13 October 2016
EMA/CHMP/623089/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trisenox

International non-proprietary name: arsenic trioxide

Procedure No. EMEA/H/C/000388/II/0058

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Background information on the procedure 5
1.1. Type II variation 5
1.2. Steps taken for the assessment of the product 5

2. Scientific discussion 6
2.1. Introduction 6
2.2. Non-clinical aspects 8
2.2.1. Ecotoxicity/environmental risk assessment 8
2.2.2. Discussion on non-clinical aspects 8
2.2.3. Conclusion on the non-clinical aspects 9
2.3. Clinical aspects 9
2.3.1. Introduction 9
2.4. Clinical efficacy 10
2.4.1. Dose response study 10
2.4.2. Main study 11
2.4.3. Discussion on clinical efficacy 40
2.4.4. Conclusions on the clinical efficacy 41
2.5. Clinical safety 41
2.5.1. Discussion on clinical safety 59
2.5.2. Conclusions on clinical safety 61
2.5.3. PSUR cycle 61
2.6. Risk management plan 62
2.7. Update of the Product information 65
2.7.1. User consultation 65

3. Benefit risk assessment 65
3.1. Therapeutic Context 65
3.1.1. Disease or condition 65
3.1.2. Available therapies and unmet medical need 65
3.1.3. Main clinical studies 66
3.2. Favourable effects 66
3.3. Uncertainties and limitations about favourable effects 66
3.4. Unfavourable effects 67
3.5. Uncertainties and limitations about unfavourable effects 67
3.6. Effects Table 68
3.7. Benefit-risk assessment and discussion 69
3.7.1. Importance of favourable and unfavourable effects 69
3.7.2. Balance of benefits and risks 69
3.7.3. Additional considerations on the benefit-risk balance 70
3.8. Conclusions 70

4. Recommendations 70

5. EPAR changes 71

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
Ara-C	Cytosine arabinoside
ASH	American Society of Hematology
AST	Aspartate aminotransferase
ATO	Arsenic trioxide
ATRA	All-trans retinoic acid
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIR	Cumulative incidence of relapse
CR	Complete remission
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DIC	Disseminated intravascular coagulation
ECG	Electrocardiogram
EFS	Event-free survival
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30
EU	European union
Fpen	Market penetration factor
GIMEMA	Gruppo Italiano Malattie Ematologiche de ll'Adulto (Italian cooperative group)
HCR	Hematologic complete remission
hERG	Human ether-a-go-go related gene
HR	Hazard ratio
iv	Intravenous(ly)
MAA	Marketing authorization application
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network

NCI	National cancer institute
OS	Overall survival
PECsw	Predicted Environmental Concentration in surface water
PETHEMA	Programa de Estudio y Tratamiento de las Hemopatías Malignas
PML	Promyelocytic leukemia
QOL	Quality of life
QTc	Corrected QT
RARA	Retinoic acid receptor-alpha
RR	Relapse rate
RT-PCR	Reverse-transcriptase polymerase chain reaction
SmPC	Summary of Product Characteristics
SOC	System organ class
SPC	Supplementary Protection Certificate
WBC	White blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Teva B.V. submitted to the European Medicines Agency on 9 March 2016 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include induction of remission, and consolidation in adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene for Trisenox.

As a consequence, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated regarding the posology, efficacy and safety information and warnings. In addition, a Risk Management Plan is introduced. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pierre Demolis Co-Rapporteur: Daniela Melchiorri

Timetable	Actual dates
Submission date	9 March 2016
Start of procedure:	26 March 2016
CHMP Rapporteur Assessment Report	24 May 2016
CHMP Co-Rapporteur Assessment Report	26 May 2016
PRAC Rapporteur Assessment Report	3 June 2016
PRAC members comments	6 June 2016
Updated PRAC Rapporteur Assessment Report	16 June 2016
PRAC Outcome	17 June 2016
CHMP members comments	13 June 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 June 2016
Request for supplementary information (RSI)	23 June 2016
CHMP Rapporteur Assessment Report	12 September 2016
PRAC Rapporteur Assessment Report	21 September 2016
PRAC members comments	21 September 2016
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	29 September 2016
CHMP members comments	3 October 2016
Updated CHMP Rapporteur Assessment Report	7 October 2016
Opinion	13 October 2016

2. Scientific discussion

2.1. Introduction

Acute promyelocytic leukemia (APL) is a potentially life threatening rare subtype of acute myeloid leukemia (AML) characterized by the presence of the Promyelocytic Leukemia Retinoic Acid Receptor Alpha (PML-RARα) fusion transcript. One subtype of AML accounting for approximately 10 % of AML cases is acute promyelocytic leukemia (APL). The annual incidence of APL in the European Union (EU) is reported to be 0.14/100,000 (Sant et al 2010).

APL is identified as AML-M3 by the FAB classification, and is characterised by several distinct pathological features: (i) the morphology of the promyelocytic cells with granulocytic features in their cytoplasm as observed by bone aspirates smears stained with H&E, (ii) The cytological examination shows a specific t(15;17)(q24.1;q21.1) translocation and gene rearrangement which generates a fusion transcript of the PML (promyelocyte) and RAR-α (retinoic acid receptor-α) genes, and finally (iii) an decrease in white blood cell count where 75% of APL patients <10G/L.

The first-line treatment of APL is currently based on the combination of all-trans retinoic acid (ATRA) with chemotherapy (mainly anthracyclines) during both treatment induction and consolidation (see i.e. Lo-Coco et al 2010). Treatment characteristics may change according to disease risk (Fey and Buske 2013).

With ATRA plus idarubicin (AIDA protocol), the 6-year overall survival (OS) and cumulative incidence of relapse (CIR) rates are 87.4% and 10.7%, respectively. However, with the available treatments, the early death rate, mainly due to late diagnosis and haemorrhagic complications, is still high (18 to 21%), the 2-year relapse rate is 8 to 10% and the development of potentially fatal differentiation syndrome is always possible. Moreover, the exposure to anthracyclines has been associated with death in remission due to late cardiotoxicity and the onset of secondary leukemia (2 to 5% patients).

Trisenox (arsenic trioxide or ATO) is currently authorised for the induction and consolidation treatment of relapsed/refractory APL patients. However, recent studies with ATO have shown high efficacy and reduced haematological toxicity in patients with newly diagnosed APL (see i.e. Estey et al 2006, Ghavamzadeh et al 2011, Mathews et al 2006, Ravandi et al 2009).

The treatment for APL as changed over the years and has progressively increased the CR:

- In 1973, the therapy consisted of Daunorubicin+ massive platelet transfusions which resulted in up to 80% CR, 40 to 50% prolonged CR (Bernard et al, 1973).
- In 1988, the use of all-transretinoic acid (ATRA) which promotes the differentiation of APL cells resulted in 90% CR (Huang et al, 1988).
- In 1991, the use of ATRA+ chemotherapy increased the CR to 90% but still had a 25% relapse rate (ASH plenary 1991).
- In 1997, the maintenance treatment with ATRA and low dose chemotherapy reduced relapses 5 to 10% relapses (ASH plenary 1993).
- In 2000, AraC treatment was found to be unnecessary in standard at risk patients (Sanz et al, 2004)
- Standard treatment currently provides a CR of 90% and approximately 80% cures, but 9-10% of patients have an early death, 5% death in patients in CR, 5-10% patients relapse and 1-2% of patients developing MDS and AML
- Patients having an early death or death in CR are mainly older patients because of their lower tolerability to chemotherapy.

The current indication for Trisenox is as follows:

TRISENOX is indicated for induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene. Previous treatment should have included a retinoid and chemotherapy.

The response rate of other acute myelogenous leukaemia subtypes to TRISENOX has not been examined.

The marketing authorisation holder (MAH) applied for the following indication: TRISENOX is indicated for induction of remission, and consolidation in adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ⩽ 10 x 103/μl) characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.

The recommended indication for approval is: TRISENOX is indicated for induction of remission, and consolidation in adult patients with: Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ⩽ 10 x 103/μl) in combination with all trans retinoic acid (ATRA) characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene (SmPC section 4.1).

The recommended dose is as follows:

Induction treatment schedule

TRISENOX must be administered intravenously at a dose of 0.15 mg/kg/day, given daily until complete remission is achieved. If complete remission has not occurred by day 60, dosing must be discontinued.

Consolidation schedule

TRISENOX must be administered intravenously at a dose of 0.15 mg/kg/day, 5 days per week. Treatment should be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles (SmPC section 4.2).

2.2. Non-clinical aspects

No new non clinical data with the exception of ERA have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The applicant has performed a Phase I assessment, as specified in the ERA guideline. Based on the common definition of an organic substance in chemistry in the REACH guidance, PBT and vPvB criteria are not applicable to inorganic substances and log K_{ow} determination for trisenox is not required.

The calculation of the predicted environmental concentration in surface water (PEC_{SW}) based on the default F_{pen} value for an orphan indication and taking into account the maximal total dose of trisenox per patient for induction and consolidation (9 mg) converted to a daily dose per patient was below the threshold of 0.01 µg/l. Thus, there is no need for a Phase II environmental fate and effect analysis.

Table 1. Summary of results

Substance (INN / Invented Name):Arsenic Trioxide / Trisenox			
CAS-number (if available): 1327-53-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *K*ow		NA	
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	0.00225*	µg/L	<0.01 threshold
Other concerns (e.g. chemical class)		N	N

NA Not applicable for inorganic substances

*Calculated using a daily dose of 9 mg and default Fpen for orphan indication of 0.0005.

2.2.2. Discussion on non-clinical aspects

The environmental risk assessment for trisenox was conducted according to the current guideline. The predicted logK_{ow} for trisenox is inferior to 4.5, threshold for screening so no further investigation are

required provided that the Log Dow values can be supported by experimental data. The PECsw is lower than the action limit of 0.01 µg/l the contribution of the current therapeutic use of trisenox seems to be minor compared to the existing environmental level.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of arsenic trioxide.

Considering the above data, arsenic trioxide is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

- Tabular overview of clinical studies

Study identifier (type of study) Total number of centers with enrolled subjects Country(ies)	**Objective(s) of the study**	**Study design and type of control**	**Test product(s) Dosage regimen Route of administration**	**Number of subjects: Treated Completed study M/F (enrolled) Age range (y) (enrolled)**	**Healthy subjects or diagnosis of patients**	**Duration of treatment**	**Study status Type of report**
APL0406 (efficacy and safety) 40 centres of the Gruppo Italiano Malattie Ematologiche de ll'Adulto (Italian cooperative group (GIMEMA) and 27 centres of the German-Austrian AML Study Group and Study Alliance	Primary: To compare EFS for ATRA+ATO vs ATRA+CHEMO Secondary: to compare ATRA+ATO vs ATRA+CHEMO regarding CR, OS, and CIR toxicity profile kinetics of MRD duration of patient hospitalization QOL	Phase 3 Prospective, randomized, multicentre, controlled, open-label, non-inferiority study	**ATRA+ATO**: ATRA 45 mg/m^2 + ATO 0.15 mg/kg) daily until CR followed by ATO 5 days/week (4 weeks on/4 weeks off for 4 courses) and ATRA 45 mg/m^2 (2 weeks on/2 weeks off for 7 courses). **ATRA+CHEMO**: ATRA 45 mg/m^2 + idarubicin 12 mg/m^2 for induction, on select days (2, 4, 6, and 8) then 3 cycles of ATRA + anthracycline-based for consolidation, and low-dose ATRA+CHEMO for maintenance.	**Original cohort:** 156 (eligible) ATRA+ATO: 77 ATRA+CHEMO: 79 76M/80F 18 to <71 years **Extended cohort** Total: 266 (eligible) ATRA+ATO: 129 ATRA+CHEMO: 137 130M/136F 18 to <71 years	Newly diagnosed, genetically-confirmed, classified as low to intermediate-risk (WBC ≤10x10^9/L) APL.	**Original cohort** Median follow-up 34-months	Ongoing Publications Lo-Coco et al 2013a
						Median follow-up 53 months	Lo-Coco et al submitted for publication 2015
						Extended cohort: Median follow-up 36-months	Platzbecker et al 2014 Platzbecker et al submitted for publication 2016

Study identifier (type of study) Total number of centers with enrolled subjects Country(ies)	Objective(s) of the study	Study design and type of control	Test product(s) Dosage regimen Route of administration	Number of subjects: Treated Completed study M/F (enrolled) Age range (y) (enrolled)	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report
AML17 (efficacy and safety) 81 centres in United Kingdom, Denmark, and New Zealand	Primary: To compare QOL and toxicity and resource usage of patients receiving ATRA+ATO vs ATRA+CHEMO. Secondary: To compare ATRA+ATO vs ATRA+CHEMO regarding CR, OS, and relapse rates kinetics of MRD and To correlate plasma arsenic levels with disease response and treatment-related toxicities in APL patients allocated to receive ATO therapy.	Phase 3 Randomised, open-label, controlled, multicentre	**ATRA+ATO:** ATRA 45 mg/m^2 daily as an oral dose until remission or day 60, then in a 2 weeks on/2 weeks off schedule + IV ATO 0.3 mg/kg on days 1-5 of each course, and at 0.25 mg/kg twice weekly in weeks 2–8 of course 1 and weeks 2-4 of courses 2-5. High-risk patients could have an initial dose of the immunoconjugate gemtuzumab ozogamicin (6 mg/m^2 IV). **ATRA+CHEMO**: ATRA (dosage as above) + IV idarubicin 12 mg/m^2 on days 2, 4, 6, and 8 for course 1, then 5 mg/m^2 on days 1–4 of course 2; mitoxantrone 10 mg/m^2 on days 1-4 of course 3, and idarubicin at 12 mg/m^2 on day 1 of the fourth and final course.	Total: 235 (eligible) ATRA+ATO: 116 ATRA+CHEMO: 119 120M/115F ≥16 years	Patients with APL (confirmed by the PML–RARA transcript), but without significant cardiac/pulmonary comorbidities or active malignancy High-risk patients were defined as having a WBC blood cell count >10×10^9 cells/L	Median follow-up 30.5 months	Completed Publication Burnett et al 2015

APL=acute promyelocytic leukaemia, ATO=arsenic trioxide; ATRA=All-transretinoic acid; CHEMO=chemotherapy; CIR=cumulative incidence of relapse; CR=complete remission; EFS=event-free survival; F=female; IV=intravenous; M=male; MRD=minimal residual disease; OS=overall survival; PML=promyelocytic leukemia; QOL=quality of life; RARA=retinoic acid receptor alpha; WBC=white blood cell; y=year.

