arms. Treatment failure was defined as any of the following events: no achievement of hematologic complete remission (HCR) after induction therapy, no achievement of molecular complete remission (CR) after three consolidation courses, relapse (molecular or hematologic, whichever was detected first), and death.

Secondary end points included rate of HCR after induction, overall survival (OS) at 2 years, disease-free survival (DFS), cumulative incidence of relapse (CIR, defined as the time from HCR achievement to either molecular or hematologic relapse, whichever was detected first), incidence and severity of hematologic and nonhematologic toxic episodes during treatment (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events), kinetics of minimal residual disease, and self-assessed QoL.

OS was defined as the time from diagnosis to death from any cause. DFS was defined as the time from HCR achievement to relapse (either molecular or hematologic), persistence of polymerase chain reaction (PCR) positivity after consolidation, death, or date of last follow-up for patients alive in first molecular CR. Induction death was defined as death occurring at any time during induction therapy, before the achievement of HCR. CIR was calculated from the date of HCR until first relapse (either molecular or hematologic relapse) considering death in CR as a competing risk.

### Statistical Analysis

All patients enrolled onto the study were analyzed following an intent-to-treat principle. Characteristics of patients were summarized by cross-tabulations (categorical variables) and quantiles (eg, median; for continuous variables). Nonparametric tests were applied for comparisons between groups ($\chi^2$ and Fisher's exact test for categorical variables; Mann-Whitney *U* test and Kruskal-Wallis test for continuous variables). Survival distributions (OS, EFS, and DFS) were estimated using the Kaplan-Meier method. 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.

## RESULTS

### Enrollment and Patient Characteristics

The enrollment period was from October 2007 to January 2013. A total of 276 patients with low- or intermediate-risk APL were randomly assigned. Genetic tests excluded *PML-RARA*–positive APL in six patients (five patients randomly assigned to

ATRA-ATO and one randomly assigned to ATRA-CHT). Of the remaining 270 patients, four patients did not start allocated treatment (two treatment refusals, both in the ATRA-CHT arm, and two major violations, both in the ATRA-ATO arm). Therefore, 266 patients (129 randomly assigned to ATRA-ATO and 137 randomly assigned to ATRA-CHT) were included in the intent-to-treat analysis. The disposition of the patients and reasons for exclusion are shown in Figure 1.

The main demographic, clinical, and laboratory features of the 266 patients eligible for analysis are listed in Table 1. There were no significant differences in the baseline characteristics between the two cohorts. The present analysis was performed in December 2015 with a median follow-up time of 40.6 months (range, 0.1 to 83.6 months).

### *Induction Therapy*

Four patients died during induction in the ATRA-CHT group. The causes of death were DS (n = 2), ischemic stroke (n = 1), and bronchopneumonia (n = 1). All deaths were recorded in the initial series,[20] and no further deaths occurred in the second cohort of 110 patients enrolled in the postamendment period from March 2011 to January 2013. One hundred twenty-seven patients in the ATRA-ATO arm and 136 patients in the ATRA-CHT arm were evaluable for induction response. HCR was documented in 127 patients (100%) and 132 patients (97%) in the ATRA-ATO and ATRA-CHT arms, respectively ($P = .12$). For two patients who started induction in the ATRA-ATO arm, the assigned treatment was terminated early. For one of these patients, a protocol violation occurred (early evaluation of bone marrow aspirate at day +13 with inappropriate diagnosis of resistant disease). This patient was alive at 2 years from diagnosis. In the other patient, treatment was permanently withdrawn by the treating physician as a result of toxicity (QTc prolongation and electrolyte abnormalities at day +3), and the patient was lost to follow-up. In one patient in the ATRA-CHT arm, treatment was discontinued as a result of an unknown reason, and the patient was lost to follow-up.

