Short and Long-term Quality of Life in patients with Acute Promyelocytic Leukemia (APL)

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per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

Disclosures

- TEVA
- LUNDBECK
- BMS
- INCYTE
- AMGEN

Can we use Toxicity Criteria as surrogate for Patient's Quality of Life?

…they cannot

Common Terminology Criteria for Adverse Events (CTCAE)

The most widely used method for quantifying harm from treatment experienced by patients

Laboratory - based information

- Anemia
- Neutropenia
- QT prolongation

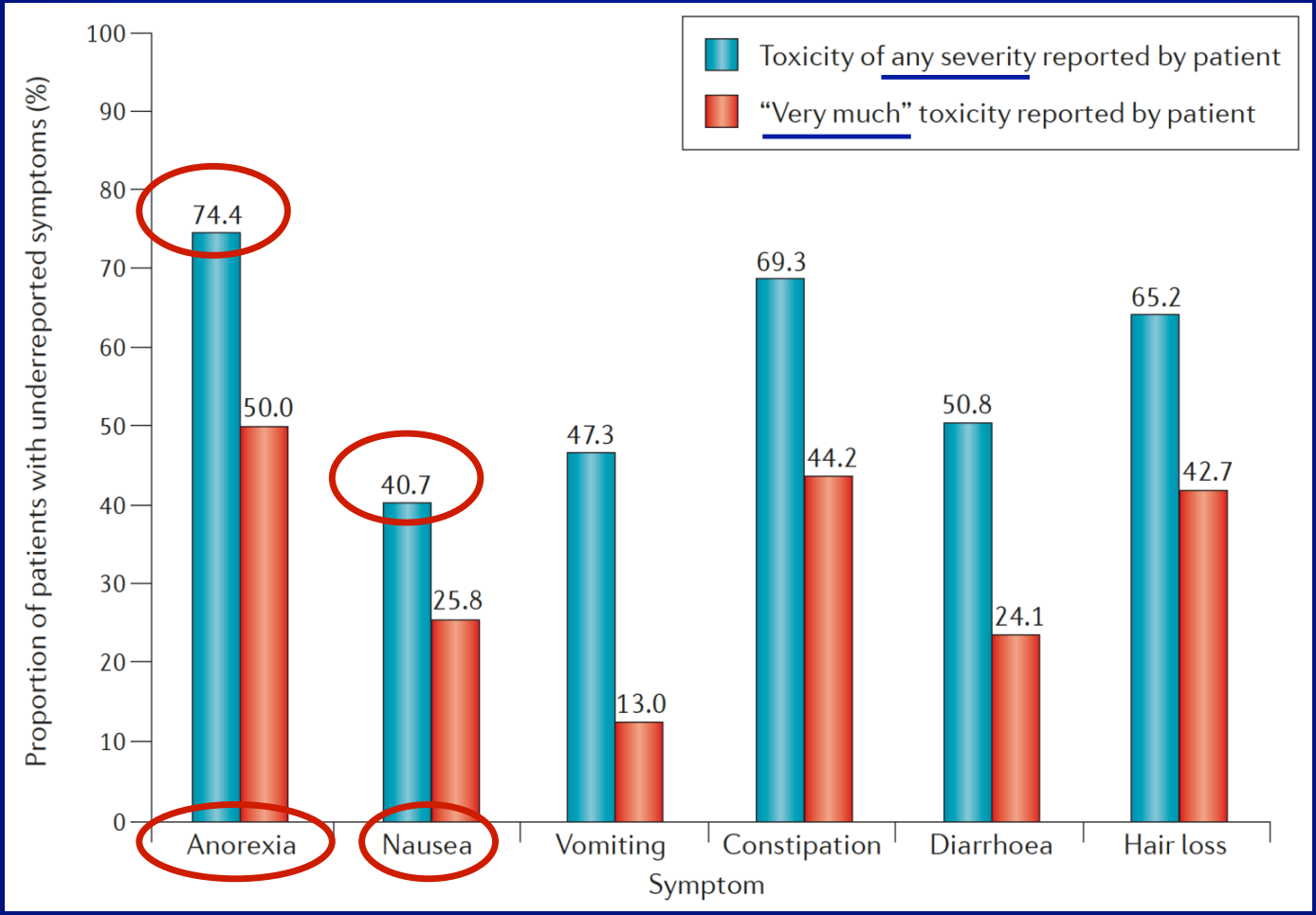
Direct Clinician observation or Physician judgment

-Rash
-Pain
-Fatigue

Di Maio M et al. Nat Rev Clin Oncol 13: 319-325, 2016; Fromme E, et al, J Clin Oncol 22:3485-90, 2004; Dueck AC et al, JAMA Oncol. 1:1051-9, 2015

Underreporting of Treatment-Related Toxicities by Physicians

(Di Maio et al., Nat Rev Clin Oncol. 2016 May;13:319-25)



(data taken from three large RCTs in patients with solid tumors)

Major paradigm-shift in the way the effects of therapy are to be documented: Patient-Reported Outcome (PRO)-CTCAE

In 2008 the NCI began developing a PRO version of the CTCAE in order to bring the patient perspective on toxicity reporting into widespread use in oncology

Dueck AC et al, JAMA Oncol. 2015 Nov;1(8):1051-9

Research

Original Investigation

Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

Amylou C. Dueck, PhD; Tito R. Mendoza, PhD; Sandra A. Mitchell, PhD, CRNP, AOCN; Bryce B. Reeve, PhD; Kathleen M. Castro, RN, MS, AOCN; Lauren J. Rogak, MA; Thomas M. Atkinson, PhD; Antonia V. Bennett, PhD; Andrea M. Denicoff, MS, RN, ANP; Ann M. O'Mara, PhD, RN, FAAN; Yuelin Li, PhD; Steven B. Clauser, PhD, MPA; Donna M. Bryant, MSN, ANP-BC, OCN, CCRC; James D. Bearden III, MD, FACP; Theresa A. Gillis, MD; Jay K. Harness, MD; Robert D. Siegel, MD, FACP; Diane B. Paul, AAS; Charles S. Cleeland, PhD; Deborah Schrag, MD, MPH; Jeff A. Sloan, PhD; Amy P. Abernethy, MD, PhD; Deborah W. Bruner, RN, PhD, FAAN; Lori M. Minasian, MD, FACP; Ethan Basch, MD, MSc; for the National Cancer Institute PRO-CTCAE Study Group