The MAH has submitted an application based on the analysis of efficacy of data obtained from:

- Pivotal data

-Study APL0406, original cohort (Lo-Coco and al 2013a, Lo-Coco and al 2013b, Lo-Coco and al 2015)

-Study APL0406, extended cohort (Platzbecker and al 2014, Platzbecker and al 2016)

- Supportive data

-Study AML17 (Burnett et al 2015)

-Literature review of studies with ATO alone or ATRA+ATO in first-line APL.

2.4. Clinical efficacy

2.4.1. Dose response study

No formal analyses were performed for the evaluation of dose-response or blood level response relationships in the APL0406 and AML17 studies.

The dose and schedule selected for study APL0406 are based on the currently approved dose and schedule for the relapsed/refractory APL patient population, adapted for use in first-line treatment on the basis of favourable clinical research results reported from a Phase 2 study of ATRA+ATO (Ravandi et al 2009). This study showed that the ATRA+ATO combination was safe and effective in first-line treatment of patients with low- to intermediate-risk APL at a dose of 0.15 mg/kg/day.

During induction, patients in the APL0406 study in the ATRA+ATO group received ATRA 45 mg/m^2+ATO 0.15mg/kg daily until CR for up to 60 days (10 days longer than the currently approved dose for the relapsed setting in Europe, but the same duration as the recommendation in the current United States Product Insert, [USPI]). During consolidation, patients in Study APL0406 received ATO 0.15 mg/kg/day 5 days/week (4 weeks on/4 weeks off for 4 courses); in currently approved labelling for the relapsed population, ATO is administered 0.15 mg/kg/day 5 days/week for 5 weeks.

The dosing schedule in the AML17 study was based on the dose used in a Phase 2 study with ATO in myelodysplastic syndrome (Vey et al 2006) in order to improve compliance.

2.4.2. Main study

APL-0406

The study was a prospective, randomized, multicenter, open-label, phase 3 non-inferiority trial, designed to compare arsenic trioxide (ATO) combined to ATRA versus standard ATRA and anthracycline-based chemotherapy (AIDA regimen) for newly diagnosed, non-high-risk acute promyelocytic leukaemia patients.

Methods

Study participants

The study population comprised newly diagnosed patients with low- to intermediate-risk APL (WBC count at diagnosis ≤10 x 10^9/L) aged 18 to 71 years.

Main inclusion criteria (published APL0406 study protocol)

- Newly diagnosed APL by cytomorphology, confirmed also by molecular analysis
- Age ≥ 18 < 71 years
- WHO performance status 0-2 included
- WBC at diagnosis ≤ 10 x 10^9/L
- Serum total bilirubin ≤ 3.0 mg/dL (≤ 51µmol/L)
- Serum creatinine ≤ 3.0 mg/dL (≤ 260 µmol/L [≤ 265 µmol/L according to Lo-Coco et al. 2013).

Genetic confirmation of diagnosis was carried out by reference laboratories and was mandatory for patient eligibility. However, in order to avoid delay in treatment initiation, patients could be randomized on the basis of morphologic diagnosis only and before the results of genetic tests were available. A genetic diagnosis of APL was established by detection of the PML/RARA fusion gene by means of RT-PCR assay, demonstration of the t(15;17) translocation by conventional karyotyping or fluorescence in situ hybridization (FISH), or evidence of a microspeckled PML pattern with the use of an indirect immunofluorescence assay.

Main exclusion criteria (published APL0406 study protocol)

- Other active malignancy at time of study entry
- Lack of diagnostic confirmation at genetic level
- Significant arrhythmias
- Neuropathy
- Other cardiac contraindications for intensive chemotherapy (L-VEF <50%)

- Uncontrolled, life-threatening infections

- Severe non-controlled pulmonary or cardiac disease

- Women who are either pregnant or breast feeding, or of child-bearing potential,

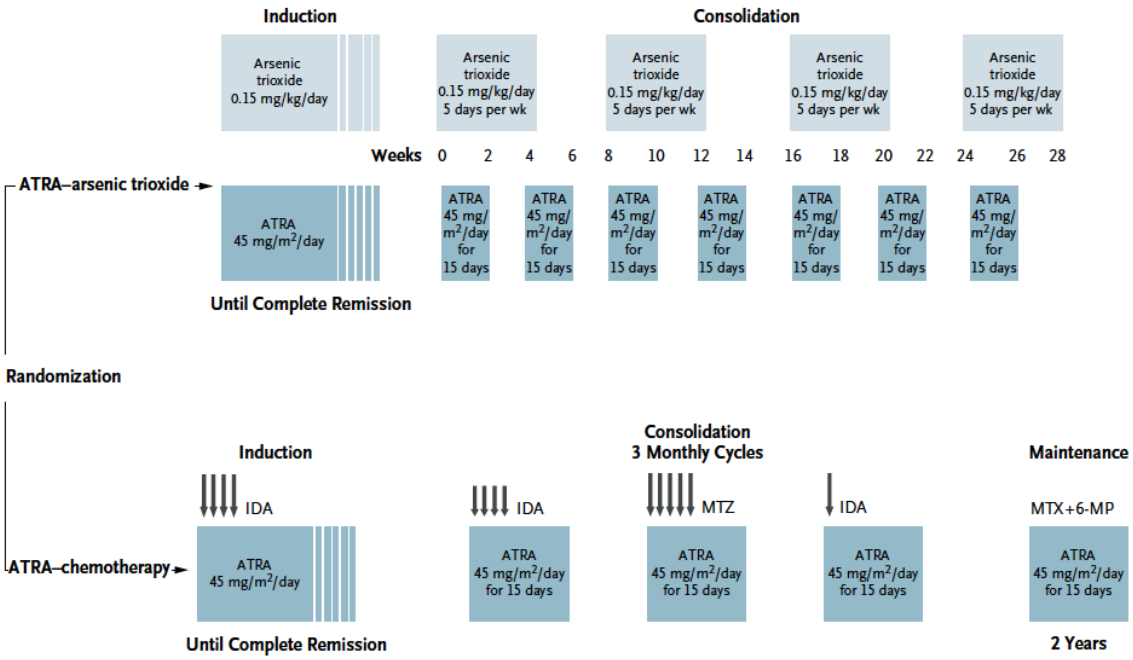
- EKG abnormalities: congenital long QT syndrome; history or presence of significant ventricular or atrial tachyarrhythmia, clinically significant resting bradycardia (<50 beats per minute), QTc > 450 msec on screening EKG (using the QTcF formula), right bundle branch block plus left anterior hemiblock, bifascicular block.

Treatments

Patients randomized to the ATRA+ATO arm received ATRA 45 mg/m^2 + ATO 0.15mg/kg daily until CR or up to a maximum of 60 days, followed by ATO 5 days/week (4 weeks on/4 weeks off for 4 courses) and ATRA (2 weeks on/2 weeks off for 7 courses).

Patients randomized to the ATRA+chemotherapy arm received the standard ATRA+idarubicin regimen (45 and 12 mg/m^2, respectively) for induction therapy, followed by 3 cycles of anthracycline-based consolidation. Patients who tested negative for PML/RARA by RT-PCR at recovery from the third consolidation cycle went on to receive maintenance therapy for up to 2 years consisting of methotrexate 15 mg/m^2 weekly, 6-mercaptopurine 50 mg/m^2/day, and ATRA 45 mg/m^2/day for 15 days every 3 months (see Figure 1).

Figure 1: Treatment Groups (APL-0406)



Supportive measures and management of complications

In study APL0406, prednisone (0.5 mg/kg/day) was also administered from day 1 until the end of induction, to prevent differentiation syndrome (DS). In case DS was suspected, a switch to dexamethasone was indicated. Hydroxyurea was permitted in patients who developed leucocytosis (WBC

count is > 10 x109/L) after initiation of therapy. Hydroxyurea was discontinued when WBC count returned to <10 x109/L.

At the earliest manifestations of suspected differentiation syndrome, ATRA, arsenic trioxide, or both were temporarily discontinued and intravenous dexamethasone was administered at a dose of 10 mg every 12 hours until the disappearance of signs and symptoms for a minimum of 3 days.

Objectives

The primary objective was to compare, in newly diagnosed APL patients treated with ATO combined to ATRA or receiving ATRA plus chemotherapy (AIDA regimen), the event-free survival (EFS) rate.

Secondary objectives included the following:

- To compare complete remission (CR), overall survival (OS) and Cumulative incidence of relapse (CIR) rates in the two arms

- To compare the toxicity profile in the two arms

- To compare the kinetics of MRD in the two arms

- To compare the duration of patient hospitalisation in the two arms

- To compare Quality of Life (QoL) between treatment arms

Outcomes/endpoints

The primary study end point was event-free survival at 2 years after diagnosis, with treatment failure defined as any of the following: no achievement of hematological complete remission (HCR) after induction therapy, no achievement of molecular complete remission (CRm) after 3 consolidation courses, molecular relapse, hematological relapse, or death.

Hematologic complete remission and hematologic (morphologic) relapse were defined according to the National Cancer Institute (NCI) workshop definitions (Cheson et al. 2003).

The secondary endpoints were to compare: the rates of hematologic complete remission (HCR) after induction, the rates of OS and CIR at 2 years, both OS and CIR were defined according to the IWG definitions, the incidence of haematological and non-haematological toxicity episodes during treatment (CTCAE version 3) , the rate of molecular remission after the third consolidation cycle, the kinetics of minimal residual disease (PML/RARA transcript level reduction after induction and during consolidation), the duration of patient hospitalization and the HR-QOL at end of the induction phase and at end of the third consolidation cycle (measured by EORTC QLQ-C30; version 3]).

Responses were defined according to the International Working Group (IWG) definitions (Cheson et al. 2003):
- Hematologic CR (CR and CR with incomplete blood count recovery [CRi]) defined as:

- Complete remission (CR): <5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. There should be no blasts with Auer rods or persistence of extramedullary disease, and an absolute neutrophil count >1,000/µL and platelets of

100,000/µL.

- Morphological CRi: all the above criteria for CR except for residual neutropenia (<1,000/µL) or thrombocytopenia (<100,000/µL)

- Molecular CR: absence of PML/RARA hybrid transcript by reverse-transcriptase polymerase chain reaction (RT-PCR) in the bone marrow sample collected at the end of the third consolidation course (both groups), using RT-PCR assay with sensitivity comprised between 10^{-3} and 10^{-4} positive cells (Lo-Coco et al 1999).

- Resistant disease: all patients who fail to achieve HCR and who do not die during the induction phase.

- Molecular resistant disease: defined as the persistence of the PML/RARA hybrid transcript in bone marrow at the end of the third consolidation course. Molecular resistance should always be confirmed in 2 consecutive marrow samples taken 2 weeks apart, with second positivity confirmed by a national reference laboratory.

- Induction deaths: all patients who die during the induction phase, before a CR has been demonstrated.

Disease-free survival rate (DFS) was also recorded and defined as the time from achievement of HCR to relapse (either molecular or haematological), persistence of polymerase chain reaction (PCR) positivity after consolidation therapy or death, which ever occurred first. Data on patients who were still alive and in first CRm were censored at the time of the most recent follow-up visit.

Relapse was evaluated according to the following:

- Haematological relapse: reappearance of >5% abnormal promyelocytes in the bone marrow at any time during follow-up, associated with RT-PCR positivity for the PML/RARA hybrid gene

- Molecular relapse: conversion from RT-PCR negative to positive for the PML/RARA hybrid gene in the bone marrow samples collected at any time after the third consolidation cycles, confirmed in 2 successive bone marrow samples collected 2 weeks apart with second positivity confirmed by a national reference laboratory, with a persistent morphologic HCR.

- Extramedullary relapse: should be based on tissue diagnosis and/or liquor cytology in case a meningeal relapse. Extramedullary APL relapse should be genetically obtained by RT-PCR or anti-PML staining.

Sample size

A target sample of 162 patients was to be randomized in a 1:1 ratio to receive ATRA–arsenic trioxide or ATRA-chemotherapy. This sample size was calculated, according to the Farrington and Manning formulas (Farrington et Manning,1990) to achieve 92% power to demonstrate non-inferiority between the two groups for the primary efficacy endpoint (2-year event-free survival rate) with a 2-sided significance level of 0.05, assuming an expected event-free survival rate in the reference and experimental group of 85% and 95%, respectively. Additional assumptions included a pre-specified non-inferiority margin of 5% and an expected rate of loss of 10%.

After the enrolment completion of the original cohort, the study was expanded and restarted "to reach an optimal compliance" regarding QoL evaluation which was a study secondary objective (Amendment 1 to Protocol). The sample size was increased to a new target of 276 patients with an additional cohort of 114 patients with the aim at detecting at least a difference of 10 points between treatment arms in the "fatigue" scale of the EORTC QLQ -C30. Considering a two-sided Mann-Whitney test with alpha set to 5% and 80% power assuming a standard deviation of 23 points on the "fatigue" scale (based on similar patients reported in the EORTC QLQ-C30 reference value manual), 90 patients per arm were to be analysed. Assuming a missing data rate of 35%, then the target overall number of patients needed was set to 276 (138 per arm, i.e. further 57 per arm).

Randomisation

Randomization was centralized and stratified by institution, with patients randomized in a 1:1 ratio to receive ATRA–arsenic trioxide or ATRA-chemotherapy.