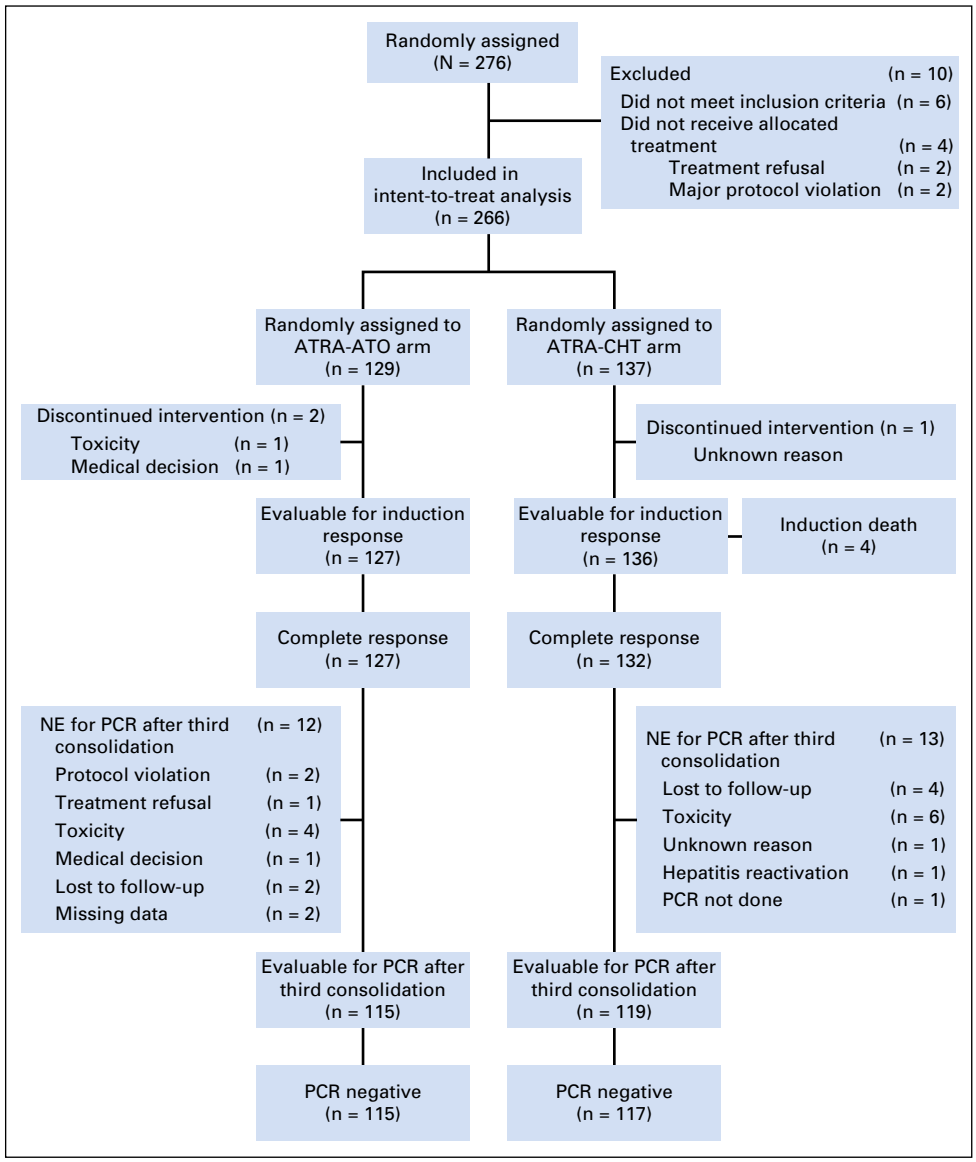


**Fig 1.** Study enrollment, random assignment, and retention. ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy; NE, not evaluable; PCR, polymerase chain reaction.

**Table 1.** Demographic, Clinical, and Laboratory Characteristics of the Eligible Patients

| Characteristic | ATRA-ATO (n = 129) | ATRA-CHT (n = 137) | *P* |
|---|---|---|---|
| Median age, years (range) | 46.6 (18.8-70.2) | 46.6 (18-70.3) | .84 |
| Sex, No. (%) | | | .45 |
| Male | 60 (46.5) | 70 (51.1) | |
| Female | 69 (53.5) | 67 (48.9) | |
| Median WBC, $\times 10^9$/L (range) | 1.4 (0.32-10) | 1.5 (0.3-9.61) | .83 |
| Median platelets, $\times 10^9$/L (range) | 36.5 (3-224) | 31.5 (3-236) | .19 |
| Sanz risk, No. (%) | | | .52 |
| Low | 57 (45.2) | 55 (41.3) | |
| Intermediate | 69 (54.7) | 78 (58.6) | |
| *PML-RARA* isoform, No. (%) | | | .35 |
| Long | 83 (68.6) | 78 (62.9) | |
| Short | 38 (31.4) | 46 (37.1) | |
| Missing | 8 (7) | 13 (10) | |
| *FLT3*-ITD, No. (%) | | | .59 |
| Mutated | 26 (25.5) | 22 (22.2) | |
| Unmutated | 76 (74.5) | 77 (77.8) | |
| Missing | 27 (21) | 38 (28) | |

Abbreviations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy; ITD, internal tandem duplication.

Leukocytosis greater than $10 \times 10^9$/L developed during induction in 56 patients (43%) receiving ATRA-ATO and was successfully managed in all patients with hydroxyurea as per protocol recommendation. Moderate and severe DS (defined as in Montesinos et al[24]) occurred during induction in 16 patients (13%) and five patients (4%) in the ATRA-ATO arm and in nine patients (7%) and eight patients (6%) in the ATRA-CHT arm, respectively ($P = .38$), and was fatal in two patients in the ATRA-CHT arm. In eight patients (four patients in each arm), indeterminate DS (defined according to Frankel et al[25]) was reported.

### Consolidation Therapy

Of 259 patients who proceeded to consolidation therapy, 234 patients (115 in the ATRA-ATO arm and 119 in the ATRA-CHT arm) were evaluable for molecular response after the third consolidation cycle. Twelve of 127 patients in the ATRA-ATO arm went off protocol before the bone marrow assessment after third consolidation as a result of major protocol violation (n = 2), consent withdrawal (n = 1), medical decision (n = 1), loss to follow-up (n = 2), toxicity (n = 4), or missing data (n = 2). In the ATRA-CHT arm, 13 of 132 patients did not undergo bone marrow evaluation after third consolidation because of major protocol violation (PCR not performed, n = 1), loss to follow-up (n = 4), toxicity (n = 6), hepatitis reactivation (n = 1), or missing data (n = 1). Six patients (one in the ATRA-ATO arm and five in the ATRA-CHT arm) died in CR. The patient in the ATRA-ATO group died of bronchopneumonia driven by H1N1 virus. Of the five deaths in the ATRA-CHT group, one was caused by hemorrhagic shock, one by pulmonary embolism, two by bronchopneumonia, and one by secondary myelodysplastic syndrome.

Molecular evaluation of *PML-RARA* by RT-PCR after third consolidation showed PCR negativity in all patients in the ATRA-ATO arm, whereas two (1.7%) of 119 patients in the ATRA-CHT arm tested positive by PCR and were considered as having molecular resistance. Of these, one patient was treated with ATO salvage therapy followed by allogeneic stem-cell transplantation and remained in second CR 14 months after transplantation. In the other patient, a second PCR test after the end of consolidation did not confirm PCR positivity. The patient was continued on ATRA and low-dose CHT maintenance and remained in remission for greater than 24 months.

### Maintenance Therapy (ATRA-CHT Arm)

All 117 patients in the ATRA-CHT arm who completed consolidation and tested RT-PCR negative for *PML-RARA* proceeded to maintenance. Excluding the nine patients who experienced relapse during maintenance, 20 patients did not complete maintenance as a result of toxicity (n = 4), treatment refusal (n = 3), major protocol violation (n = 1), or other reasons (n = 12).