Regulatory Stakeholders perspective on Patient-Reported Outcomes (PRO)

US Food and Drug Administration (FDA) and European Medicines Agency (EMA)

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach, and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448
Tel: 800-835-4709 or 301-827-1800; E-mail: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

or

Office of Communication, Education, and Radiation Programs
Division of Small Manufacturers, International, and Consumer Assistance, HFZ-220
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Rockville, MD 20850-4307
DSMICA E-mail: dsmica@cdrh.fda.gov
DSMICA Fax: 301-443-8818
(Tel) Manufacturers Assistance: 800-638-2041 or 301-443-6597
(Tel) International Staff: 301-827-3993
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

FDA (USA)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 April 2016
EMA/CHMP/292464/2014
Committee for Medicinal Products for Human Use (CHMP)

Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man

The use of patient-reported outcome (PRO) measures in oncology studies

Draft agreed by Oncology Working Party	December 2013
Adopted by CHMP for release for consultation	22 May 2014
Start of public consultation	17 June 2014
End of consultation (deadline for comments)	30 November2014
Agreed by Oncology Working Party	November 2015
Adopted by CHMP	1 April 2016
Date for coming into effect	1 November 2016

EMA (Europe)

ATRA-Chemotherapy vs. ATRA-Arsenic Trioxide:

Is there a QoL difference ?

Burnett A, et al, Lancet Oncol, 2015 Oct;16(13):1295-305

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

Alan K Burnett, Nigel H Russell, Robert K Hills, David Bowen, Jonathan Kell, Steve Knapper, Yvonne G Morgan, Jennie Lok, Angela Grech, Gail Jones, Asim Khwaja, Lone Friis, Mary Frances McMullin, Ann Hunter, Richard E Clark, David Grimwade, for the UK National Cancer Research Institute Acute Myeloid Leukaemia Working Group

Background Acute promyelocytic leukaemia is a chemotherapy-sensitive subgroup of acute myeloid leukaemia characterised by the presence of the *PML–RARA* fusion transcript. The present standard of care, chemotherapy and all-*trans* retinoic acid (ATRA), results in a high proportion of patients being cured. In this study, we compare a chemotherapy-free ATRA and arsenic trioxide treatment regimen with the standard chemotherapy-based regimen (ATRA and idarubicin) in both high-risk and low-risk patients with acute promyelocytic leukaemia.

Lancet Oncol 2015; 16: 1295-1305

Published Online September 15, 2015 http://dx.doi.org/10.1016/S1470-2045(15)00193-X

Efficace F, et al, J Clin Oncol. 2014 Oct 20;32(30):3406-12

VOLUME 32 · NUMBER 30 · OCTOBER 20 2014

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

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

Fabio Efficace, Franco Mandelli, Giuseppe Avvisati, Francesco Cottone, Felicetto Ferrara, Eros Di Bona, Giorgina Specchia, Massimo Breccia, Alessandro Levis, Simona Sica, Olimpia Finizio, Maria Grazia Kropp, Giuseppe Fioritoni, Elisa Cerqui, Marco Vignetti, Sergio Amadori, Richard F. Schlenk, Uwe Platzbecker, and Francesco Lo-Coco

Fabio Efficace, Franco Mandelli, Francesco Cottone, and Marco Vignetti, Gruppo Italiano Malattie Ematologiche dell'Adulto; Giuseppe Avvisati, Università Campus Biomedico; Massimo Breccia, Università "La Sapienza,"; Simona Sica, Università Cattolica Sacro Cuore; Sergio Amadori and Francesco Lo-Coco, Università Tor Vergata; Francesco Lo-Coco, Fondazione Santa Lucia, Roma; Felicetto Ferrara, Ospedale Cardarelli; Olimpia Finizio, Ospedale Cardarelli, Napoli; Eros Di Bona, Ospedale San Bortolo, Vicenza; Giorgina Specchia, Università di Bari, Bari; Alessandro Levis,