Blinding (masking)

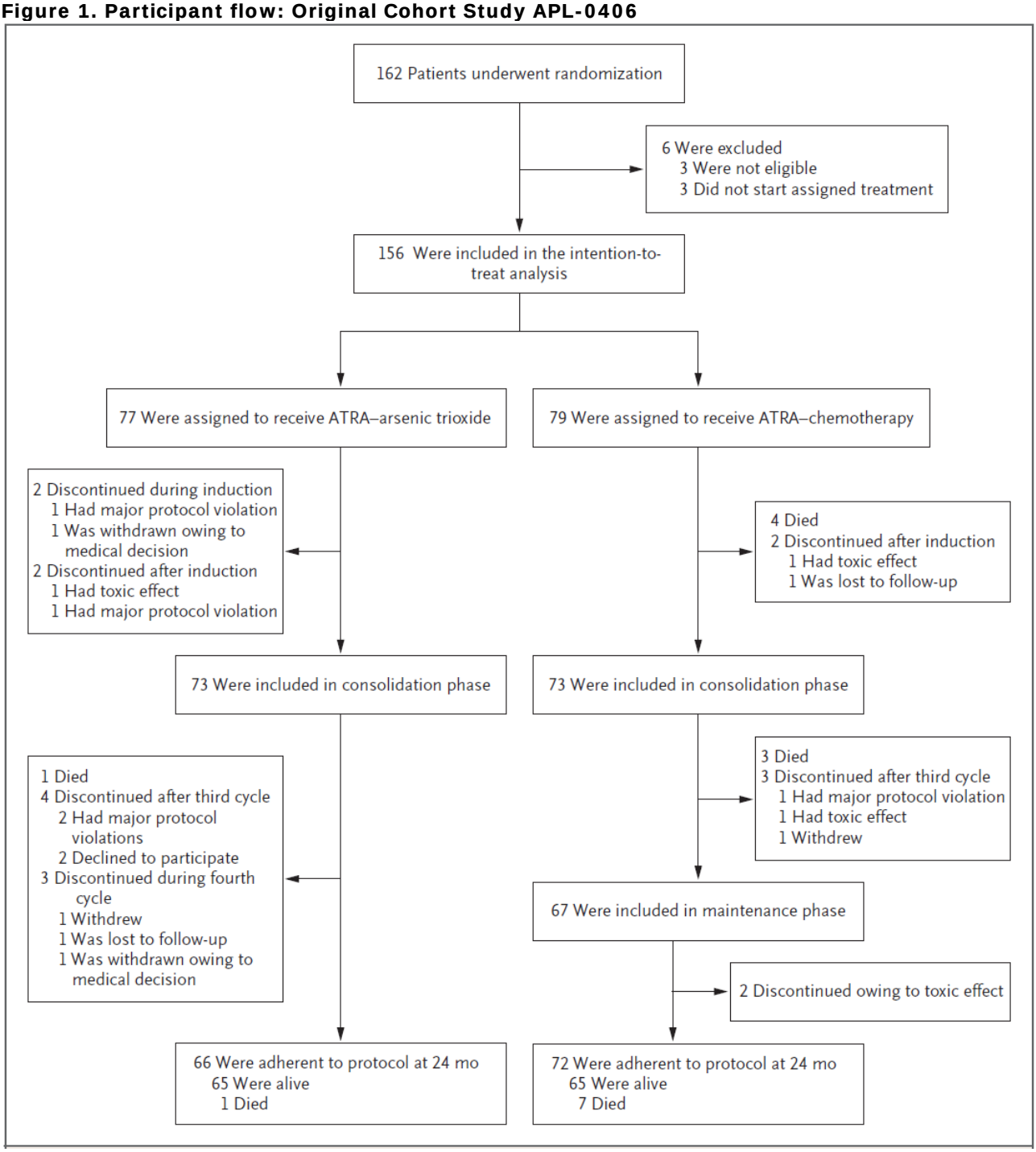
Study APL0406 was an open label study.

Statistical methods

All efficacy analyses were based on the intention-to-treat principle. For the primary efficacy analysis for noninferiority, a per-protocol analysis was also carried out. Noninferiority was assessed by estimating the two-sided 95% confidence interval for the between-group difference in crude rates of 2-year EFS and checking that the lower bound was not lower than −5%. The robustness of the results was confirmed by means of a sensitivity analysis that addressed all relevant scenarios for the patients who could not be evaluated, with the assumption of a poor outcome for all patients, a favorable outcome for all patients, or a poor outcome for patients in the ATRA–arsenic trioxide group and a favorable outcome for those in the ATRA–chemotherapy group.

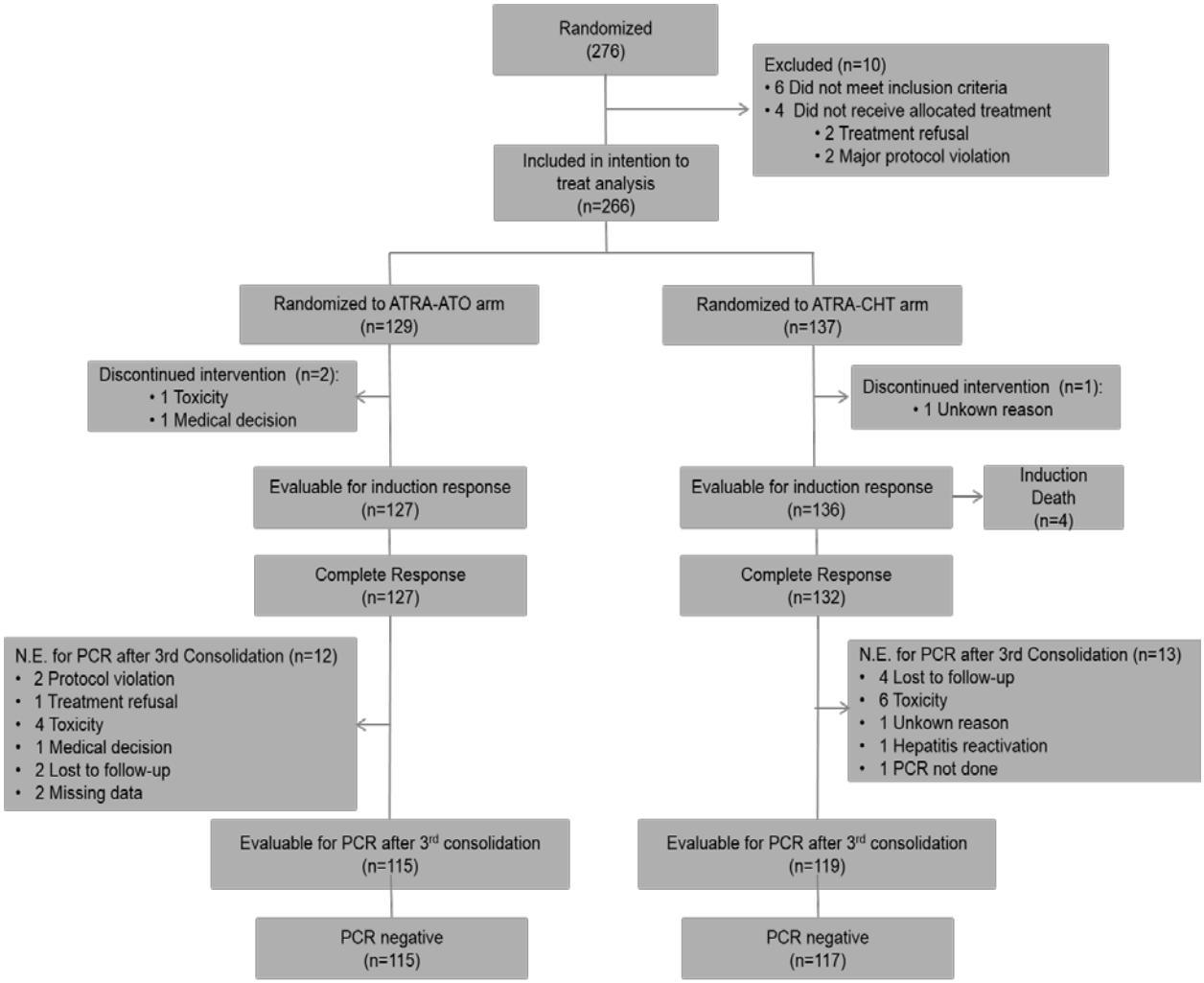
Results

Figure 1. Participant flow: Original Cohort Study APL-0406



Study APL0406: extended cohort

Figure 2. Patient Disposition: Extended Cohort Study APL0406



Recruitment

Enrolment of the pre-specified 162 patients in the original cohort was started in October 2007 and was completed in September 2010. The study was expanded and restarted in March 2011 to increase the accrual to a new target of 276 (original cohort + 114) patients, i.e. the extended cohort. Recruitment was completed on January 2013. A total of 40 centres from the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) and 27 centres from the German–Austrian Acute MyeloidLeukemia Study Group and Study Alliance Leukemia participated in the study by enrollingat least one patient.

Conduct of the study

One amendment to the study protocol was issued on December 2010, in order to increase the target accrual from 162 to 276 subjects (further 57 patients per arm) to reach an optimal compliance with

respect to the QoL questionnaires. The observed compliance of 65% and of 55% at the end of induction and at the end of the third consolidation cycle, respectively, was in fact lower than expected and considered insufficient to perform the planned analysis (QoL was a secondary endpoint in study APL0406).

Baseline data

Table 2: Demographic, Clinical, and Biological Characteristics of the Patients at Diagnosis (Study APL-0406)

Characteristic	ATRA–Arsenic Trioxide (N=77)	ATRA–Chemotherapy (N=79)
Age — yr		
Median	44.6	46.6
Range	19.1–70.2	18.7–70.2
Sex — no. (%)		
Male	40 (52)	36 (46)
Female	37 (48)	43 (54)
White-cell count — $\times 10^{-9}$/liter		
Median	1.49	1.60
Range	0.32–10.00	0.30–9.61
Platelet count — $\times 10^{-9}$/liter		
Median	31	27
Range	3–224	3–236
Risk level — no. (%)†		
Low	33 (43)	27 (34)
Intermediate	44 (57)	52 (66)
PML-RARA isoform — no. (%)		
Long	45 (58)	48 (61)
Short	31 (40)	29 (37)
Data missing	1 (1)	2 (3)
FLT3-ITD mutation — no./total no. (%)	14/65 (22)	16/63 (25)

† A low risk level was defined as a white-cell count of no more than 10×109 per litre and a platelet count of more than 40×109 per litre at presentation, and an intermediate risk level as a white-cell count of no more than 10×109 per litre and a platelet count of no more than 40×109 per litre at presentation.

Numbers analysed

Original cohort

The original cohort comprised 162 patients with 159 randomized to treatment. The following analysis sets were identified:

- Intent-to-treat population: The ITT analysis set included all treated randomized patients (77 patients randomized to ATRA+ATO and 79 to ATRA+chemotherapy).
- Modified ITT (mITT): 6 patients could not be evaluated at 24 months for the primary analysis and

were not included in the mITT analysis set (74 patients randomized to ATRA+ATO and 76 to ATRA+chemotherapy).

- Per-protocol population: the per-protocol analysis set included patients who received protocol treatment as scheduled (66 randomized to ATRA+ATO and 72 to ATRA+chemotherapy). The per-protocol analysis was conducted for the primary efficacy analysis proving non-inferiority in terms of 2-year EFS.
- HR-QoL population: for the HR-QoL evaluation, of the 156 patients randomized, 150 were eligible at the end of induction therapy and 142 at the end of the third consolidation course.
- Safety population: The safety analysis set included all patients who received at least 1 dose of study treatment.

Extended cohort

The extended cohort comprises overall 276 patients: 266/276 patients were included in the extended cohort ITT analysis set (129 randomized to ATRA+ATO and 137 to ATRA+chemotherapy). All analyses for the extended cohort used the ITT analysis set.

Outcomes and estimation

Induction Therapy

A total of 77 patients in the ATRA–arsenic trioxide group and 79 patients in the ATRA–chemotherapy group could be evaluated for a response to induction therapy. Hematologic complete remission was achieved in all 77 patients in the ATRA–arsenic trioxide group (100%) and in 75 of the 79 patients in the ATRA–chemotherapy group (95%) (P = 0.12). The median time to hematologic complete remission was 32 days (range, 22 to 68) in the ATRA–arsenic trioxide group and 35 days (range, 26 to 63) in the ATRA–chemotherapy group (P = 0.61).

Consolidation Therapy

A total of 146 of 152 patients in hematologic complete remission proceeded to consolidation therapy.

After the third consolidation cycle, molecular complete remission was achieved in all 145 patients who could be evaluated for a molecular response (75 in the ATRA–arsenic trioxide group and 70 in the ATRA–chemotherapy group). Four patients in the ATRA–arsenic trioxide group did not proceed to the fourth consolidation cycle (2 declined to continue treatment and 2 had major protocol violations). Three patients in the ATRA–arsenic trioxide group did not complete the fourth consolidation course owing to withdrawal of consent, loss to follow-up, and the treating physician's decision.

Maintenance Therapy

A total of 67 of the 70 patients who completed consolidation therapy in the ATRA–chemotherapy group proceeded to maintenance therapy. Three patients went off protocol after consolidation therapy owing to withdrawal of consent, a major protocol violation, and a toxic effect. Two patients did not complete maintenance therapy because of prolonged myelosuppression (>50 days).

Primary efficacy endpoint: Event-Free Survival

EFS results for the original cohort are summarised in Table 3 and figure 3.

Table 3: Analyses of Primary Endpoint in Pivotal Study APL0406 Original Cohort

	ATRA+ATO N=77	ATRA+Chemotherapy N=79	P-value
34-month follow-up, 2-year event-free survival (EFS)			
mITT analysis set	97% (72/74)	86% (65/76)	Treatment difference: 11 (95% CI: 2 to 22) <0.001 for non-inferiority 0.02 for superiority
Per protocol analysis set	97% (64/66)	85% (61/72)	Treatment difference: 12 (95% CI: 2 to 23) <0.001
53-month follow-up, 50-month EFS			
ITT analysis set	96% (71/74) (95% CI: 92-100)	81% (61/76) (95% CI: 73-91)	0.0034

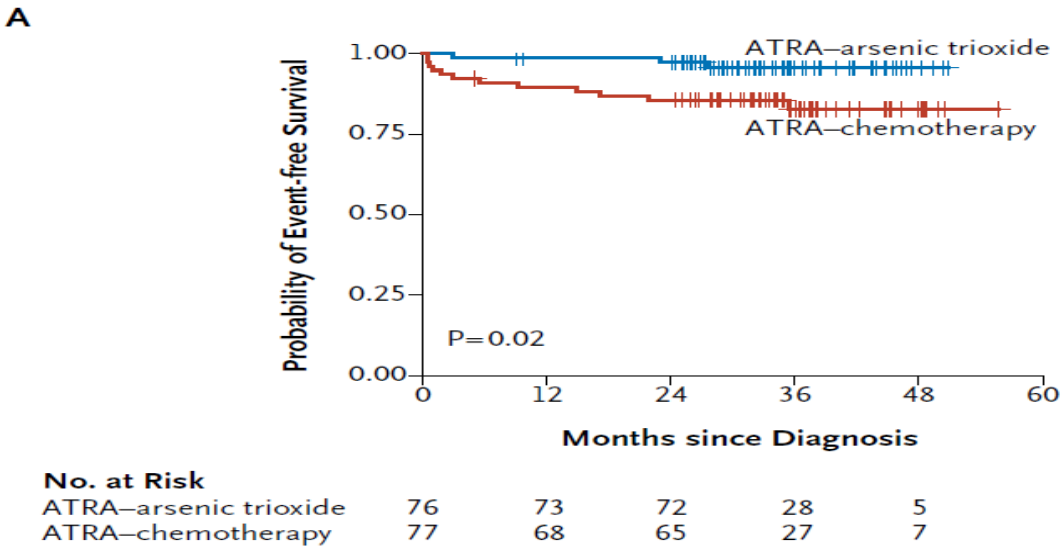
Source: Lo-Coco et al 2013a, Lo-Coco 2015
ATO=arsenic trioxide, ATRA=all-trans retinoic acid, CI=confidence interval, ITT=intent-to-treat, mITT=modified intent-to-treat

Original cohort (median follow-up: 34.4 months):

Of the 156 patients in the ITT analysis set, 150 (96%) could be evaluated for the primary endpoint and comprised the mITT analysis set. Six patients could not be evaluated for EFS at 24 months because a molecular evaluation was not performed after the third consolidation cycle or follow-up was insufficient.