### Toxicities

Hematologic and nonhematologic toxicities are listed in Tables 2 and 3, respectively. A total of 95 serious adverse events (SAEs) were reported in 65 patients. Of these, 43 and 52 SAEs were reported in patients receiving ATRA-ATO and ATRA-CHT, respectively. The complete list of detailed SAEs is reported in Appendix Table A1 (online only).

*Hematologic toxicity.* As shown in Table 2, a significantly higher number of patients in the ATRA-CHT arm compared with the ATRA-ATO arm experienced grade 3 or 4 neutropenia and thrombocytopenia lasting more than 15 days ($P < .001$). Episodes of febrile neutropenia (including fever of unknown origin and

**Table 2.** Hematologic Toxicity

| | Induction | | First Consolidation | | Second Consolidation | | Third Consolidation | |
|---|---|---|---|---|---|---|---|---|
| Toxicity and Treatment Arm | No. (%) | *P* | No. (%) | *P* | No. (%) | *P* | No. (%) | *P* |
| Neutropenia (grade 3-4 lasting > 15 days) | | < .001 | | < .001 | | < .001 | | < .001 |
| ATRA-ATO | 61 (35) | | 8 (16) | | 7 (7) | | 5 (15) | |
| ATRA-CHT | 109 (64) | | 40 (67) | | 90 (92) | | 28 (85) | |
| Thrombocytopenia (grade 3-4 lasting > 15 days) | | < .001 | | < .001 | | < .001 | | < .001 |
| ATRA-ATO | 74 (38) | | 6 (26) | | 6 (7) | | 8 (23) | |
| ATRA-CHT | 120 (62) | | 17 (74) | | 77 (93) | | 26 (76) | |
| Infection and FUO | | < .001 | | .54 | | < .001 | | 1.0 |
| ATRA-ATO | 30 (23) | | 10 (8) | | 4 (3) | | 2 (1.6) | |
| ATRA-CHT | 75 (55) | | 8 (6) | | 46 (38) | | 2 (1.7) | |

Abbreviations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy; FUO, fever of unknown origin.

  

**Table 3.** Nonhematologic Toxicity

| Toxicity and Treatment Arm | Induction | | First Consolidation | | Second Consolidation | | Third Consolidation | |
|---|---|---|---|---|---|---|---|---|
| | No. (%) | *P* | No. (%) | *P* | No. (%) | *P* | No. (%) | *P* |
| Hepatic toxicity (grade 3-4) | | < .001 | | .11 | | .49 | | |
| ATRA-ATO | 51 (40) | | 5 (4) | | 1 (0.8) | | 0 | |
| ATRA-CHT | 4 (3) | | 1 (0.7) | | 0 | | 0 | |
| QTc prolongation | | .0022 | | .11 | | .11 | | .23 |
| ATRA-ATO | 11 (8.5) | | 3 (2) | | 3 (2) | | 2 (1.5) | |
| ATRA-CHT | 1 (0.7) | | 0 | | 0 | | 0 | |
| Cardiac function (grade 3-4) | | .06 | | | | | | |
| ATRA-ATO | 0 | | 0 | | 0 | | 0 | |
| ATRA-CHT | 5 (3.7) | | 0 | | 0 | | 0 | |
| Neurotoxicity (all grades) | | .48 | | .02 | | .01 | | .006 |
| ATRA-ATO | 1 (0.7) | | 5 (4.2) | | 6 (5) | | 7 (5.9) | |
| ATRA-CHT | 0 | | 0 | | 0 | | 0 | |
| GI toxicity (grade 3-4) | | < .001 | | 1.0 | | .03 | | 1.0 |
| ATRA-ATO | 3 (2) | | 0 | | 0 | | 0 | |
| ATRA-CHT | 25 (18.2) | | 1 (0.8) | | 6 (4.9) | | 0 | |
| Hypercholesterolemia | | .55 | | .13 | | .14 | | .27 |
| ATRA-ATO | 14 (10) | | 19 (16) | | 19 (16) | | 16 (14) | |
| ATRA-CHT | 12 (8.7) | | 12 (9.6) | | 12 (9.7) | | 11 (9) | |
| Hypertriglyceridemia | | 0.76 | | .49 | | .12 | | .5 |
| ATRA-ATO | 29 (22) | | 22 (18.4) | | 17 (14.4) | | 16 (14) | |
| ATRA-CHT | 29 (22) | | 19 (15.2) | | 10 (8) | | 13 (11) | |

Abbreviations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy.

documented infections counted together) were also significantly more frequent in the ATRA-CHT arm than in the ATRA-ATO arm. In particular, in the ATRA-ATO and ATRA-CHT arms, 30 and 75 episodes were documented during the induction course ($P < .001$), 10 and eight occurred during the first consolidation cycle ($P = .54$), four and 46 occurred during the second consolidation cycle ($P < .001$), and two and two occurred during the third consolidation cycle ($P = 1.0$), respectively.

*Other toxicities.* Significant elevation of liver function tests (grade 3 or 4 according to National Cancer Institute Common Terminology Criteria for Adverse Events) was more frequent in the ATRA-ATO arm (44%) compared with the ATRA-CHT (3%) arm across all treatment cycles ($P < .001$). Toxicity resolved in all patients with temporary discontinuation of ATO and/or ATRA or of low-dose CHT during maintenance (for patients in the ATRA-CHT arm). QTc prolongation, defined as QTc greater than 450 milliseconds for men and greater than 460 milliseconds for women with correction calculated using the Framingham formula, was observed in 15 patients (11%) in the ATRA-ATO arm and one patient in the ATRA-CHT arm ($P < .001$) throughout the treatment cycles. There were no cases of life-threatening cardiac arrhythmias; however, ATO was permanently discontinued in one of the 15 patients, and the patient went off protocol. Neurotoxicity mainly consisting of reversible peripheral nerve neuropathy was observed in a greater proportion of patients in the ATRA-ATO arm and occurred during consolidation. Finally, GI toxicity and cardiac function abnormalities were significantly more frequent in the ATRA-CHT arm (Table 3).