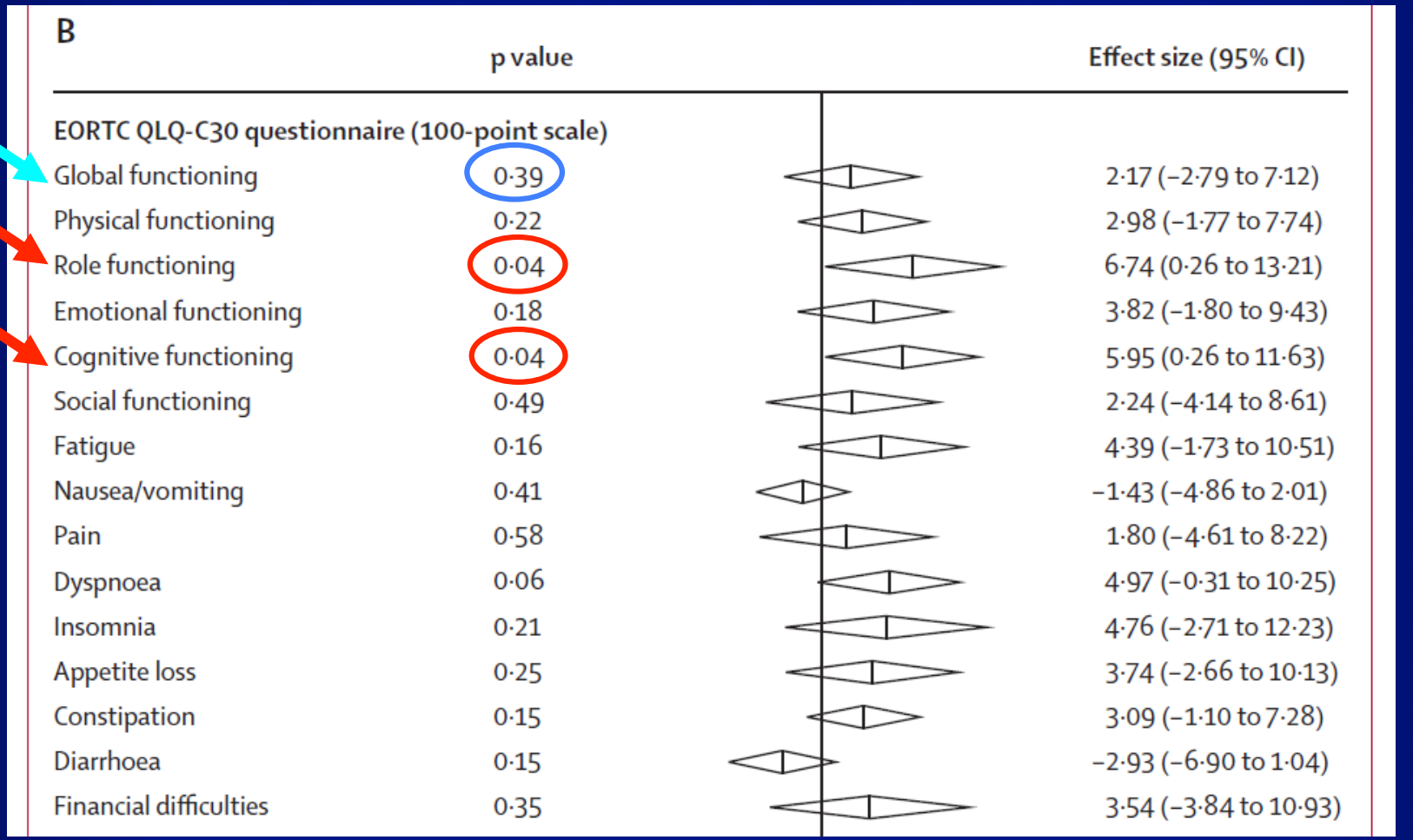
A B S T R A C T

Purpose

A randomized clinical trial compared efficacy and toxicity of standard all-*trans*-retinoic acid (ATRA) plus chemotherapy versus ATRA plus arsenic trioxide in patients with newly diagnosed, low- or intermediate-risk acute promyelocytic leukemia (APL). Here, we report health-related quality-of-life (HRQOL) results.

EORTC QLQ-C30 Scales: difference between treatment arms

Burnett A, et al, Lancet Oncol, 2015 Oct;16(13):1295-305



B

	p value	Effect size (95% CI)
EORTC QLQ-C30 questionnaire (100-point scale)		
Global functioning	0·39	2·17 (−2·79 to 7·12)
Physical functioning	0·22	2·98 (−1·77 to 7·74)
Role functioning	0·04	6·74 (0·26 to 13·21)
Emotional functioning	0·18	3·82 (−1·80 to 9·43)
Cognitive functioning	0·04	5·95 (0·26 to 11·63)
Social functioning	0·49	2·24 (−4·14 to 8·61)
Fatigue	0·16	4·39 (−1·73 to 10·51)
Nausea/vomiting	0·41	−1·43 (−4·86 to 2·01)
Pain	0·58	1·80 (−4·61 to 8·22)
Dyspnoea	0·06	4·97 (−0·31 to 10·25)
Insomnia	0·21	4·76 (−2·71 to 12·23)
Appetite loss	0·25	3·74 (−2·66 to 10·13)
Constipation	0·15	3·09 (−1·10 to 7·28)
Diarrhoea	0·15	−2·93 (−6·90 to 1·04)
Financial difficulties	0·35	3·54 (−3·84 to 10·93)

−15 −10 −5 0 5 10 15

Favoring ATRA-Idarubicin

Favoring ATRA-ATO

A randomized Phase III trial to compare Arsenic Trioxide (ATO) versus standard chemotherapy in APL patients

Lo Coco F, et al, N Engl J Med. 2013 Jul 11;369(2):111-21.