The 2-year EFS rate was 97% in the ATRA+ATO group and 86% in the ATRA+chemotherapy group; a difference of 11 percentage points between the treatment groups (95% CI: 2 to 22), p-value <0.001 for non-inferiority (see Figure below).

Figure 3: Study APL0406 Original Cohort – EFS, Median Follow-up 34.4 months



(Modified from Lo-Coco et al. 2013)

Original cohort (median follow-up: 53 months):

After a median follow-up of 53 months, the EFS estimate at 50 months for the 156 patients of the original cohort in the ITT analysis was still statistically significant, being 96% for the ATRA+ATO group and 81% for the ATRA+chemotherapy group (p value 0.0034).

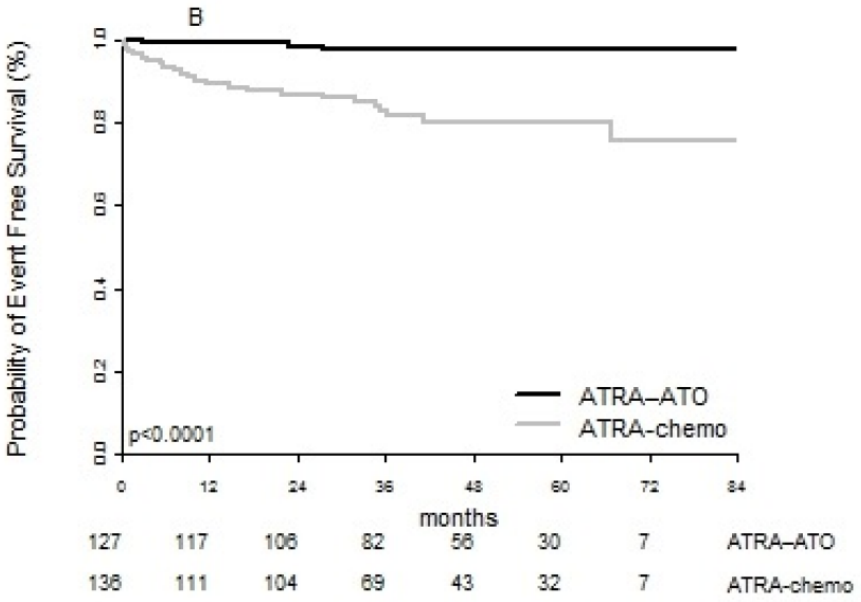
Post-remission events in the ATRA+chemotherapy group included 6 relapses and 5 deaths in remission (1 of which due to secondary leukaemia), while in the ATRA+ATO group there were 2 relapses and 1 death in remission, with no further events being recorded in this treatment group after the original publication.

Extended cohort

The median duration of follow-up for the last analysis was 40.6 months (range: 0.1-83.6 months). Of the 266 patients in the ITT analysis set, 209 (79%) could be evaluated for the primary endpoint (106 and 103 in the ATRA+ATO and ATRA+CHT arms, respectively). The missing patients (n=57) were not evaluable due to lack of molecular evaluation after the third consolidation cycle or insufficient follow-up.

For the 98 evaluable patients at 50 months (55 ATRA+ATO and 43 ATRA+chemotherapy), the 2 year EFS rate was 98% in the ATRA+ATO group and 87% in the ATRA+chemotherapy group; a difference of 11 percentage points between the treatment groups (p-value <0.0001). K-M curves are presented in Figure 4:

Figure 4: Study APL0406 Extended Cohort – EFS, Median Follow-up 40.6 month



(Modified from Platzbecker et al. 2016)

Secondary endpoints

Original cohort (median follow-up: 34.4 months):

The results for the secondary endpoints in the original cohorts of study APL0406 are summarized in Table 4:

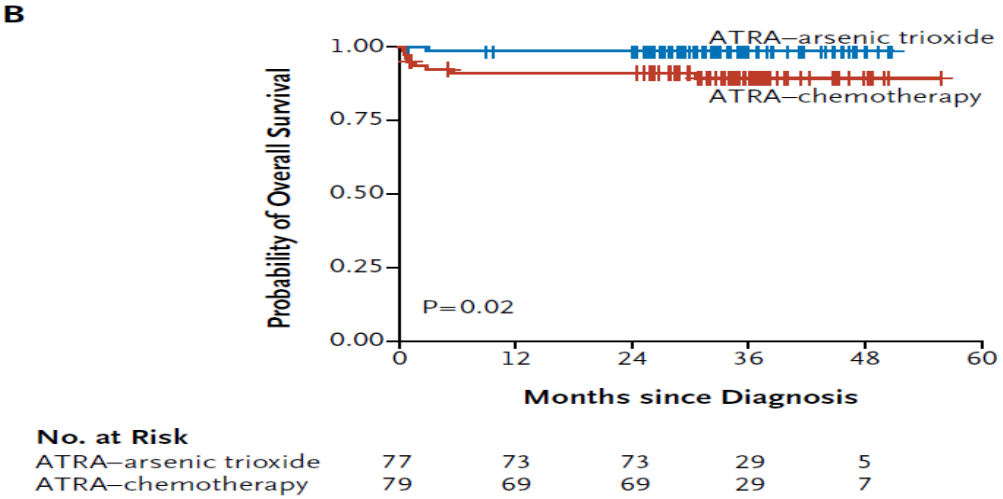
Table 4: Secondary Efficacy Endpoint Results from Pivotal Study APL0406 Original Cohort

Endpoint	ATRA+ATO N=77	ATRA+Chemotherapy N=79	p-value
Median 34-month follow-up			
Hematologic complete remission (HCR)	100% (77/77)	95% (75/79)	0.12
Median time to HCR, days	32; range 22-68	35; range, 26-63	0.61
2-year overall survival (OS)	99% (95% CI: 96-100)	91% (95% CI: 85-97)	0.02
2-year disease-free survival (DFS)	97% (95% CI: 94-100)	90% (95% CI: 84-97)	0.11
2-year cumulative incidence of relapse (CIR)	1% (95% CI: 0-4)	6% (95% CI: 0-11)	0.24
Log reduction of PML/RARA transcripts			
Diagnosis to post-induction 1	2.91; range 0.27-8.85	3.13; range 0.26-9.44	0.27
Post-induction 1 to post consolidation 3	5.37; range 0.00-8.46	5.52; range 0.00-8.00	0.72
Molecular complete remission post consolidation 3	100% (75/75 evaluable)	100% (70/70 evaluable)	NA
Median 53-month follow-up			
50-month OS	99% (95% CI: 96-100)	88% (95% CI: 81-96)	0.0062

Source: Lo-Coco et al 2013a, Lo-Coco et al 2015
ATO=arsenic trioxide, ATRA=all-trans retinoic acid, CI=confidence interval, CIR=cumulative incidence of relapse, DFS=disease-free survival, EFS=event-free survival, HCR=hematologic complete remission, ITT=intent-to-treat, NA=not available, PML/RARA=promyelocytic leukemia retinoic acid receptor-alpha, OS=overall survival
Results are for the ITT analysis set with evaluable data

The difference between treatment groups for 2-year OS rate was statistically significant favouring ATRA+ATO over ATRA+chemotherapy, being 99% in the ATRA+ATO group and 91% in the ATRA+chemotherapy group (p-value 0.02) (see Figure 5).

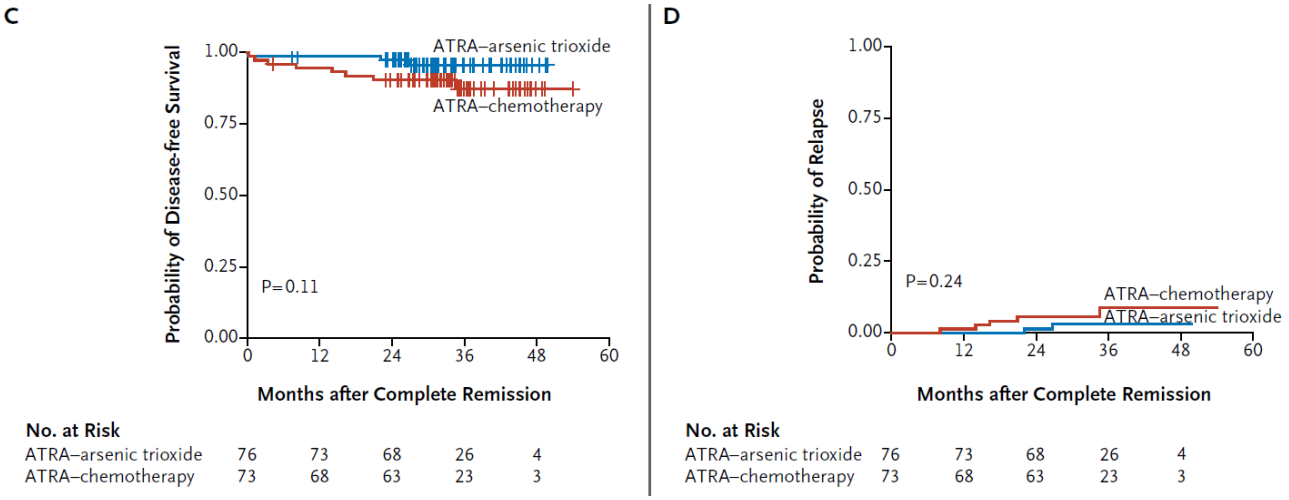
Figure 5: Study APL0406 Original Cohort – OS, Median Follow-up 34.4 months



(Modified from Lo-Coco et al. 2013)

Results for the secondary endpoints 2 year DFS and 2-year CIR are presented in Figure 6.

Figure 6. Study APL0406 Original Cohort –DEF and CIR, Median Follow-up 34.4 months



(Modified from Lo-Coco et al. 2013)

Original cohort (median follow-up: 53 months):

After a median follow-up of 53 months, the estimate at 50-months for OS was 99% for the ATRA+ATO group and 88% for the ATRA+chemotherapy (p-value 0.0062).

Extended cohort:

The efficacy results from the extended cohort are summarised in Table 6 and figures 7 and 8 (modified from Platzbecker et al 2016):

Table 5: Efficacy Results on secondary endpoints (Study APL0406 Extended Cohort)

	24 month estimates		**50 month estimates**		
Endpoint	**ATRA+ATO N=129**	**ATRA + Chemotherapy N=137**	**ATRA+ATO N=55**	**ATRA + Chemotherapy N=43**	**P-value[a]**
Hematologic complete remission (HCR) after induction	100% (127/127)	97% (132/136)			0.12
Overall survival (OS)	99% (95% CI: 98-100)	95% (95% CI: 91-99)	99% (95% CI: 98-100)	93% (95% CI: 88-98)	0.0073
Disease free survival (DFS)	98% (95% CI: 96-100)	89% (95% CI: 84-95)	97% (95% CI: 94-100)	83% (95% CI: 76-90)	0.0003
Cumulative incidence of relapse (CIR)	0.9% (95% CI: 0-2.7)	8.2% (95% CI: 3.3-13.2)	1.9% (95% CI: 0-4.5)	14% (95% CI: 7.1-20.6)	0.0013

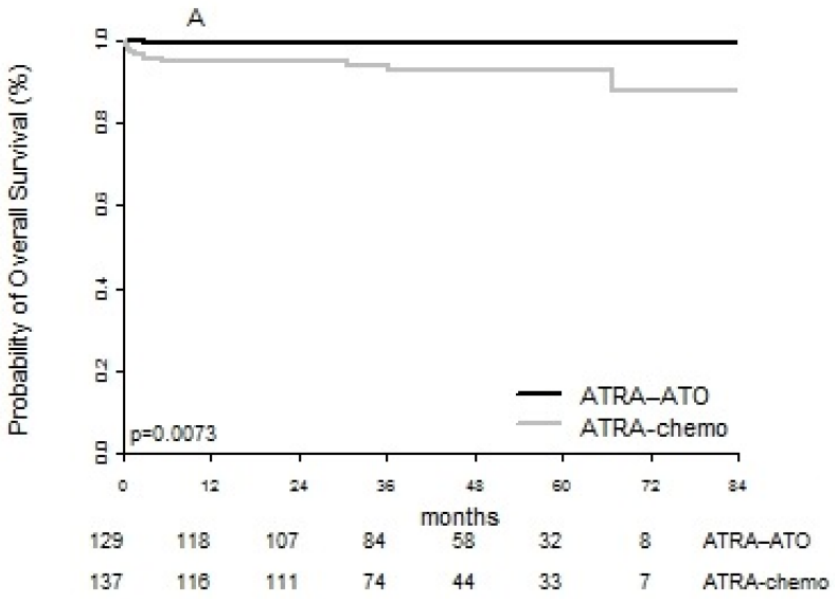
Source: modified from Platzbecker et al 2016

[a] p-value for 2-year EFS and 5-year OS, DFS and CIR

ATO=arsenic trioxide, ATRA=all-trans retinoic acid, CI=confidence interval, CIR=cumulative incidence of relapse, DFS=disease-free survival, HCR=hematologic complete remission, ITT=intent-to-treat, OS=overall survival