## Outcomes

All outcome estimates calculated at 24 and 50 months are listed in Table 4, whereas outcome curves are shown in Figure 2.

*Primary end point.* A total of 263 patients (127 and 136 in the ATRA-ATO and ATRA-CHT arms, respectively) were evaluable for EFS according to the intent-to-treat analysis. In the ATRA-ATO group, 98.3% of patients (95% CI, 95.9% to 100%) were event free at 24 months from random assignment, compared with 86.8% in the ATRA-CHT group (95% CI, 81.1% to 92.8%; $P < .001$). At 50 months, EFS estimates were 97.3% (95% CI, 94.3% to 100%) and 80.0% (95% CI, 72.9% to 88.0%) in the ATRA-ATO and ATRA-CHT groups, respectively. Although 263 patients is not the full intent-to-treat complement for EFS evaluation, the number of unevaluable patients was small.

The noninferiority analysis was carried out in 229 patients with sufficient follow-up (beyond 24 months). Of these patients,

**Table 4.** Outcome Results

| Outcome and Treatment Arm | Probability, % (95% CI) | | *P* |
|---|---|---|---|
| | 24 Months | 50 Months | |
| Overall survival | | | .0073 |
| ATRA-ATO | 99.2 (97.7 to 100) | 99.2 (97.7 to 100) | |
| ATRA-CHT | 94.8 (91.1 to 98.6) | 92.6 (87.9 to 97.5) | |
| Event-free survival | | | < .001 |
| ATRA-ATO | 98.3 (95.9 to 100) | 97.3 (94.3 to 100) | |
| ATRA-CHT | 86.8 (81.1 to 92.8) | 80.0 (72.9 to 88.0) | |
| Disease-free survival | | | < .001 |
| ATRA-ATO | 98.3 (95.9 to 100) | 97.3 (94.3 to 100) | |
| ATRA-CHT | 89.4 (84.1 to 95.0) | 82.6 (75.6 to 90.3) | |
| Cumulative incidence of relapse | | | .0013* |
| ATRA-ATO | 0.9 (0 to 2.7) | 1.9 (0.0 to 4.5) | |
| ATRA-CHT | 8.2 (3.3 to 13.2) | 13.9 (7.1 to 20.6) | |

Abbreviations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy.
*Gray test.

98.15% in the ATRA-ATO group (106 of 108 patients) were alive and event free at 24 months, compared with 85.95% of patients in the ATRA-CHT group (104 of 121 patients), with a difference in the EFS rates at 2 years of 12.2% (95% CI, 4.3% to 20.1%); because the lower bound of the 95% CI for this difference was ≥ 5%, the noninferiority of ATRA-ATO was confirmed ($P < .001$).

Seventeen patients experienced relapse during follow-up. Of these, two relapses occurred in the ATRA-ATO arm at 22 and 27 months, and 15 occurred in the ATRA-CHT arm at a median time of 14.0 months (range, 2.5 to 39.8 months). In four patients, relapse was detected at the molecular level before hematologic relapse, leading to administration of pre-emptive salvage therapy. Two patients in the ATRA-CHT arm and none in the ATRA-ATO arm developed a therapy-related myeloid neoplasm. Of these, one patient with therapy-related myelodysplastic syndrome died as a result of disease progression, whereas in the other patient, a therapy-related acute myeloid leukemia was diagnosed, and the patient remained alive in CR 14 months after undergoing allogeneic stem-cell transplantation.

*Secondary end points.* The 24- and 50-month OS, DFS, and CIR rates for patients in the two arms are listed in Table 4. The results of the kinetics of molecular response and impact of *FLT3* status will be reported in a separate publication.

Regarding QoL, the results of the current extended series broadly confirm previously reported findings[26] on the benefits of ATRA-ATO versus ATRA-CHT after induction therapy. The previous main observation that fatigue severity (as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30) was significantly lower in the group treated with ATRA-ATO versus ATRA-CHT after induction therapy ($P = .034$)[26] was fully confirmed in this larger patient population ($P = .008$). A long-term QoL analysis has been planned, and full details will be reported separately.

## DISCUSSION

This study shows that, compared with ATRA-CHT, the ATRA-ATO combination significantly improved both survival and relapse risk in patients with newly diagnosed, low- or intermediate-risk APL. Compared with our previous report in which no significant differences in DFS and CIR rates were found, we report here that the