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

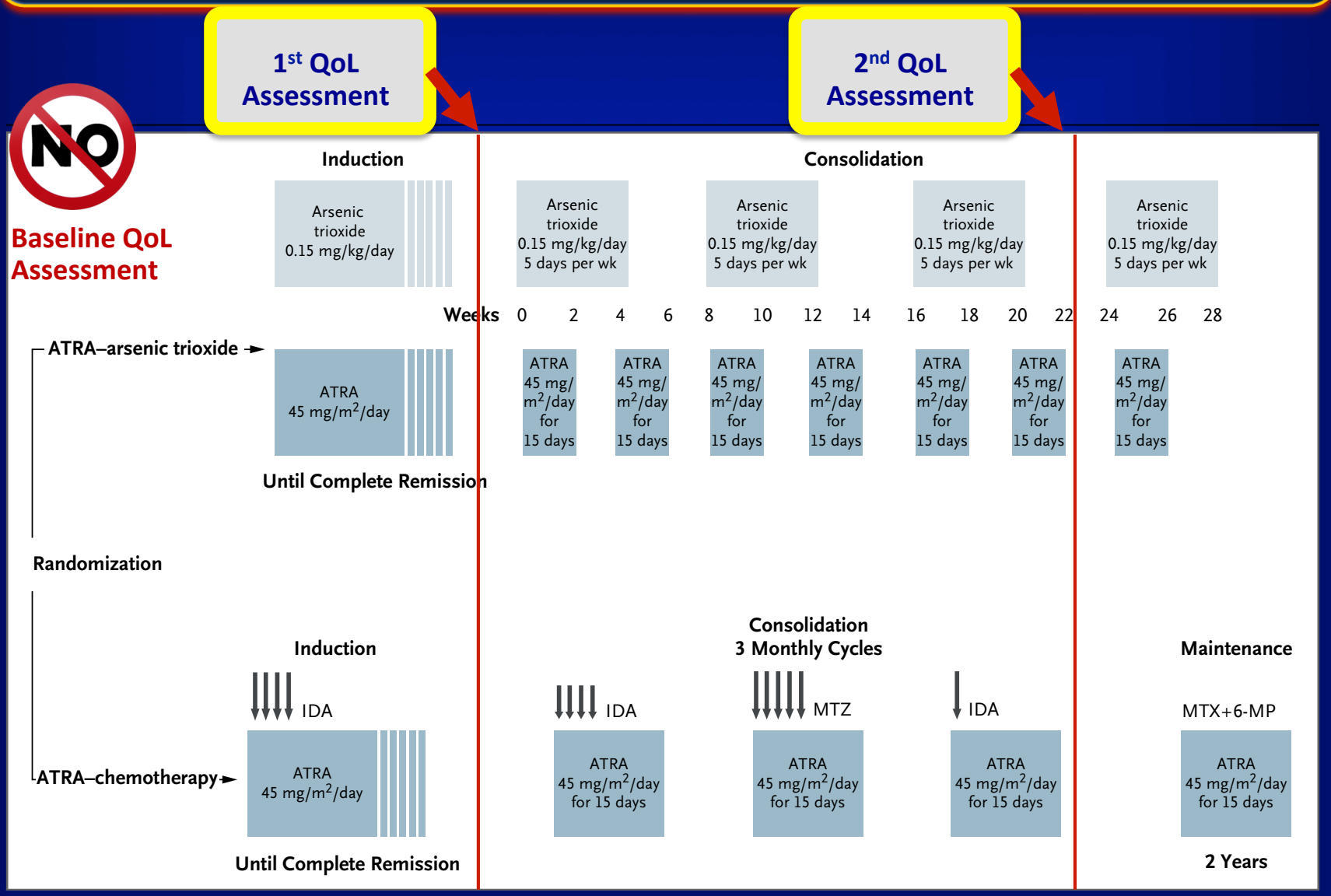
F. Lo-Coco, G. Avvisati, M. Vignetti, C. Thiede, S.M. Orlando, S. Iacobelli, F. Ferrara, P. Fazi, L. Cicconi, E. Di Bona, G. Specchia, S. Sica, M. Divona, A. Levis, W. Fiedler, E. Cerqui, M. Breccia, G. Fioritoni, H.R. Salih, M. Cazzola, L. Melillo, A.M. Carella, C.H. Brandts, E. Morra, M. von Lilienfeld-Toal, 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

RESULTS

Complete remission was achieved in all 77 patients in the ATRA–arsenic trioxide group who could be evaluated (100%) and in 75 of 79 patients in the ATRA–chemotherapy group (95%) (P=0.12). The median follow-up was 34.4 months. Two-year event-free survival rates were 97% in the ATRA–arsenic trioxide group and 86% in the ATRA–chemotherapy group (95% confidence interval for the difference, 2 to 22 percentage points; P<0.001 for noninferiority and P=0.02 for superiority of ATRA–arsenic trioxide). Overall survival was also better with ATRA–arsenic trioxide (P=0.02). As compared with ATRA–chemotherapy, ATRA–arsenic trioxide was associated with less hematologic toxicity and fewer infections but with more hepatic toxicity.

Treatment schema ATRA+Chemo vs. ATRA+ATO

Lo Coco F, et al, N Engl J Med. 2013 Jul 11;369(2):111-21.