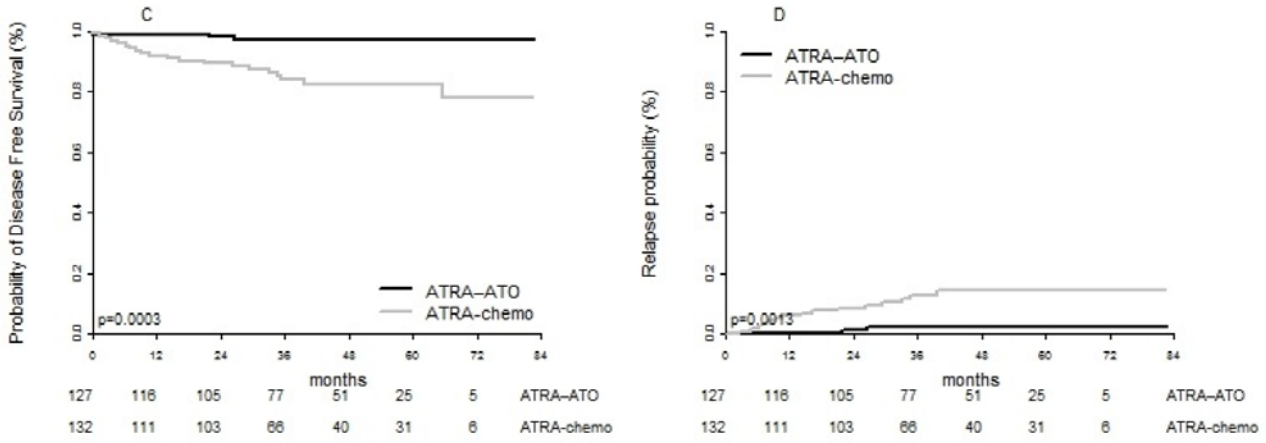
Results are for the ITT analysis set unless specified otherwise

Figure 7: Study APL0406 Extended Cohort – OS, Median Follow-up 40.6 months



(Modified from Platzbecker et al. 2016)

Figure 8: Study APL0406 Extended Cohort – DFS and CIR, Median Follow-up 40.6 months



(Modified from Platzbecker et al. 2016)

Seventeen patients relapsed during follow-up. Of these, 2 relapses occurred in the ATRA+ATO group at 22 and 27 months from diagnosis, respectively, and 15 occurred in the ATRA+chemotherapy group at a median time of 14.0 months (range: 2.5-39.8). In 4 cases relapse as detected at the molecular level before hematologic relapse leading to administration of pre-emptive salvage therapy.

The kinetics of PML/RARA transcript reduction after induction and consolidation therapy was assessed in 63 unselected patients. No significant differences were seen between the treatment groups.

Secondary endpoint: HR-QoL

The HR-QOL analysis was reported for the original cohort (see Efficace et al. 2014). Of 156 patients analyzed in the primary analysis, 150 were eligible for HR-QOL evaluation at end of induction therapy and 142 at end of third consolidation course. Overall compliance with HR-QOL forms was 80%. After

induction, 115 HRQOL forms were received of 150 expected (compliance, 77%), whereas after consolidation phase, 119 forms were received of 142 expected (compliance, 84%). No statistically significant differences were found in compliance rates between treatment arms (data not shown). Patient characteristics by HRQOL compliance at first assessment (i.e., end of induction therapy) are listed in Table below.

Table 6. Demographic, clinical and biologic characteristics of patients with and without HRQOL assessment after induction therapy (Efficace et al. 2014)

	Without HRQOL Assessment (n = 41)		With HRQOL Assessment (n = 115		
Characteristic*	No.	%	No.	%	P†
Sex					.030
Male	14	34.1	62	53.9	
Female	27	65.9	53	46.1	
Age, years					.740
Mean	45.7		44.9		
SD	16.5		14.0		
Median	48		45		
Range	18.7-69.7		19.1-70.2		
WBC count, × 10^9/L					.995
Mean	2.6		2.3		
SD	2.6		2.2		
Median	1.5		1.5		
Range	0.3-9.6		0.3-10.0		
Platelet count, × 10^9/L					.611
Mean	38.3		48.5		
SD	35.5		47.0		
Median	28		31		
Range	5.0-193.0		3.0-236.0		
Risk level‡					.159
Low	12	29.3	48	41.7	
Intermediate	29	70.7	67	58.3	
PML-RARA isoform					.621
Long	23	56.1	70	60.9	
Short	17	41.5	43	37.4	
Missing	1	2.4	2	1.7	
Hemoglobin count, g/dL					.083
Mean	9.0		9.6		
SD	1.8		2.0		
Median	8.6		9.2		
Range	5.6-12.9		4.3-14.6		
Any toxicity§					.774
No	5	12.2	12	10.4	
Yes	36	87.8	103	89.6	

Abbreviations: HRQOL, health-related quality of life; SD, standard deviation.
*Variables were measured at baseline, except for toxicity, which was measured during induction phase.
†Fisher's exact test used for sex, risk level, *PML-RARA* isoform, and any toxicity; Wilcoxon Mann-Whitney test used for remaining variables.
‡Low risk level defined as WBC count ≤ 10 × 10^9/L and platelet count > 40 × 10^9/L at presentation; intermediate risk level defined as WBC count ≤ 10 × 10^9/L and platelet count ≤ 40 × 10^9/L at presentation.
§Grades 3 to 4 during induction phase.

Fatigue was the only scale with a statistically significant overall difference between treatment groups (p-value 0.022) (see Table 7).

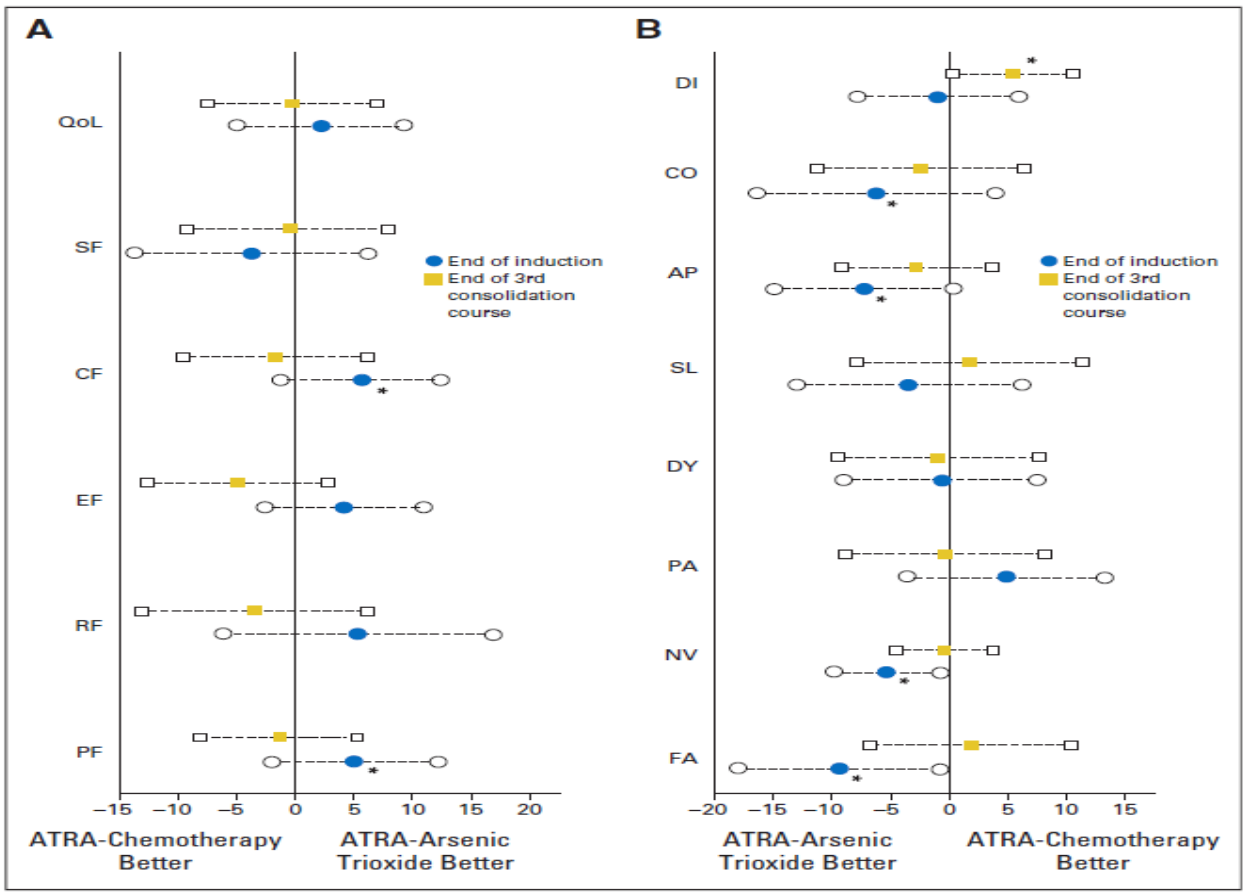
Table 7: Estimated EORTC QOL-C30 mean scores and SDs by treatment arm and HRQOL assessment (Efficace et al. 2014)

	ATRA Plus Arsenic Trioxide*				ATRA Plus Chemotherapy*				
	After Induction		After Third Consolidation Course		After Induction		After Third Consolidation Course		
EORTC QLQ-C30 Scale	Mean Score	SD	Mean Score	SD	Mean Score	SD	Mean Score	SD	P†
Functional Scales									
Physical functioning	80.9	21.5	80.6	20.6	75.6	23.5	81.9	21.5	.147
Role functioning	68.0	34.8	72.4	29.7	62.5	38.1	75.8	31.0	.280
Emotional functioning	81.2	21.0	74.7	24.0	76.8	23.0	79.6	25.1	.088
Cognitive functioning	87.2	21.1	80.8	24.5	81.4	23.1	82.4	25.8	.089
Social functioning	68.8	30.2	77.5	26.5	72.4	33.1	78.0	27.6	.778
Global health status/QOL	67.2	21.8	72.7	22.4	64.7	24.1	72.9	23.4	.761
Symptom Scales									
Fatigue	29.1	25.7	29.8	26.4	38.4	28.1	27.9	27.4	.022
Nausea/vomiting	3.1	13.9	5.3	13.1	8.3	15.2	5.7	13.5	.095
Pain	16.1	25.3	16.9	26.3	11.1	27.8	17.2	27.4	.467
Dyspnea	15.8	24.8	16.7	26.6	16.3	27.1	17.5	27.6	.978
Insomnia	16.2	28.7	21.2	30.0	19.4	31.4	19.4	31.2	.614
Appetite loss	5.6	22.6	5.3	19.9	12.7	24.8	8.1	21.0	.183
Constipation	14.5	30.5	5.3	27.6	20.6	33.4	7.7	28.6	.489
Diarrhea	8.6	20.6	7.8	15.9	9.5	22.5	2.3	16.3	.106

Abbreviations: ATRA, all-*trans*-retinoic acid; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQOL, health-related quality of life; QOL, quality of life; SD, standard deviation.
*Mean scores and corresponding SDs estimated by linear mixed model with unrestricted covariance structure.
†For each scale, *P* value stems from overall F statistic testing null hypothesis that differences between two treatment arms were equal to zero for all time points.

When considering single time points (see Figure 9), fatigue severity was significantly lower in the group treated with ATRA+ATO (p-value 0.034) after induction therapy.

Figure 9:Estimated differences in (A) and (B) symptom scales of European Organisation for Recearch and treatment of cancer QOQ-C30 mean scores and 95% CIs between all-trans-retinoid acid and (ATRA) plus arsenic trioxide and ATRA plus chemotherapy arms at end of induction therapy and end of third consolidation course.



Mean fatigue scores of patients treated with ATRA+ATO versus those treated with ATRA+chemotherapy were 29.1 (SD=25.7) and 38.4 (SD=28.1), respectively, a difference of 9.3 (95% CI: 17.8 to 0.7), reflecting a clinically relevant difference. After the third consolidation course, however, severity of fatigue was not significantly different between treatment groups (p-value 0.660).

After induction therapy, there were also small but clinically relevant differences in severity of nausea/vomiting, difference 5.1 (95% CI: 9.7 to 0.5); appetite loss 7.1 (95% CI: 14.6 to 0.5); and constipation 6.1 (95% CI: 16.3 to 4.0), favouring patients treated with ATRA+ATO versus those treated with ATRA+chemotherapy. With regard to functional aspects, clinically relevant (albeit small) differences favouring patients treated with ATRA+ATO over ATRA+chemotherapy were observed for physical 5.3 (95% CI: 1.9 to 12.4) and cognitive functioning 5.9 (95% CI: 1.2 to 12.9).

After third consolidation course, only severity of diarrhoea showed a small clinically relevant difference of 5.5 (95% CI: 0.4 to 10.6), favouring patients treated with ATRA+chemotherapy over those treated with ATRA+ATO. For all other symptoms and functional scales, the magnitude of estimated mean score differences between treatment groups was trivial.

Mean observed HRQOL scores after induction were compared between patients who returned the questionnaire after consolidation therapy and those who did not, and no statistically significant differences

were found between groups (data not shown). Univariablelogistic regression analysis showed that the missing data mechanismwas independent of age, risk level, haemoglobin, time from diagnosis,and

toxicity during induction. However, sex was significantlyassociated with higher likelihood of missing data (P=.044).