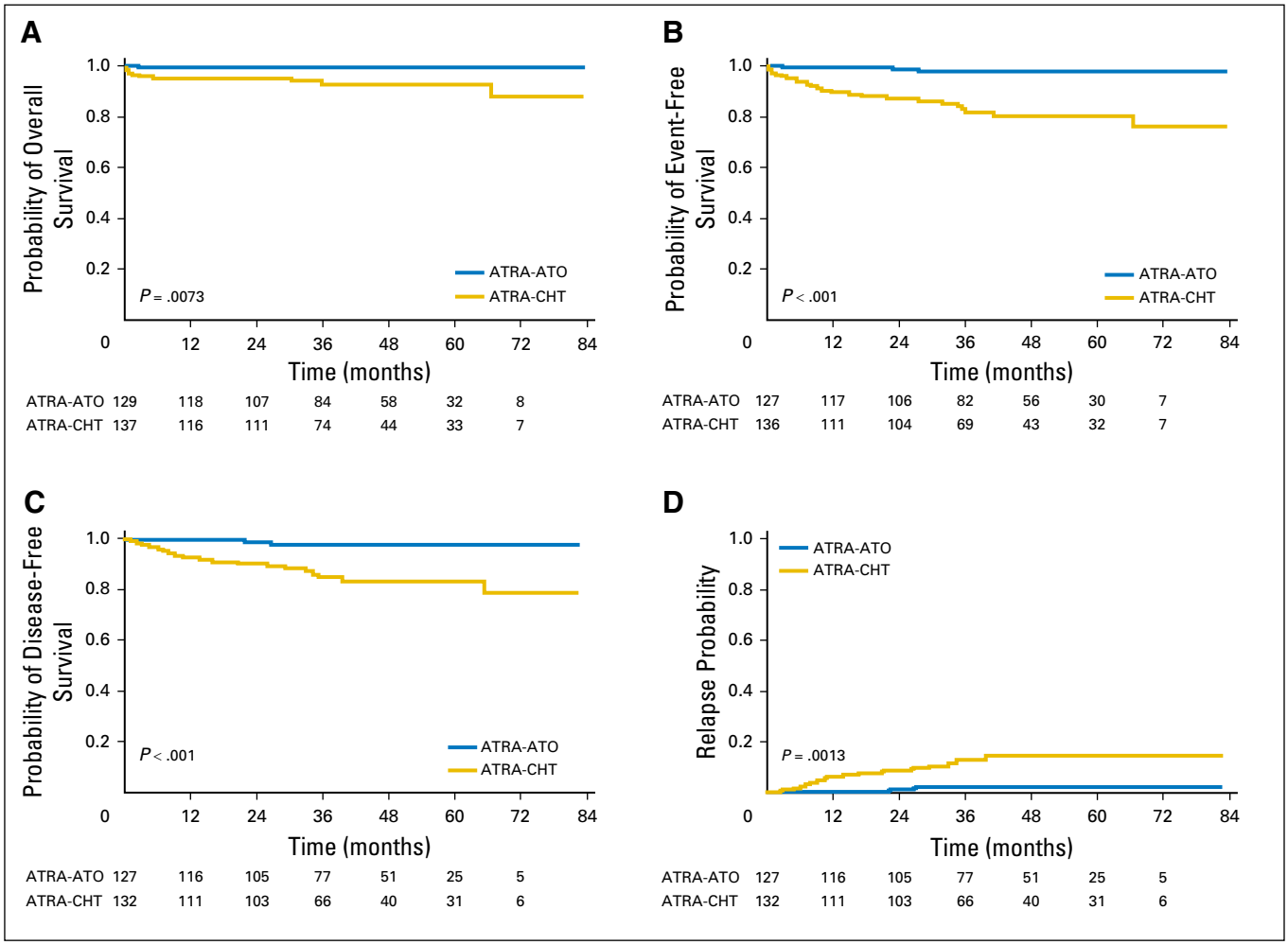


**Fig 2.** Outcome estimates. (A) Overall survival. (B) Event-free survival. (C) Disease-free survival. (D) Relapse. ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy.

  

CHT-free approach based on ATRA-ATO resulted in higher antileukemic efficacy. In addition, the present analysis conducted in a substantially extended cohort of patients with prolonged follow-up revealed significantly improved differences in all other analyzed outcomes (EFS, OS, and DFS) compared with the initial report.[20] These data indicate that the advantage of ATRA-ATO over ATRA-CHT increases over time and that the inclusion of ATO in the treatment of low- or intermediate-risk APL not only reduces mortality and hematologic toxicity, but also results in improved and sustained antileukemic activity. Neither additional fatal events nor further relapses were recorded in patients randomly assigned to ATRA-ATO in this extended cohort. By contrast, new relapses, two instances of molecular resistance (ie, testing PCR positive after third consolidation), and two therapy-related myeloid neoplasms were observed in the group of patients receiving ATRA-CHT.

A recent study conducted in the United Kingdom by the National Cancer Research Institute (NCRI) reported similar results in terms of EFS and relapse rate, with patients treated with ATRA-ATO showing significantly better outcomes.[21] At variance from our study, the NCRI trial used an ATO schedule consisting of two or three weekly administrations at increased doses and included no maintenance in the ATRA-CHT arm (which was otherwise derived from the same ATRA and idarubicin [AIDA] protocol used in our study). Furthermore, the study included patients with high-risk disease, for whom a provision was made to use one or two 6 mg/m$^2$ doses of gemtuzumab ozogamicin during the first 4 days of induction. This important study independently confirmed the advantage of including ATO in first-line management of APL, suggesting that the benefit is also observed in high-risk patients. In this respect, however, it should be noted that a total of 57 patients with high-risk disease were included in the comparison and that the efficacy of ATO in this patient subset may be difficult to analyze given the addition of a potent anti-APL agent such as gemtuzumab ozogamicin.[21] A randomized trial comparing ATRA-ATO to the AIDA2000 protocol[5] and involving several European cooperative groups will be started soon to further investigate this issue.

The toxicity profiles in the current study were comparable to those observed for the two cohorts in the original series. For patients receiving ATRA-ATO, adverse effects mainly consisted of frequent increase of liver enzymes, QTc prolongation, and hyperleukocytosis. In almost all patients, this toxicity was reversible and manageable with temporary drug interruption and dose adjustments as per protocol recommendations, including the addition of hydroxyurea (the only cytotoxic agent allowed for the control of hyperleukocytosis). The study from the United Kingdom[21] reported similar toxicities for patients in the ATO group in terms of DS and cardiac adverse effects, but a lower incidence of grade 3 or 4 hepatic toxicity, probably as a result of the different schedule. Regarding medium- and long-term toxicity, the absence of secondary therapy-related myeloid neoplasms at the extended follow-up in the ATRA-ATO cohort also represents a major improvement in the treatment of a disease where high cure rates are achieved.

In conclusion, in line with results of pilot studies[18,19] and those of the recent randomized NCRI trial,[21] our results support the use of ATRA-ATO in patients with newly diagnosed APL and point to this strategy as the new standard of care for low- or intermediate-risk patients. Studies exploring the role of ATRA-ATO are warranted in other APL subsets including high-risk, pediatric, and elderly patients.

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Disclosures provided by the authors are available with this article at www.jco.org.