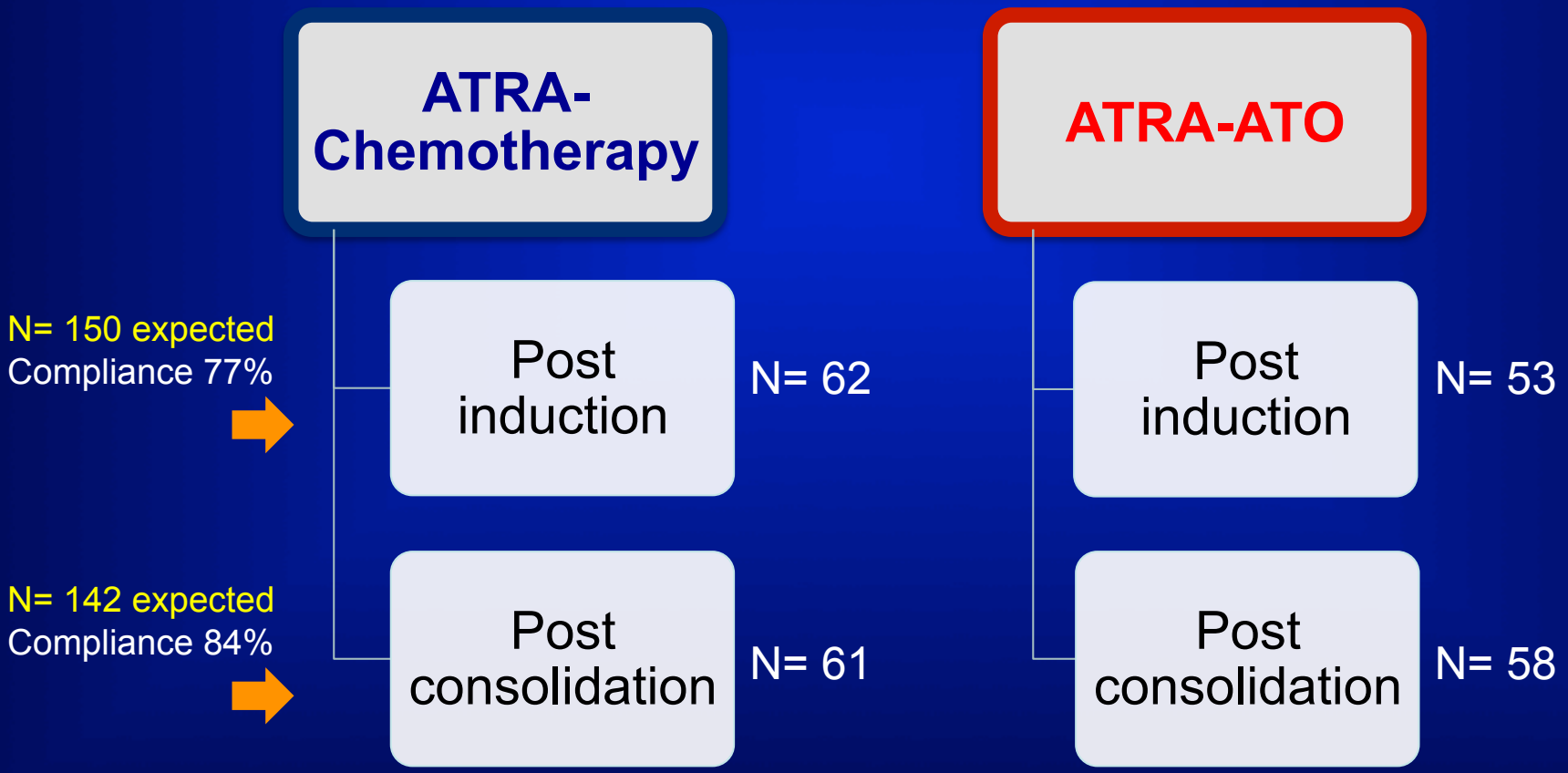
Results and QoL COMPLIANCE

Between October 2007 and September 2010, 162 patients were enrolled.

Genetic tests excluded a diagnosis of PML/RARA-positive APL in 3 patients. Three of 159 patients with genetically proven APL did not start allocated treatment.

156 patients

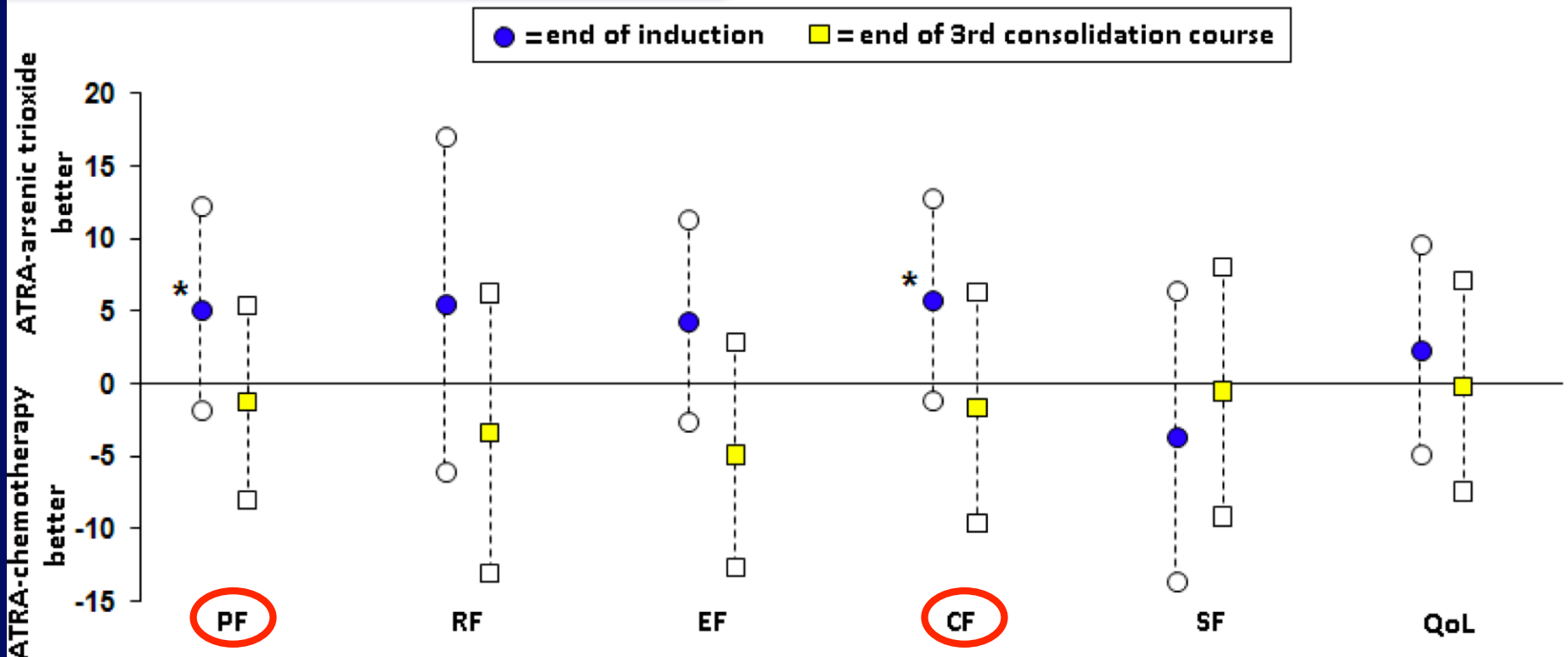
who received at least one dose of the assigned therapy after randomization.