Ancillary analyses

Not available.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8. Summary of efficacy for trial APL0406

Title: A randomised phase III study to compare arsenic trioxide (ATO) combined to ATRA versus standard ATRA and anthracycline-based chemotherapy (AIDA regimen) for newly diagnosed, non-high-risk acute promyelocytic leukaemia			
Study identifier	APL0406		
Design	Prospective, open-label, multicenter, controlled, randomized, non-inferiority Phase 3 trial		
Hypothesis	Non-inferiority of ATRA-ATO vs ATRA+chemotherapy in terms of 2-year EFS		
Treatments groups	**ATRA-ATO arm**		ATRA 45 mg/m^2 + ATO 0.15mg/kg daily until CR or up to a maximum of 60 days, followed by ATO 5 days/week (4 weeks on/4 weeks off for 4 courses) and ATRA (2 weeks on/2 weeks off for 7 courses). Allocated to intervention: Original cohort (n=77)
	ATRA+chemotherapy arm		AIDA regimen (ATRA 45 mg/m^2 and idarubicin 12 mg/m^2) for induction therapy, followed by 3 cycles of anthracycline-based consolidation. Maintenance therapy for up to 2 years consisting of methotrexate 15 mg/m^2 weekly, 6-mercaptopurine 50 mg/m^2/day, and ATRA 45 mg/m^2/day for 15 days every 3 months Allocated to intervention: Original cohort (n=79)
Endpoints and definitions	Primary Endpoint	2-year event free survival (EFS)	Time from the date of randomization to the date of first documentation of treatment failure defined as no achievement of hematological complete remission after induction therapy, no achievement of molecular complete remission (CRm) after 3 consolidation courses, molecular relapse, hematological relapse, death
	Secondary endpoint	2-year overall survival (OS)	Time from the date of randomization to the date of death
	Secondary endpoint	2-year CIR	Cumulative incidence of relapse according to the IWG definitions
	Secondary endpoint	Hematologic complete remission (HCR	Proportion of subjects with <5% blasts in bone marrow, absence of extramedullary disease, an absolute neutrophil count >1,000/µL and platelets of 100,000/µL
	Secondary endpoint	MCR	rate of molecular remission after the third consolidation cycle

Results and Analysis			
Analysis description	**Analysis in the Original cohort**		
Analysis population and time point description	Intent To Treat (ITT) population, median 34-month follow-up		
Descriptive statistics and estimate variability	Treatment group	ATRA-ATO	ATRA+chemotherapy
	Number of subject	77	79
	2-year EFS (%)	97	86
	95% CI	Difference: 11 percentage points (2 to 22)	
	2-year OS (%)	99	91
	95% CI	(96-100)	(85-97)
	2-year CIR (%)	1	6
	95% CI	(0-4)	90-11)
	HCR (%)	100	95
	95% CI	-	-
	MCR (%)	100	100
	95% CI	-	-
	Intent To Treat (ITT) population, median 53-month follow-up		
	50 months EFS (%)	96	81
	95% CI	(92-100)	(73-91)
	50 months OS (%)	99	88
	95% CI	(96-100)	(81-96)
Effect estimate per comparison	**Primary endpoint: 2-year EFS**	Comparison groups	ATRA-ATO vs ATRA+chemotherapy
		P-value	<0.001 non-inferiority 0.02 superiority
	Secondary endpoint: 2-year OS	Comparison groups	ATRA-ATO vs ATRA+chemotherapy
		P-value	0.02
	Secondary endpoint: 2-year CIR	Comparison groups	ATRA-ATO vs ATRA+chemotherapy
		P-value	0.24
	Secondary endpoint: HCR	Comparison groups	ATRA-ATO vs ATRA+chemotherapy
		P-value	0.12
	Secondary endpoint: MCR	Comparison groups	ATRA-ATO vs ATRA+chemotherapy
		P-value	NA
	Primary endpoint: 50 months EFS	Comparison groups	ATRA-ATO vs ATRA+chemotherapy
		P-value	0.0034
	Secondary endpoint: 50 months OS	Comparison groups	ATRA-ATO vs ATRA+chemotherapy
		P-value	0.0062
Notes			

Analysis performed across trials (pooled analyses and meta-analysis)

Meta-analysis of ATRA+ATO versus ATRA Monotherapy

A meta-analysis was conducted to compare the effects of the combination therapy of ATRA+ATO with ATRA monotherapy in patients with newly diagnosed APL (Ma and Yang 2015).

Methods

The studies were retrieved from PubMed, EMBASE, Cochrane Library, ChinaInfo and China National Knowledge Infrastructure databases from the inception to 20 June 2014. Eligible studies were selected based on the predefined criteria, and the literature quality was independently assessed by 2 investigators according to the inclusion and exclusion criteria.

The following criteria were required for inclusion in the meta-analysis:

- Study was a randomized controlled trial or a prospective controlled clinical trial
- Participants of the study were patients with newly diagnosed APL
- ATO + ATRA combination therapy was designated as the experimental group, while the ATRA monotherapy was used for the control group
- Study reported symptoms of CR, early mortality, relapse, dryness of mouth, liver dysfunction, skin reaction or gastrointestinal reaction.

In contrast, studies were excluded if:

- They were retrospective studies
- The study did not provide complete data to be statistically analyzed
- the study was a literature review, comment or other nonpublication report
- the participants of the study were patients with recurrence of APL

The pooled effect size was relative risk (RR) and its 95% CI. Heterogeneity among studies was assessed by Cochran's Q and the I^2 statistic test, and $p < 0.05$ or $I^2 > 50\%$ was considered to be heterogeneous; when heterogeneity was detected, the random effects model was selected to calculate the summary RRs and their 95% CIs using the method of DerSimonian and Laird. Otherwise, the fixed effects model with the inverse variance method was applied to calculate the pooled effect size. Publication bias was examined by a funnel plot.

Results

A total of 1934 articles were identified in the initial search after removing duplicate articles. No publication bias was noted. Overall, a total of 8 articles containing 480 cases were included, among which 264 were assigned to the ATRA+ATO group and the other 216 to the ATRA group (see Figure 10 and Table 9).

Figure 10: Flow diagram of the literature search and study selection (Ma and Yang 2015)

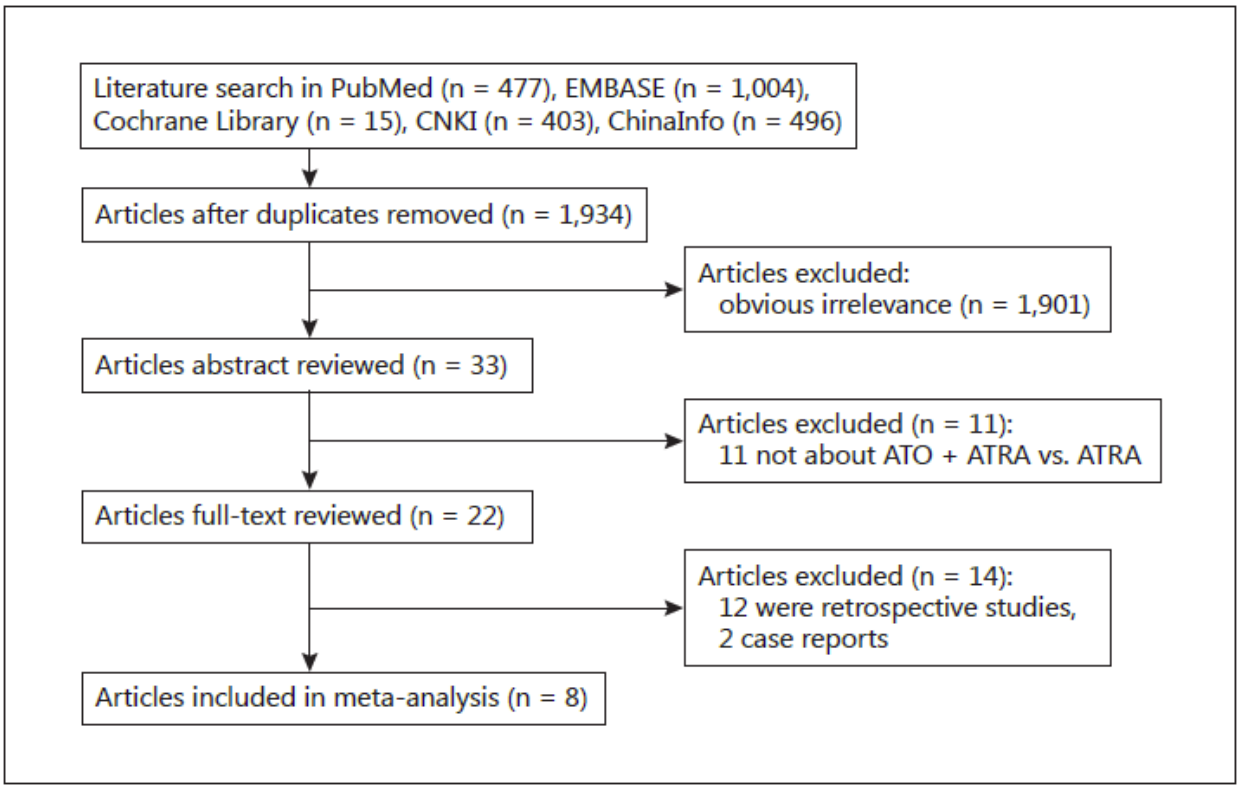


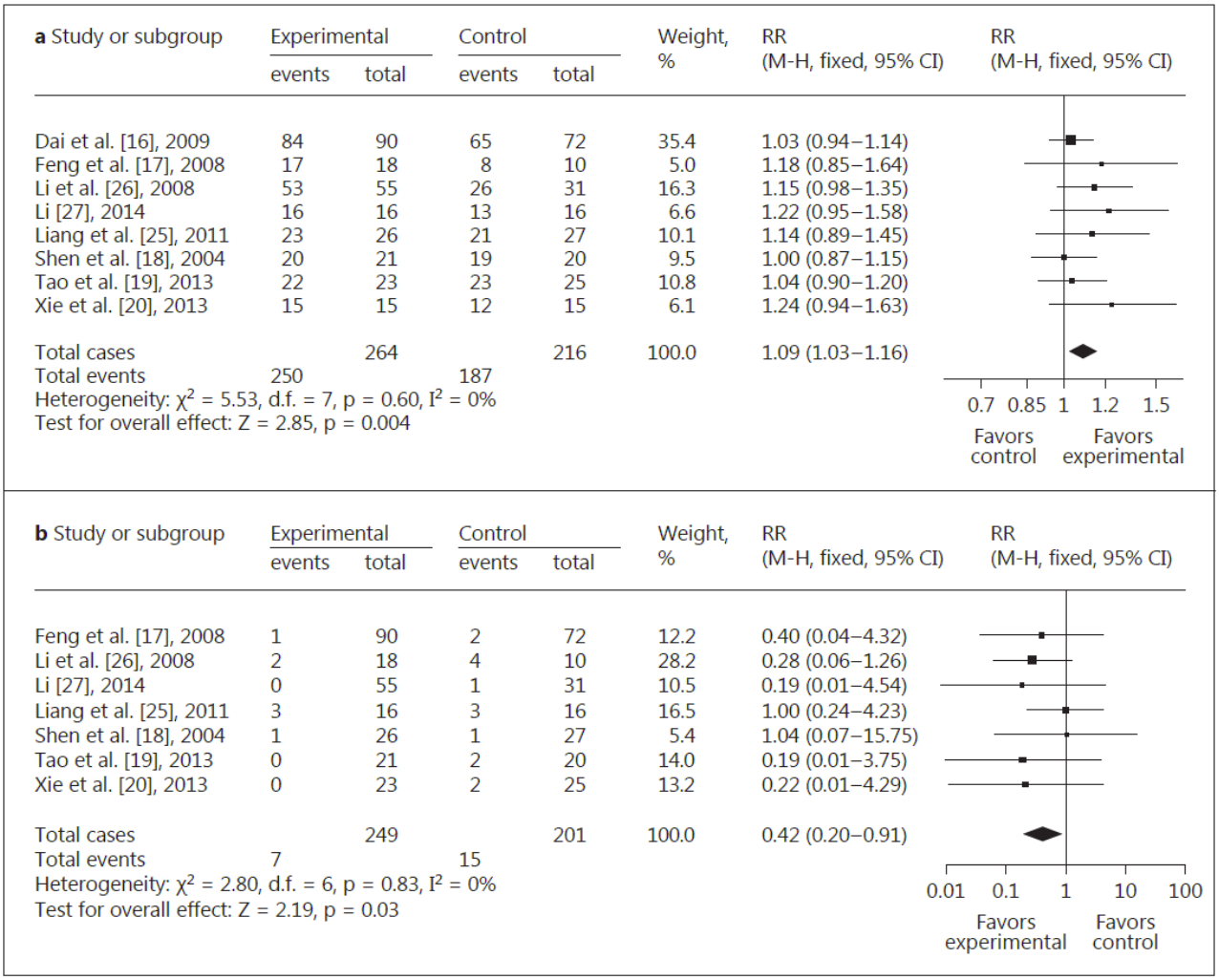
Table 9. Characteristics of the 8 included studies (Ma and Yang 2015)

First author	Year	Type of study	Sex (m/f), n		Age, years		Treatment program	
			combination	ATRA	combination	ATRA	combination	ATRA
Shen [18]	2004	RCT	21 (12/9)	20 (12/8)	34 (14–62)	30.5 (14–74)	0.16 mg/kg/day, 25 mg/m^2/day	25 mg/m^2/day
Dai [16]	2009	CCT	90 (54/36)	72 (39/33)	32 (14–67)	34 (14–69)	10 mg/day, 40 mg/m^2/day	40 mg/m^2/day
Liang [25]	2011	RCT	26 (14/12)	27 (12/15)	35.27 (14.13)	42.59 (15.10)	0.16 mg/kg/day, 25 mg/m^2/day	25 mg/m^2/day
Li [26]	2008	CCT	55 (n.a.)	31 (n.a.)	35 (13–70)	35 (13–70)	0.16 mg/kg/day, 25 mg/m^2/day	25 mg/m^2/day
Feng [17]	2008	RCT	18 (10/8)	10 (6/4)	30 (9–54)	37 (19–55)	0.1% As_2O_3 10 ml, 20–30 mg/day	20–30 mg/day
Tao [19]	2013	RCT	23 (14/9)	25 (17/8)	33 (18–62)	33 (18–62)	10 mg/day, 25 mg/m^2/day	25 mg/m^2/day
Li [27]	2014	RCT	16 (9/7)	16 (8/8)	30 (9–43)	31 (11–45)	10 mg/day, 40–90 mg/day	40–90 mg/day
Xie [20]	2013	RCT	15 (n.a.)	15 (n.a.)	35 (17–49)	35 (17–49)	10 mg/day, 40 mg/day	30–90 mg/day

Combination: treatment with ATO and ATRA; n.a. = not available.

The meta-analysis showed that ATRA+ATO combination therapy significantly improved the CR rate with RR of 1.09 (95% CI: 1.03 to 1.16), p-value 0.004; decreased the early mortality rate, RR of 0.42, (95% CI: 0.20 to 0.91) p-value); and relapse rate (RR) of 0.17 (95% CI: 0.07 to 0.42) p-value <0.0001) (see Figure 11).

Figure 11. Forest plots for the primary outcomes. a. Forest plot of CR. b. Forest plot of early mortality (Ma and Yang 2015)



Systematic literature review

Methods

A systematic literature review was conducted with the objective of identifying all published clinical studies in first-line APL, where ATO was included in any phase of the treatment regimen. The search was conducted in October 2015 using the Ovid interface to search Medline, Embase and Cochrane. The search was restricted to English language and studies published after 1st January 2005. Conference abstracts that were published in a form that was accessible using the search engines below were included; individual conference websites were not searched separately.