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## REFERENCES


1. Tallman MS, Andersen JW, Schiffer CA, et al: All-trans retinoic acid in acute promyelocytic leukemia: Long-term outcome and prognostic factor analysis from the North American Intergroup protocol. Blood 100:4298-4302, 2002

2. Asou N, Kishimoto Y, Kiyoi H, et al: A randomized study with or without intensified maintenance chemotherapy in patients with acute promyelocytic leukemia who have become negative for PML-RARalpha transcript after consolidation therapy: The Japan Adult Leukemia Study Group (JALSG) APL97 study. Blood 110:59-66, 2007

3. Lengfelder E, Haferlach C, Saussele S, et al: High dose ara-C in the treatment of newly diagnosed acute promyelocytic leukemia: Long-term results of the German AMLCG. Leukemia 23:2248-2258, 2009

4. Adès L, Guerci A, Raffoux E, et al: Very long-term outcome of acute promyelocytic leukemia after treatment with all-trans retinoic acid and chemotherapy: The European APL Group experience. Blood 115: 1690-1696, 2010

5. Sanz MA, Montesinos P, Rayón C, et al: Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: Further improvements in treatment outcome. Blood 115: 5137-5146, 2010

6. Avvisati G, Lo-Coco F, Paoloni FP, et al: AIDA 0493 protocol for newly diagnosed acute promyelocytic

leukemia: Very long-term results and role of maintenance. Blood 117:4716-4725, 2011

**7.** Iland H, Bradstock K, Seymour J, et al: Results of the APML3 trial incorporating all-trans-retinoic acid and idarubicin in both induction and consolidation as initial therapy for patients with acute promyelocytic leukemia. Haematologica 97: 227-234, 2012

**8.** Burnett AK, Hills RK, Grimwade D, et al: Inclusion of chemotherapy in addition to anthracycline in the treatment of acute promyelocytic leukaemia does not improve outcomes: Results of the MRC AML15 trial. Leukemia 27:843-851, 2013

**9.** Sanz MA, Grimwade D, Tallman MS, et al: Management of acute promyelocytic leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 113:1875-1891, 2009

**10.** Wang ZY, Chen Z: Acute promyelocytic leukemia: From highly fatal to highly curable. Blood 111: 2505-2515, 2008

**11.** Montesinos P, González JD, González J, et al: Therapy-related myeloid neoplasms in patients with acute promyelocytic leukemia treated with all-trans-retinoic acid and anthracycline-based chemotherapy. J Clin Oncol 28:3872-3879, 2010

**12.** de Thé H, Le Bras M, Lallemand-Breitenbach V: The cell biology of disease: Acute promyelocytic leukemia, arsenic, and PML bodies. J Cell Biol 198: 11-21, 2012

**13.** Mathews V, Chendamarai E, George B, et al: Treatment of acute promyelocytic leukemia with single-agent arsenic trioxide. Mediterr J Hematol Infect Dis 3:e2011056, 2011

**14.** Breccia M, Lo-Coco F: Arsenic trioxide for management of acute promyelocytic leukemia: Current evidence on its role in front-line therapy and recurrent disease. Expert Opin Pharmacother 13: 1031-1043, 2012

**15.** Shao W, Fanelli M, Ferrara FF, et al: Arsenic trioxide as an inducer of apoptosis and loss of PML/RAR alpha protein in acute promyelocytic leukemia cells. J Natl Cancer Inst 90:124-133, 1998

**16.** Ghavamzadeh A, Alimoghaddam K, Rostami S, et al: Phase II study of single-agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia. J Clin Oncol 29:2753-2757, 2011

**17.** Mathews V, George B, Lakshmi KM, et al: Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: Durable remissions with minimal toxicity. Blood 107: 2627-2632, 2006

**18.** Estey E, Garcia-Manero G, Ferrajoli A, et al: Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. Blood 107:3469-3473, 2006

**19.** Ravandi F, Estey E, Jones D, et al: Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J Clin Oncol 27:504-510, 2009

**20.** Lo-Coco F, Avvisati G, Vignetti M, et al: Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 369:111-121, 2013

**21.** Burnett AK, Russell NH, Hills RK, et al: Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): Results of a randomised, controlled, phase 3 trial. Lancet Oncol 16:1295-1305, 2015

**22.** National Comprehensive Cancer Network: NCCN Guidelines: Acute Myeloid Leukemia. Version 1.2015. www.nccn.org

**23.** Seftel MD, Barnett MJ, Couban S, et al.: A Canadian consensus on the management of newly diagnosed and relapsed acute promyelocytic leukemia in adults. Curr Oncol 21:234-250, 2014

**24.** Montesinos P, Bergua JM, Vellenga E, et al: Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: Characteristics, outcome, and prognostic factors. Blood 113: 775-783, 2009

**25.** Frankel SR, Eardley A, Lauwers G, et al: The "retinoic acid syndrome" in acute promyelocytic leukemia. Ann Intern Med 117:292-296, 1992

**26.** Efficace F, Mandelli F, Avvisati G, et al: Randomized phase III trial of retinoic acid and arsenic trioxide versus retinoic acid and chemotherapy in patients with acute promyelocytic leukemia: Health-related quality-of-life outcomes. J Clin Oncol 32: 3406-3412, 2014

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**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**