Quality of Life difference Post Induction and Post Consolidation

Efficace F, et al, J Clin Oncol. 2014 Oct 20;32(30):3406-12

Functional aspects / Global QoL

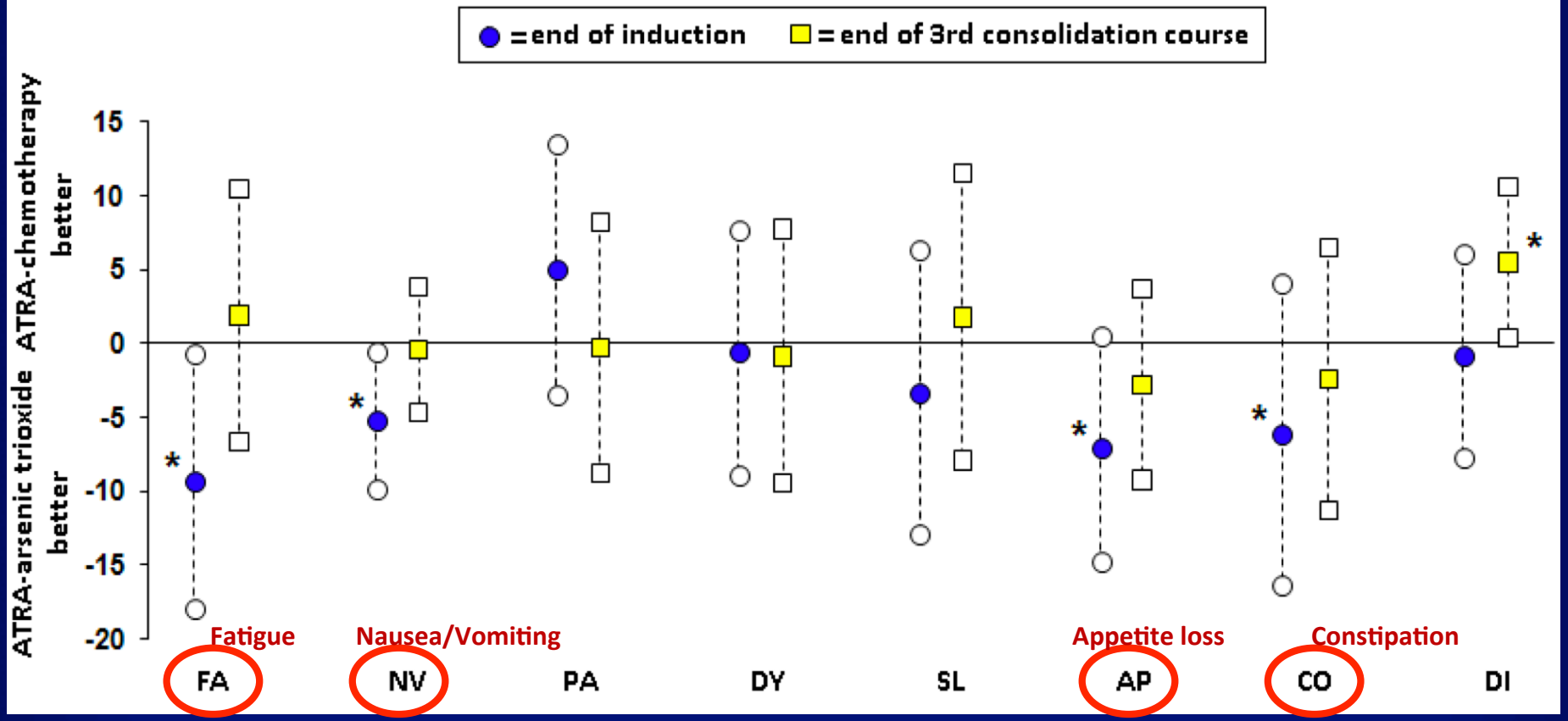


* Clinically meaningful difference; (based on Cocks K, et al., J Clin Oncol. 2011;29:89-96).

Quality of Life difference Post Induction and Post Consolidation

Efficace F, et al, J Clin Oncol. 2014 Oct 20;32(30):3406-12

Symptom Severity



* Clinically meaningful difference; (based on Cocks K, et al., J Clin Oncol. 2011;29:89-96).

Study update on 263 APL patients (Platzbecker U, et al, J Clin Oncol. 2017 Feb 20;35(6):605-612)

VOLUME 35 · NUMBER 6 · FEBRUARY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Improved Outcomes With Retinoic Acid and Arse
Compared With Retinoic Acid and Chemothera
Non–High-Risk Acute Promyelocytic Leukemia: I
of the Randomized Italian-German APL0406 Tr

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

Author affiliations and support information (if applicable) appear at the end of this article.

A B S T R A C T

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, × 10^9/L (range)	1.4 (0.32-10)	1.5 (0.3-9.61)	.83
Median platelets, × 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)	

viations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, che-apy; ITD, internal tandem duplication.

QoL Results:

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.

Fatigue better with ATO vs Chemo

(P=.034)

What is the added value of this research?

These findings further supported the use of Arsenic Trioxide (ATO) as preferred first-line treatment in APL patients, given the QoL advantages found **after Induction therapy**

- ✓ Fatigue,
- ✓ Appetite loss,
- ✓ Nausea/vomiting,
- ✓ Constipation,
- ✓ Physical functioning
- ✓ Cognitive functioning.

Efficace F, et al, J Clin Oncol. 2014 Oct 20;32(30):3406-12.

Quality of Life in the Approval of Arsenic Trioxide in Patients with APL

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 Octobe
EMA/CHMI
Committee

Asse

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3.2. Favourable effects

Results from pivotal study APL0406 support the use of ATRA-ATO in first line APL. With respect to the primary endpoint, the 2-year EFS rates observed (97% with ATRA-ATO and 86% with ATRA+chemotherapy (p=0.02 for superiority) are considered adequate to demonstrate the superiority of ATRA-ATO to ATRA+chemotherapy. These results are considered of high clinical relevance; especially taking into account that the majority of relapses in APL are usually recorded within 2 years from the achievement of response (i.e., 75% and 65% of relapses occurred within 2 year from the end of treatment in the AIDA-0493 and AIDA-2000 studies, respectively). EFS results observed in the per-protocol analysis at different median follow-up (50-month EFS rate was 96% with ATRA-ATO vs 81% with ATRA+chemotherapy, p=0.0034) and in the extended cohort (the 2-year EFS rate was 98% in the ATRA+ATO group and 87% in the ATRA+chemotherapy group, p <0.0001) were all consistent with the primary analysis and supported its robustness.