The employed inclusion and exclusion criteria are summarised in Table below:

Table 10: Inclusion/exclusion criteria

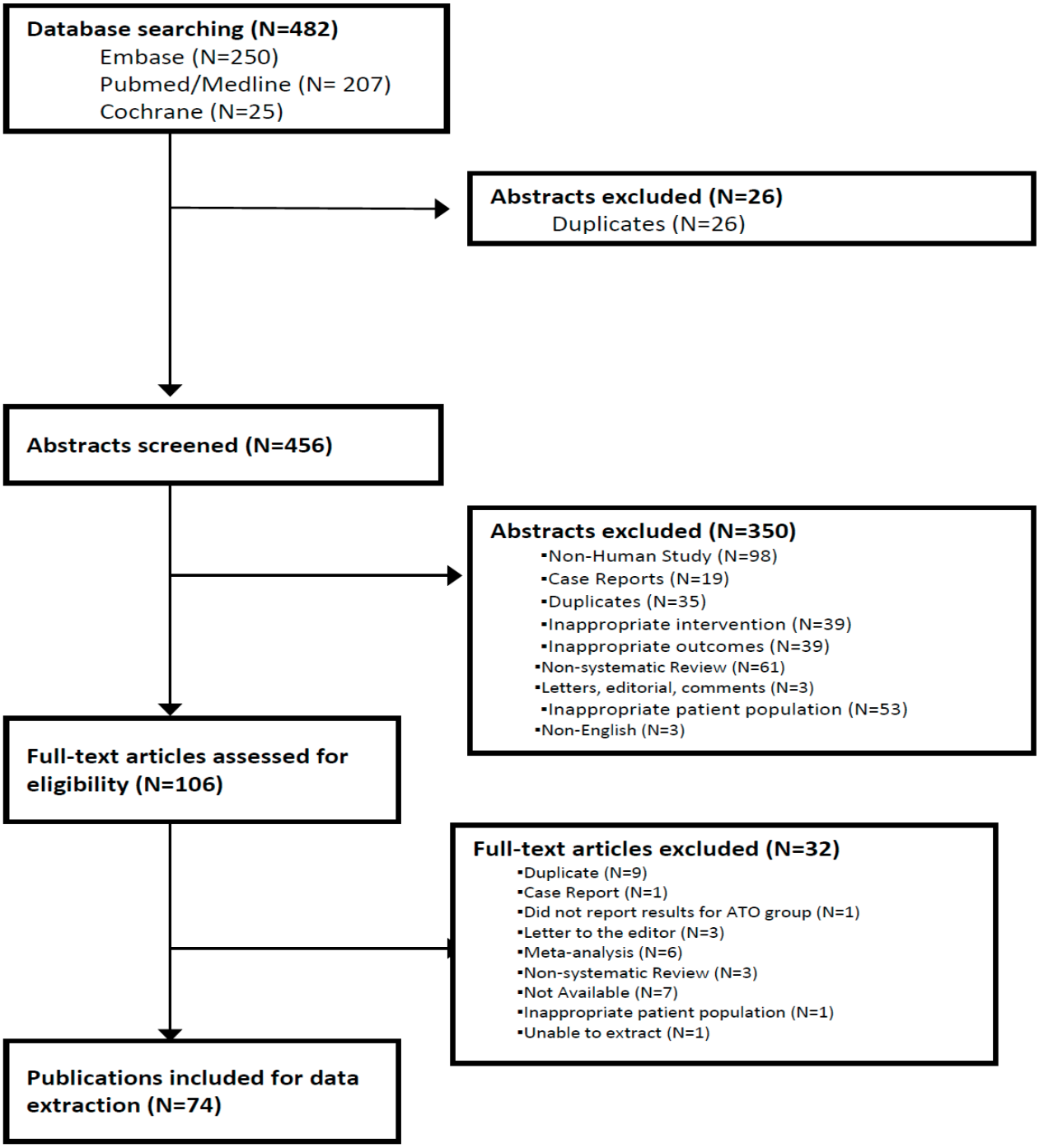
Inclusion Criteria	Exclusion Criteria
Study population	Incorrect patient population (e.g. not first-line APL)
Primary diagnosis of APL	Does not include ATO in treatment regimen
Not previously treated	No relevant study outcomes
Interventions	Incorrect study design (e.g. letters, editorials, case reports)
ATO required to be part of treatment regimen for at least 1 arm	Non-human studies
Study design	Non-English studies
Any with clinical outcomes (efficacy, safety)	Duplicates
Outcomes	
Adverse events	
Overall Survival	
Progression-free, disease-free, or recurrence-free survival	
Response	
Other criteria	
Humans	
English language	

Results

After removing 26 duplicates, a total of 456 references were identified from the literature search.

Following the initial screening 350 publications did not meet the pre-specified inclusion criteria. Of the 106 potentially relevant full text articles (and abstracts) that underwent further screening, 74 were selected for data extraction. The figure below displays the number of studies excluded at each step and the reasons for exclusion.

Figure 12: Flow diagram of publication selection process



The 74 extracted studies were assessed for their patient inclusion criteria. They consisted of both single-arm studies and controlled studies. The controlled studies included randomized controlled cohorts as well as retrospective or prospective cohorts. The majority studies included a mix of high and low risk patient, and sometimes both adults and children were treated in the same study. One subgroup was identified and analysed separately in the results: studies only including children (n=8).Five efficacy endpoints of interest were captured in the systematic literature review: OS, CR, EFS, DFS and CIR.

Studies without Chemotherapy in Any Treatment Phase

Twenty-eight of the 33 studies without chemotherapy provided at least one efficacy endpoint. On the

whole, studies using a combination regimen of ATO + ATRA had better outcomes than those with ATO alone. Studies with only ATO in the treatment regimen reported five-year OS ranging 64.4% to 83.9%, while studies with ATO and ATRA combination reported five-year OS ranging from 88.0% to 100%. CR after induction ranged from 50.0% to 92.0% for studies using ATO alone, compared to 89.0% to 100% for the combination arms. Lastly, five-year EFS ranged from 68-0% to 75.0% for ATO alone studies, and increased to 86.0% to 94.1% in combination therapy studies.

Studies with Chemotherapy in Any Treatment Phase

Thirty-seven of the 41 studies without chemotherapy provided at least one efficacy endpoint. On the whole, patients using ATO at any point in the treatment regimen had better outcomes than those treatment arms without ATO. Studies with an ATO-containing regimen reported 5-year OS ranging from 64.7% to 100%, while studies without an ATO-containing regimen reported five-year OS ranging from 45.0% to 100%. CR after induction ranged from 80.0% to 100% for regimens containing ATO, compared to 57.0% to 100% for those without ATO. Lastly, five-year DFS ranged from 86.6% to 100% for ATO-containing regimens, and decreased to 64.8% to 100% in non ATO containing regimens.

Studies with Paediatric Patients

All eight studies with only paediatric patients provided at least one efficacy endpoint. On the whole, paediatric patients using ATO at any point in the treatment regimen had better outcomes than those treatment arms without ATO. Paediatric studies with an ATO-containing regimen reported five-year OS ranging from 83.9% to 100%, while studies without an ATO-containing regimen reported five-year OS ranging from 73.3% to 91.8%. CR after induction ranged from 80.0% to 100% for paediatric regimens containing ATO, compared to 93.3% to 95.3% for those without ATO. Five-year EFS ranged from 72.7% to 94.1% for ATO-containing paediatric regimens, and decreased to 60.0% to 76.2% in non ATO-containing paediatric regimens. Lastly, five-year DFS ranged from 94.4% to 100% for ATO-containing paediatric regimens, and decreased to 64.8% to 80.2% in non ATO-containing paediatric regimens.

Clinical studies in special populations

No clinical study specifically conducted in special populations was submitted.

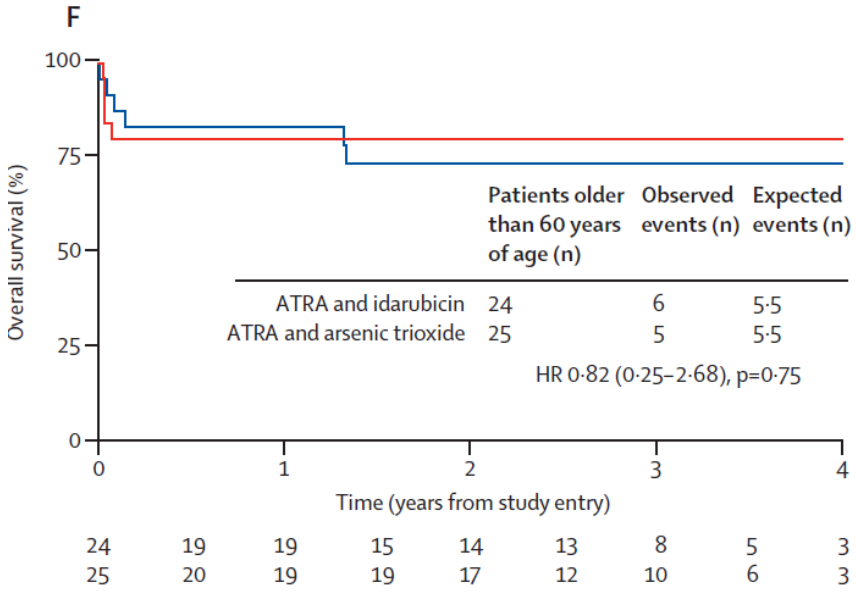
Elderly Subjects

Age is a significant prognostic factor in APL (De la Serna et al 2008). Both studies APL0406 and AML17 included newly diagnosed low- to intermediate-risk patients with APL who were > 60 years of age at study enrolment. While no formal comparisons were performed for elderly subjects between studies, each study reported similar results in patients who were ≤ 60 years of age with those who were >60 years of age.

Enrolment in Study APL0406 was limited to patients <71 years of age. A total of 35 patients were between 60.1 and 70.2 years of age. Of these, 16 patients were assigned to receive ATRA+ATO, and 19 were assigned to receive ATRA+chemotherapy. There were no significant between-group differences in the main presenting features (age, WBC and platelet counts, fibrinogen level, and coagulopathy). The 2 year EFS rates were 100% in the group receiving ATRA+ATO and 84% in the group receiving ATRA+chemotherapy (p-value 0.40).

Study AML17 included 49 patients aged between 60 and 77 years (37 low-risk and 12 high-risk patients). Of these patients, 25 received ATRA+ATO and 24 received ATRA+chemotherapy. The 4 year survival did not differ significantly between the treatment groups: 80% (95% CI: 58 to 91) in the ATRA+ATO group, compared with 74% (95% CI: 50 to 87) in the ATRA+chemotherapy group (see Figure 8).

Figure 13: Study AML17 - Outcomes in the Elderly, Intent-to-Treat Analysis Set



Source: Burnett at al 2015 Figure 3F
ATO=arsenic trioxide, ATRA=All-trans retinoic acid, HR=hazard ratio

Supportive studies

UK NCRI AML17

The trial was a phase III, randomized, open-label study to compare ATRA-ATO versus AIDA (all-trans retinoic acid + idarubicin) treatment. This study was a multicenter study with 81 centers and 235 patients randomised, of which 57 were at high risk (WBC count at diagnosis of > $10*10^9$/L) (Burnett et al. 2015).

The main inclusion criteria were: patients (≥16 years) with acute promyelocytic leukaemia, confirmed by the presence of the PML-RAR transcript and without significant cardiac or pulmonary comorbidities or active malignancy, and who were not pregnant or breastfeeding.

This trial included patients with high risk and had less frequent arsenic dosing (63 doses within 6 months) compared to the previous trial APL0406.

In this study, the bone marrow was monitored for the fusion gene, there was no maintenance treatment for patients.

Patients allocated to the ATRA and idarubicin group received four courses of treatment. ATRA 45 mg/m^2 daily was given in an oral divided dose (in two equal doses per day) for up to 60 days as part of their first course, and then at the same dose (45 mg/m^2 as an oral divided dose) on days 1 – 15 of subsequent courses. Chemotherapy was idarubicin 12 mg/m^2 intravenously on days 2, 4, 6, and 8 of course 1 and 5 mg/m^2 on days 1 – 4 of course 2; mitoxantrone 10 mg/m^2 on days 1 – 4 of course 3; and idarubicin 12 mg/m^2 on day 1 of course 4. In the ATRA and arsenic trioxide group, patients received five courses of treatment: ATRA was given at the same dose as in the other group (45 mg/m^2 daily in an oral divided dose) on days 1 – 60 of course 1 or until remission, and at the same dose on days 1 – 14 and 29 – 42 in courses 2 – 4, and days 1 14 of course 5. Arsenic trioxide was given intravenously at a dose of 0,3 mg/kg

on days 1 – 5 of each course, and then in weeks 2 – 8 of course 1 and weeks 2 – 4 of courses 2 – 5 at 0,25 mg/kg twice weekly.

High-risk patients (≥$10*10^9$ cells per L at diagnosis) could receive an initial dose of gemtuzumab ozogamicin (GO).

The primary endpoint was quality of life (EORTC QLQ-C30). Secondary outcomes were overall survival, relapse-free survival and event-free survival, and the incidence of relapse (both morphological and molecular), death without relapse, and treatment-related myelodysplastic syndrome or acute myeloid leukaemia.

Results are based on a median follow up of 30.5 months. Considering the total population (low to high risk disease which is not exactly the proposed indication for marketing authorization), data showed that:

- Difference no significative between the treatment groups in terms of quality of life ;
- CR 94% with ATRA+ATO compared with 89% with AIDA (OR=0,54 [0,21 ; 1,34], p=0,18);
- 60 day mortality was half than standard of care with 9% for AIDA compared to 5% for ATRA+ATO (HR=0,55 [0,21 ; 1,43], p=0,22);
- 4 year OS showed a noteworthy difference of 93% of ATRA-ATO compared with 89% for AIDA, but was not statistically significant (p=0,25);
- 4 year cumulative incidence of molecular relapse, was 27% with AIDA compared to 0% with ATRA+ATO (HR=0,12 [0,05 ; 0,30], p<0,0001);
- 4 year EFS show a significant difference of 91% for ATRA-ATO compared with 70% for AIDA, (HR=0,35 [0,18 ; 0,68], p=0,002);

In the low- to intermediate-risk patients, 4-year event-free survival was 92% (95% CI [84;97] in the ATRA and arsenic trioxide group vs 71% [55- 83] in the ATRA and idarubicin group (HR=0,34 ; 95%CI [0,15 ; 0,75], p=0,008) and 4-year OS was 95% (95% CI [86 - 98]) in the ATRA and arsenic trioxide group versus 90% (95% CI [81- 95]) in the ATRA and idarubicin group (HR=0,47 ; 95% CI [0,16 ; 1.39]).
Supportive care requirements were significantly lower during the first two courses of treatment for ATRA and arsenic trioxide than for ATRA and idarubicin on all measures except for antibiotic use in course 2.