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**Table A1.** Hematologic Toxicity

| Randomly Assigned Treatment | UPN | System, Organ, Class | Preferred Term | Drug 1 | Relationship 1 | Drug 2 | Relationship 2 | Outcome |
|---|---|---|---|---|---|---|---|---|
| ATRA-ATO | 1 | Investigations | ECG QT prolonged | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 2 | Infections | Pneumonia | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 2 | Respiratory, thoracic, and mediastinal disorders | Respiratory failure | ATO | Related | ATRA | Related | Unchanged |
| ATRA-ATO | 3 | Investigations | ALT increased | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 4 | Respiratory, thoracic, and mediastinal disorders | APL differentiation syndrome | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 5 | Nervous system disorders | Cerebrovascular accident | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 6 | Respiratory, thoracic, and mediastinal disorders | Dyspnea | ATO | Unrelated | — | — | Recovered |
| ATRA-ATO | 7 | Respiratory, thoracic, and mediastinal disorders | Respiratory failure | ATO | Unrelated | — | — | Recovered |
| ATRA-ATO | 8 | Cardiac disorders | Pericarditis | ATO | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-ATO | 9 | Injury poisoning and procedural complications | Maternal exposure before pregnancy | ATO | Unrelated | — | — | Recovered |
| ATRA-ATO | 10 | Hepatobiliary disorders | Hepatotoxicity | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 11 | Nervous system disorders | Cerebral hemorrhage | ATO | Related | ATRA | Related | — |
| ATRA-ATO | 12 | Vascular disorders | Intracranial aneurysm | ATO | Unrelated | ATRA | Unrelated | Unchanged |
| ATRA-ATO | 13 | Investigations | ALT increase | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 13 | Investigations | AST increase | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 14 | GI disorders | Dyspepsia | ATO | Related | — | — | Recovered |
| ATRA-ATO | 14 | Respiratory, thoracic, and mediastinal disorders | APL differentiation syndrome | ATO | Not assessable | — | — | Recovered |
| ATRA-ATO | 15 | Eye disorders | Diplopia | ATO | Not assessable | ATRA | Not assessable | Recovered |
| ATRA-ATO | 16 | Psychiatric disorders | Confusional state | ATO | Unrelated | — | — | Recovered |
| ATRA-ATO | 17 | Hepatobiliary disorders | Hypertransaminasemia | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 18 | Infections | Catheter site infection | ATO | Unrelated | — | — | Recovered |
| ATRA-ATO | 19 | Infections | Pneumonia | ATO | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-ATO | 20 | General disorders and administration site conditions | Pyrexia | ATO | Unrelated | ATRA | Unrelated | — |
| ATRA-ATO | 21 | Hepatobiliary disorders | Hepatic failure | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 21 | Respiratory, thoracic, and mediastinal disorders | APL differentiation syndrome | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 22 | Infections | Herpes zoster | — | Related | — | Related | Recovered |
| ATRA-ATO | 22 | Nervous system disorders | Hydrocephalus | ATO | Related | ATRA | Related | Unchanged |
| ATRA-ATO | 22 | Skin and subcutaneous tissue disorders | Leukocytoclastic vasculitis | ATO | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-ATO | 23 | Respiratory, thoracic, and mediastinal disorders | Pneumonia | ATO | Unrelated | ATRA | Unrelated | Fatal |
| ATRA-ATO | 24 | Respiratory, thoracic, and mediastinal disorders | Dyspnea | ATO | Unrelated | — | — | Recovered |
| ATRA-ATO | 25 | Nervous system disorders | Depression | — | — | — | — | Recovered |
| ATRA-ATO | 26 | Respiratory, thoracic, and mediastinal disorders | Retinoic acid syndrome | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 27 | Cardiac disorders | Syncope | ATO | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-ATO | 27 | Hepatobiliary disorders | Cholelithiasis | ATO | Unrelated | ATRA | Related | Recovered |
| ATRA-ATO | 27 | Investigations | Hepatic enzyme increased | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 27 | Musculoskeletal and connective tissue disorders | Fracture | ATO | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-ATO | 28 | Infections | Catheter site infection | ATO | Unrelated | — | — | Recovered |

(continued on following page)