The results in the secondary endpoints also supported the significant benefit obtained with ATRA+ATO vs. ATRA+chemotherapy: a statistically significant and clinically relevant 8% advantage in the 2-year OS rate with a consistent positive trend in terms of 2-year DFS rate was observed and was confirmed in the longer follow-up analysis and in the extension cohort. Consistently, also the CIR analysis demonstrated a clinical advantage with ATRA-ATO compared to ATRA+chemotherapy, both in the original and in the extended cohort of study APL0406. A non-statistically significant trend in favour of ATRA-ATO was also observed in terms of haematological CR (HCR 100% vs. 95%, p=0.12 in the original cohort; 100% vs. 97%, p=0.12 in the extended cohort).

With respect to QoL, a significant improvement in patients who received ATRA-ATO compared to the AIDA regimen was observed. However, this advantage was lost after consolidation.

What about oral Arsenic in APL?

Zhu HH, Huang XJ, N Engl J Med. 2014 Dec 4;371(23):2239-41

Oral Arsenic and Retinoic Acid for Non–High-Risk Acute Promyelocytic Leukemia

TO THE EDITOR: All-trans retinoic acid (ATRA) and chemotherapy are curative in patients with non–high-risk acute promyelocytic leukemia (APL) (white-cell count <10,000 per cubic millimeter). However, patients can also be cured by treatment with a combination of ATRA and arsenic trioxide without chemotherapy.[1]

The National Comprehensive Cancer Network has adopted ATRA and arsenic trioxide as the first-line treatment for APL in its 2014 guidelines,[2] although arsenic resistance may develop in some patients.[3] Whereas arsenic trioxide must be infused in the hospital, oral arsenic may in some cases be administered outside the hospital. Using a protocol that included chemotherapy in patients with APL, we recently found that oral arsenic (the realgar-indigo naturalis formula [RIF]) provided an outcome similar to that produced with intravenous arsenic trioxide.[4]

From March 2013 through February 2014, we conducted a single-center pilot study to evaluate the efficacy of oral arsenic and ATRA without

\$3,174 to \$12,698). Patients resumed their usual lifestyle during postremission therapy, and their quality of life was rated as nearly normal on the FACT-G questionnaire (Table 1, and Table S1 in the Supplementary Appendix).

N=20 APL patients

Quality of Life: secondary endpoint

Median Follow-up: 14 months

Long-term Effects of ATRA and Chemotherapy in APL survivors?

GIMEMA Trial
AIDA 0493

GIMEMA Trial
AIDA 2000

Avvisati G, et al, Blood. 2011 May 5;117(18):4716-25; Lo Coco F, et al, Blood. 2010 Oct 28;116(17):3171-9.

Inclusion criteria

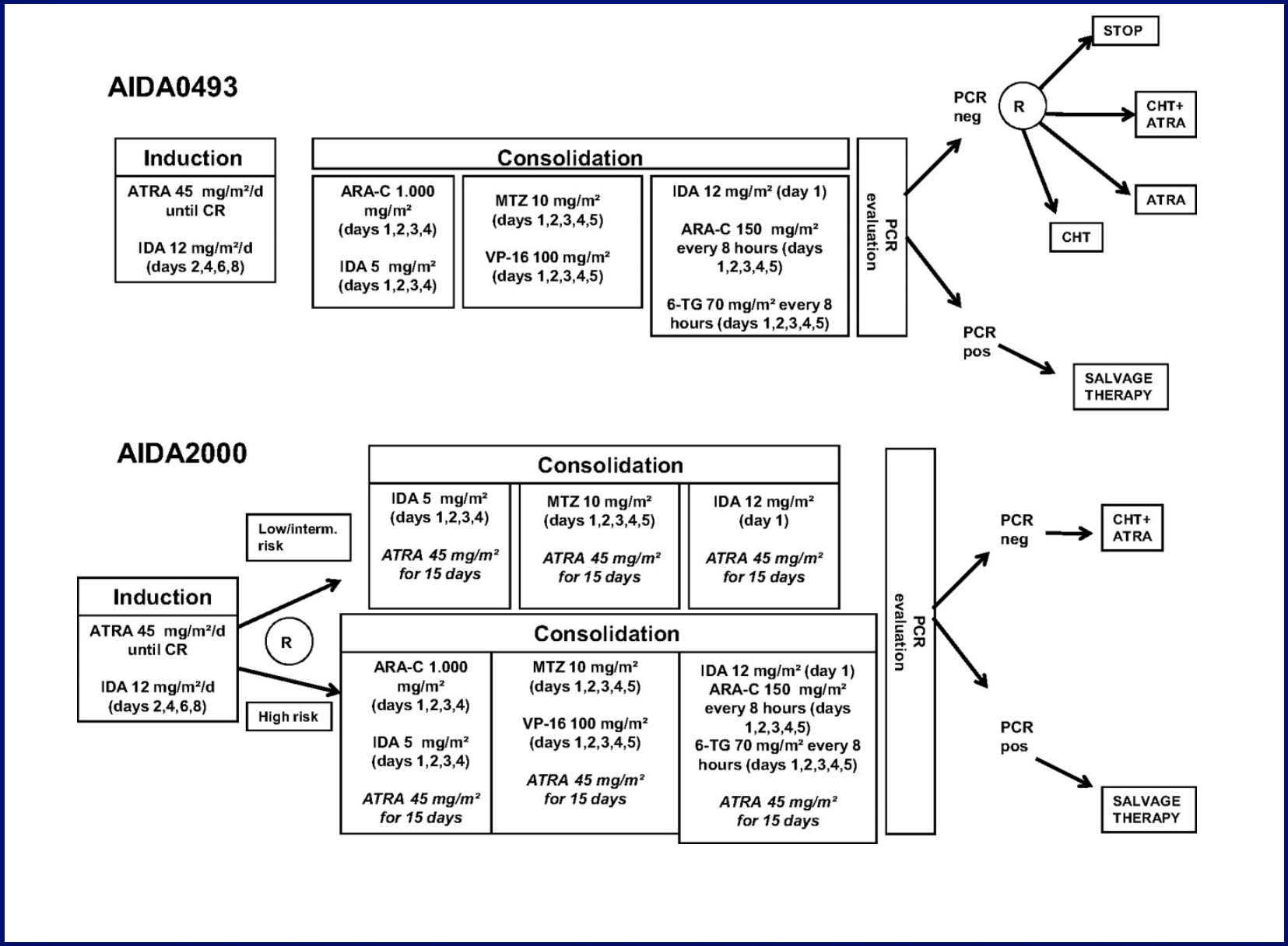
- Age ≥ 18 years at starts of this survivorship study
- Diagnosed with APL and being enrolled in GIMEMA AIDA 2000 and AIDA 0493
- Surviving the initial diagnosis for more than 5 years and in complete remission (CR).
- Informed consent provided.