**Table A1.** Hematologic Toxicity (continued)

| Randomly Assigned Treatment | UPN | System, Organ, Class | Preferred Term | Drug 1 | Relationship 1 | Drug 2 | Relationship 2 | Outcome |
|---|---|---|---|---|---|---|---|---|
| ATRA-ATO | 29 | Investigations | C-reactive protein increased | ATO | Related | — | — | Recovered |
| ATRA-ATO | 29 | Respiratory, thoracic, and mediastinal disorders | Dyspnea | ATO | Related | — | — | Recovered |
| ATRA-ATO | 30 | Infections | Febrile infection | ATO | Related | ATRA | Related | Recovered |
| ATRA-ATO | 30 | Reproductive system and breast disorders | Endometriosis | ATO | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-ATO | 31 | Cardiac disorders | Acute myocardial infarction | ATO | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-ATO | 32 | Investigations | ECG QT prolonged | ATO | Related | — | — | Recovered |
| ATRA-CHT | 33 | Respiratory, thoracic, and mediastinal disorders | Acute respiratory distress syndrome | IDA | Related | ATRA | Related | Fatal |
| ATRA-CHT | 34 | Cardiac disorders | Myocardial ischemia | IDA | Related | ATRA | Related | Recovered |
| ATRA-CHT | 35 | Respiratory, thoracic, and mediastinal disorders | Respiratory failure | IDA | Related | ATRA | Related | Fatal |
| ATRA-CHT | 35 | Respiratory, thoracic, and mediastinal disorders | Retinoic acid syndrome | IDA | Related | ATRA | Related | Fatal |
| ATRA-CHT | 36 | Cardiac disorders | Acute myocardial infarction | IDA | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-CHT | 37 | Investigations | Aminotransferases increased | IDA | Unrelated | ATRA | Unrelated | Unchanged |
| ATRA-CHT | 38 | Blood and lymphatic system disorders | Febrile neutropenia | MTX | Related | ATRA | Related | Recovered |
| ATRA-CHT | 39 | GI disorders | Pancreatitis acute | ATRA | Unrelated | — | — | Recovered |
| ATRA-CHT | 40 | Nervous system disorders | Ischemic stroke | IDA | Related | ATRA | Related | Fatal |
| ATRA-CHT | 41 | Cardiac disorders | Pericarditis | IDA | Related | ATRA | Related | Improved |
| ATRA-CHT | 42 | Cardiac disorders | Cardiac failure | IDA | Related | ATRA | Related | Recovered |
| ATRA-CHT | 43 | General disorders and administration site conditions | Pyrexia | MTX | Related | ATRA | Related | Recovered |
| ATRA-CHT | 44 | Blood and lymphatic system disorders | Febrile neutropenia | MTX | Related | ATRA | Related | — |
| ATRA-CHT | 45 | Blood and lymphatic system disorders | Bone marrow failure | MTX | Related | ATRA | Related | Improved |
| ATRA-CHT | 46 | Respiratory, thoracic, and mediastinal disorders | Pulmonary embolism | — | — | — | Not assessable | Improved |
| ATRA-CHT | 46 | Respiratory, thoracic, and mediastinal disorders | Retinoic acid syndrome | — | — | ATRA | Related | Improved |
| ATRA-CHT | 46 | Vascular disorders | Shock hemorrhagic | IDA | Unrelated | ATRA | Unrelated | Fatal |
| ATRA-CHT | 47 | Infections | Bronchopneumonia | — | — | ATRA | Related | Fatal |
| ATRA-CHT | 48 | Vascular disorders | Thrombosis | IDA | Related | ATRA | Related | Recovered |
| ATRA-CHT | 48 | Infections | Bronchopneumonia | MTX | Related | — | — | Fatal |
| ATRA-CHT | 49 | Blood and lymphatic system disorders | Febrile neutropenia | IDA | Related | ATRA | Related | Recovered |
| ATRA-CHT | 50 | Blood and lymphatic system disorders | Neutropenia | MTX | Related | ATRA | Related | Recovered |
| ATRA-CHT | 50 | Infections | Pneumonia | MTX | Related | ATRA | Related | Recovered |
| ATRA-CHT | 51 | General disorders and administration site conditions | Mucosal inflammation | IDA | Related | ATRA | Related | Recovered |
| ATRA-CHT | 51 | Vascular disorders | Pulmonary embolism | — | Unrelated | — | — | Fatal |
| ATRA-CHT | 52 | GI disorders | Inguinal hernia | MP | Unrelated | MTX | Unrelated | Recovered |
| ATRA-CHT | 53 | Blood and lymphatic system disorders | Febrile neutropenia | MTX | Related | ATRA | Related | Improved |
| ATRA-CHT | 53 | GI disorders | Anal hemorrhage | MTX | Related | ATRA | Related | Recovered |
| ATRA-CHT | 53 | Injury poisoning and procedural complications | Maternal exposures before pregnancy | ATRA | Unrelated | MP | Unrelated | Recovered |
| ATRA-CHT | 54 | Blood and lymphatic system disorders | Febrile neutropenia | — | Related | — | — | Recovered |

(continued on following page)

**Table A1.** Hematologic Toxicity (continued)

| Randomly Assigned Treatment | UPN | System, Organ, Class | Preferred Term | Drug 1 | Relationship 1 | Drug 2 | Relationship 2 | Outcome |
|---|---|---|---|---|---|---|---|---|
| ATRA-CHT | 54 | Blood and lymphatic system disorders | Febrile neutropenia | IDA | — | ATRA | — | Recovered |
| ATRA-CHT | 54 | Vascular disorders | Extradural hematoma | IDA | Unrelated | ATRA | Unrelated | Improved |
| ATRA-CHT | 55 | Respiratory, thoracic, and mediastinal disorders | Retinoic acid syndrome | IDA | Related | ATRA | Related | Improved |
| ATRA-CHT | 56 | Infections | Urinary tract infection | IDA | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-CHT | 57 | Blood and lymphatic system disorders | Febrile neutropenia | MTX | Related | ATRA | Related | Recovered |
| ATRA-CHT | 58 | General disorders and administration site conditions | Pyrexia | MP | Related | — | — | Recovered |
| ATRA-CHT | 58 | Infections | Bacteremia | IDA | Related | ATRA | Related | Recovered |
| ATRA-CHT | 58 | Infections | Infection | MP | Related | — | — | Recovered |
| ATRA-CHT | 58 | Infections | Infection | MTX | Related | ATRA | Related | Recovered |
| ATRA-CHT | 59 | Cardiac disorders | Ejection fraction decreased | MP + MTX | Unrelated | ATRA | Unrelated | Unchanged |
| ATRA-CHT | 60 | Infections | Sepsis | IDA | Related | ATRA | Related | Recovered |
| ATRA-CHT | 61 | Cardiac disorders | Pericarditis | IDA | Related | — | — | Unchanged |
| ATRA-CHT | 61 | General disorders and administration site conditions | Mucosal inflammation | MTX | Related | ATRA | Related | Recovered |
| ATRA-CHT | 61 | Respiratory, thoracic, and mediastinal disorders | Respiratory failure | — | — | — | — | Recovered |
| ATRA-CHT | 62 | GI disorders | Diarrhea | ATRA | Unrelated | — | — | Recovered |
| ATRA-CHT | 62 | GI disorders | Emesis | ATRA | Unrelated | — | — | Recovered |
| ATRA-CHT | 63 | General disorders and administration site conditions | Fever in aplasia | IDA + MTX | Related | ATRA | Related | Recovered |
| ATRA-CHT | 64 | Infections | Sepsis | IDA | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-CHT | 64 | Investigations | Hyperglycemia | MTX, MP | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-CHT | 64 | Blood and lymphatic system disorders | Febrile neutropenia | MTX | Related | ATRA | Related | Recovered |
| ATRA-CHT | 65 | Cardiac disorders | Tachyarrhythmia | Prednisone | Unrelated | ATRA | Unrelated | Recovered |
| ATRA-CHT | 65 | Infections | Pneumonia | Prednisone | Related | ATRA | Related | Recovered |

Abbreviations: APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy; IDA, idarubicin; MP, mercaptopurine; MTX, methotrexate; UPN, unique patient number.