GIMEMA - APL Survivorship Platform
(N=307 APL patients)

To investigate a number of aspects:

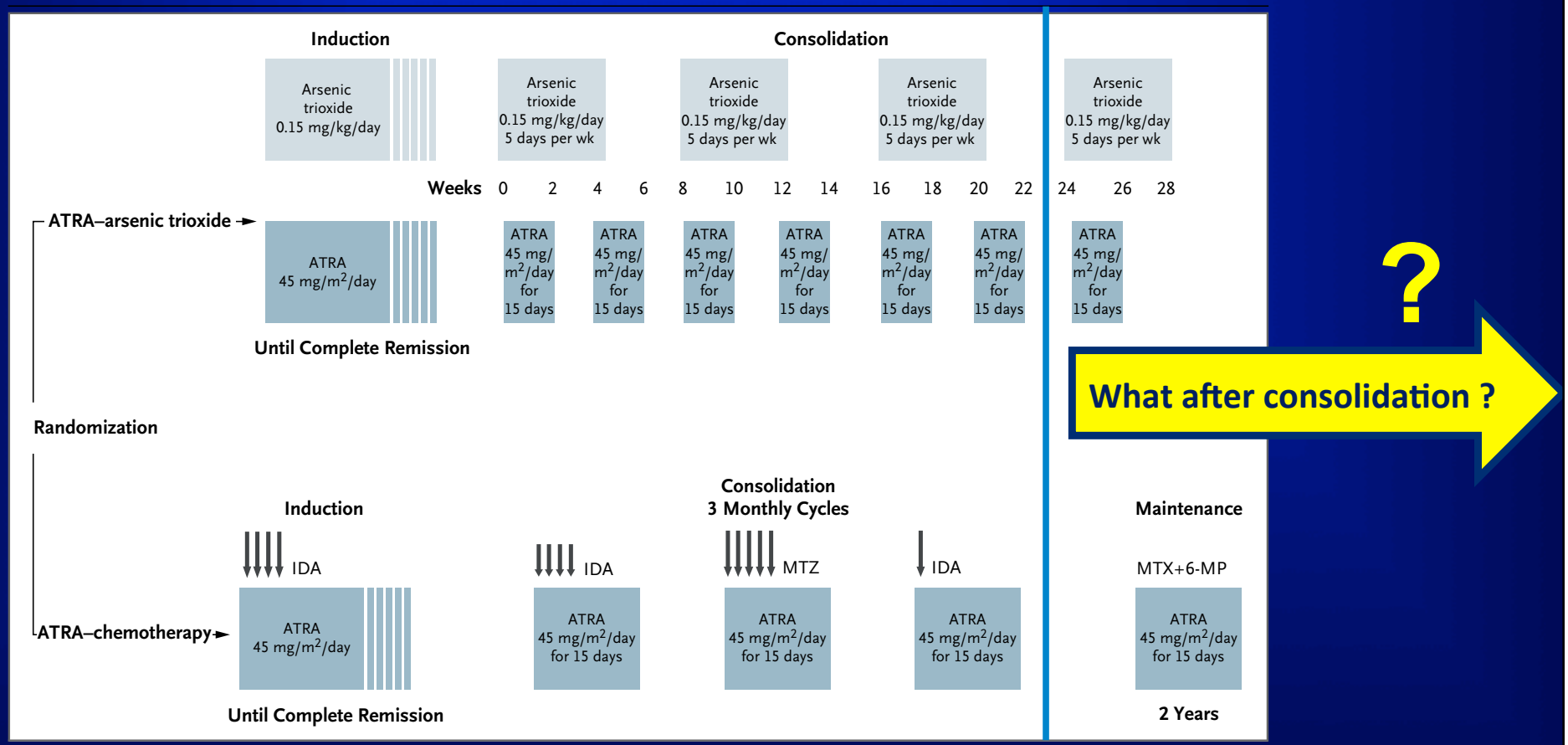
-Quality of Life
-Symptom Burden
-Long-term Comorbidity

Overview on treatment schema: AIDA 0493-AIDA 2000



What's Next?

- What are the long-term effects of ATO therapy in APL patients?
- Is there a difference in long-term QoL outcomes of patients treated with ATO *versus* those treated with standard ATRA-chemotherapy?



Conclusion

- Patient-reported QoL cannot be inferred by looking at toxicity data and help to make more informed treatment decisions.
- Overall, current QoL findings further support the use of ATRA plus ATO as preferred first-line treatment in low-intermediate risk APL patients.
- Preliminary evidence indicates that long-term APL survivors tend to report higher rates of comorbidity compared to their peers in the general population.
- More research is needed to better understand if ATRA-ATO advantages can be maintained over the long-term period and on oral ATO administration.

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- AIL