Systematic literature review of clinical data for Trisenox in acute promyelocytic leukemia (APL)

A systematic literature review was conducted with the objective of identifying all published clinical studies in first-line APL, where ATO was included in any phase of the treatment regimen. The search was conducted in October 2015 using the Ovid interface to search Medline, Embase and Cochrane. The search was restricted to English language and studies published after January 1, 2005. Conference abstracts that were published in a form that was accessible using the search engines below were included; individual conference websites were not searched separately.

Out of the 456 identified references, 74 ultimately met the pre-specified inclusion criteria and were selected for data extraction. These studies consisted of both single-arm studies and controlled studies. The controlled studies included randomized controlled trials as well as retrospective or prospective multi-arm cohorts. The majority included a mix of high and low risk patients, as well as a mix of adults and children.

The studies with at least 1 treatment arm that did not include chemotherapy as part of the treatment regimen were discussed separately from those that did include chemotherapy. Some of the studies

without chemotherapy in at least 1 arm did allow gemtuzumab ozogamicin or another chemotherapy if patient's WBC rose above a certain threshold.

The table below presents a summary of the efficacy results for the studies identified that utilized ATO in a chemotherapy free regimen (the publications of the APL0406 and AML17 studies have not been included). Only those publications reporting efficacy results are included in the table. Those studies available from abstracts rather than full papers are shown italicized. Where it has been possible to identify, follow-ups of the same study are presented sequentially, otherwise the data are presented alphabetically by year of publication.

Table 11. Supportive Literature for ATRA+ATO or ATO as First-line Treatment of APL

Reference	StudyDesign/ Treatment	n	Remission rate	Event-free survival	Disease free survival	Overall survival
Zhou et al 2005	ATO by slow IV and normal IV	105 (53 slow IV, 52 control)				14 days 96% slow IV 83% control
Alimoghaddam et al 2006	Single arm ATO induction and consolidation, and for remission induction for relapsed disease during follow-up	17	CR: 100%	8 patients relapsed from 180-895 days	6 patients died (cause of death unresponsive relapse)	Median follow-up 860 days; 72% chance of survival
Estey et al 2006	Phase II ATRA+ATO	25 low risk 19 high risk	CR: 96% in low risk group			
Ghavamzadeh et al 2006	Phase II ATO single agent	111	CR: 86%	1-year 88% 2-year: 64%	Molecular relapse 8.3%	OS for CR patients: 2-year 95% 3-year 88%
Ghavamzadeh et al 2009 abstract	*Phase II Single arm single-agent ATO*	*190 median 37 months follow-up*	*85%*		*3-year 71% 5-year 68%*	*3-year 83% 5-year 72%*
Ghavamzadeh et al 2010a abstract	*Phase II Single arm single-agent ATO*	*190 median 38 months follow-up*	*85%*		*3-year 73% 5-year 67%*	*3-year 83% 5-year 71%*
Ghavamzadeh et al 2010b abstract	*Phase II Single arm single-agent ATO*	*197*	*86%*		*2-year 90% 3-year 73% 5-year 67%*	*2-year 80% 3-year 70% 5-year 64%*
Ghavamzadeh et al 2011	Phase II Single arm single-agent ATO	197	86% (169/197)		5-year: 67%	5-year: 64%
Ghavamzadeh et al 2013 abstract	*Single-agent ATO 3 or 5 courses*	*271 3 courses: 96 5 courses: 175*			*2.5-year 73%*	*2.5-year 85%*
Mathews et al 2006	ATO	72	CR: 86% (62/72)	2-year: 75%	2-year: 87%	
Follow-up publication Matthews et al 2010a	ATO	72	CR: 86% (62/72)	5-year: 69%	5-year: 80%	5-year: 74%

Reference	StudyDesign/ Treatment	n	Remission rate	Event-free survival	Disease free survival	Overall survival
Mathews et al 2009 abstract	*Single agent ATO*	*155*	*HCR: 88% (136/155)*	*3-year: 72%*	*3-year: 81%*	*3-year: 77%*
Mathews et al 2011 abstract	*Single agent ATO*	*159*	*HCR: 87% (138/159)*	*5-year: 68%*	*5-year: 77%*	*5-year: 76%*
Ravandi et al 2010a abstract	*Phase II ATRA+ATO±GO*	*92 median 25 months follow-up*	*CR:98% (90/92)*			*5-year 90%*
Ravandi et al 2010b abstract	*Phase II ATRA+ATO±GO*	*104 73 low risk 31 high risk median 115 weeks (27 months) follow-up*	*CR:98% (102/104)*	5-year: 86%		*5-year 88%*
Zhou et al 2010	Single arm single-agent ATO in children	19 (7 with WBC >$10x10^9$ - high risk)	CR: 90% (17/19)	5-year: 73%		5-year: 84%
Bajpai et al 2011	Case review Daunorubicin+ ATRA ATO Daunarubicin+araC	33 (10 high risk)	CR 81% (21/26) 50% (2/4) 100% (3/3)	2-year: 62%	2-year: 83%	2-year: 75%
Iashi et al 2013 abstract	*Parallel groups ATRA+Chemo ATRA+ATO*	*34 patients 15 19*	*93% (14/15) 100% (19/19)*	*5-year 60% 94%*		*5-year 73% 100%*
Zhang et al 2013	Single arm single-agent ATO in ≥60 years	33 (5 with WBC >$10x10^9$ - high risk)	hematologic CR 89% (29/33)		10-year: 65%	10-year: 69%
Aznab et al 2012	*Single agent ATO*	*42*	*90% (38/42)*		*Relapse-free survival 1-year 97% 2-year 87% 3-year 79%*	*98%*
Aznab et al 2015	Single arm single-agent ATO	60	92% (55/60)		99 months	102 months
Eghtedar et al 2015	Database review ATRA + IDA ATRA+ATO	160 (including 50 high risk)	CR: 94.4% 51/54) CR: 99.1% 105/106)		10-year OS 65%	10-year OS 69%

Mathews and al (2006) and Ghavamzadeh and al (2006) relied almost exclusively on ATO monotherapy for both induction and consolidation/maintenance, although patients with high WBC count were also given hydroxyurea. A CR rate of 86% was achieved by both groups, and 3-year OS of 86% to 87% was reported in both studies. Further follow-up reported a 5-year OS of 74% (Mathews and al 2010a). In the study by Ghavamzadeh, newly diagnosed patients were treated with only 2 cycles of single-agent ATO, leading to a DFS at 2 years of only 63.7%. This led to the conclusion that 2 cycles were not enough therapy. Further follow-up reported at 5 years OS at 64% (Ghavamzadeh and al 2011). While the results of single-agent ATO were deemed to be acceptable in patients with low to intermediate risk APL, high risk patients did considerably worse in both studies. A study in Iran reported a CR rate of 100% and 72% chance of survival a median follow-up of 28 months (Alimoghaddam and al 2006). The lowest CR rate observed (50%) was reported for a sample of only 4 patients in a case review of 33 patients. The publication did not provide sufficient detail for further review of these patients (Bajpai and al 2011).

Building on preclinical data showing synergy of ATRA and ATO in vitro, studies combining the 2 agents with or without chemotherapy were undertaken. The majority of these studies was Phase 2 studies and included chemotherapy in the treatment schedules. The estimated 10-year OS for ATRA+ATO was 69% following database review (Eghtedar and al 2015). Further studies that stratified patients by risk groups

showed that ATRA+ATO-based induction and consolidation therapy were effective in patients with low- to intermediate-risk APL with a CR rate of 96% and long-term outcomes, despite the omission of chemotherapy from both induction and consolidation phases (Estey and al 2006, Ravandi and al 2010b). High risk patients (WBC >$10x10^9$/L at initial presentation) had inferior outcomes on this study, despite the addition of idarubicin or gemtuzumab ozogamicin during induction.

Single agent ATO has also been studied in newly diagnosed APL patients aged ≥ 60 (Zhang and al 2013), and children aged ≤ 15 years (Zhou and al 2010), with similar high CR rates and durable remissions.

Overall, these studies showed significant improvement in survival, although the early death rate remained high (6% to 11%) as well as 2-year relapse rate (8% to 12%).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has mainly provided results taken from the study APL0406 and the study AML17.

No formal dose-response study was conducted to investigate the optimal dose and schedule for ATO when used in combination with ATRA. Different doses and schedules of ATRA and ATO have been investigated so far in several independent clinical trials. However, with all the limitations of indirect comparisons, it is acknowledged that no significant differences in terms of efficacy outcomes were observed. The ATO dose and schedule employed in study APL0406 are similar to those already approved for the treatment of relapsed/refractory patients. The minor changes introduced in the ATO regimen in this study (mainly in terms of max. treatment duration during induction and consolidation) were made to adapt the use of ATO to a first-line regimen that included ATRA.

Supportive study AML17 was an open label, randomized, multicenter, phase 3 study designed to compare the efficacy and safety of ATRA-ATO with ATRA+chemotherapy (the AIDA regimen). The APL study was part of a larger study in patients with AML and high-risk myelodysplastic syndrome (MDS). With respect to study design, significant differences were observed between study AML17 and pivotal study APL0406. In terms of patient population, patients aged ≥ 16 years could be enrolled in study AML17, and no upper age limit was pre specified. More importantly, high risk APL patients were also accepted.

The ATRA-ATO regimen administered in study AML17 significantly differed from the one employed in the pivotal trial (i.e. ATO was administered at a higher dose [0.3 mg/kg daily] for the first 5 days of each course, followed by a twice weekly regimen at a lower dose [0.25 mg/kg]). Significant differences compared to study APL0406 were also observed in the control arm (i.e. no maintenance phase was planned). Furthermore, high-risk patients could also receive gemtuzumab ozogamicin.

Efficacy data and additional analyses

In the original cohort of the study APL0406, 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 EFS rates were 97% in the ATRA- arsenic trioxide group and 86% in the ATRA- chemotherapy group (95% CI for the difference, 2 to 22 percentage points; p<0.001 for no inferiority and p = 0.02 for superiority of ATRA- arsenic trioxide). Two-year OS probability was 99% (95% CI: 96-100) in the ATRA–arsenic trioxide group and 91% (95% CI: 85-97) in the ATRA–chemotherapy group (p = 0.02).

Health-related quality-of-life (secondary endpoint) was assessed after induction therapy and third consolidation course. A difference favouring patients treated with ATRA + ATO was found for fatigue

severity (mean score difference, -9.3; 95% CI, -17.8 to -0.7; p = .034) at end of induction therapy. HRQOL differences between treatment arms at end of consolidation showed that for several scales, differences between treatment arms were marginal.

In the extended cohort of APL0406 study, all 4 efficacy endpoints showed significant difference between the treatment groups favouring ATRA+ATO over ATRA+chemotherapy at both 24 months and at 50 months for those evaluable. The 2-year EFS rate was 98% in the ATRA+ATO group and 87% in the ATRA+chemotherapy group; a difference of 11 percentage points between the treatment groups (p= <0.0001). The 2-year OS rates were 99% in the ATRA+ATO group and 95% in the ATRA+chemotherapy group, 2-year DFS rates were 98% and 89% (p=0.0003) and 2-year CIR rates were 0.9% and 8.2% (p=0.0013). The 5-year OS rates were 99% in the ATRA+ATO group and 93% in the ATRA+chemotherapy group (p=0.0073), 5-year DFS rates were 97% and 83% (p= 0.0003) and 5-year CIR rates were 1.9% and 14% (p= 0.0013).

In the study AML17, in the low- to intermediate-risk subgroup corresponding to the proposed indication for marketing authorization, even though the primary objective of this supportive study was not reached, the EFS as a secondary objective showed a significant improvement with the ATRA-ATO combination. Indeed, 4-year EFS was 92% (95% CI: 84-97 in the ATRA and arsenic trioxide group vs 71% [95% CI: 55-83] in the ATRA and idarubicin group (HR=0,34 ; 95%CI: 0,15 -0,75), p=0,008). The 4-year OS was 95% (95% CI: 86 - 98) in the ATRA and arsenic trioxide group versus 90% (95% CI: 81- 95) in the ATRA and idarubicin group (HR=0,47 ; 95% CI: 0,16-1.39).

2.4.4. Conclusions on the clinical efficacy

Overall, the efficacy data demonstrated a clinical and statistical non-inferiority of ATRA/ATO combination therapy versus the active comparator (ATRA-chemotherapy combination), showing a clear benefit of ATRA/ATO combination therapy in the treatment of patients with low-to-intermediate-risk APL. The use of ATRA/ATO is associated with a similar rate of complete remission allowing the patients to go through the consolidation phase. These results are considered of important clinical relevance.

2.5. Clinical safety

Introduction

The MAH has submitted an application based on the analysis of safety of data obtained from:

- Study APL0406
- Study AML17
- A literature review
- Post-marketing safety data

In Study APL0406 all AEs, adverse drug reactions (ADRs), SAEs and serious unexpected adverse reactions (SUSARs) were recorded during the treatment period. No long-term safety data were collected. The protocol stated that AEs were defined in accordance with the GCP definitions (2001/20/EC). A full list of reported SAEs has been disclosed in the publication of the extended cohort study (Platzbecker et al 2016). According to the protocol for Study APL0406, during the induction and consolidation phases regular tests for serum chemistry were made including liver enzymes, electrolytes, glycaemia and renal function tests, as well as ECG. After the last consolidation cycle, neither further biochemistry testing nor ECC were done. Only regular blood counts and bone marrow aspirates were performed. Results of Grade 3 or 4 neutropenia, Grade 3 or 4 thrombocytopenia, liver toxicity, hypercholesterolemia,

hypertriglyceridemia at induction and after each consolidation cycle have been disclosed in the publication of the extended cohort (Platzbecker et al 2016). For the original cohort the only results disclosed were a comparison of the incidence of hematological and non-hematological toxicity episodes during treatment (National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE grading Version 3.0) which was a secondary endpoint of the study.

The primary objective of Study AML17 was to compare QOL and toxicity and resource usage of patients receiving the ATRA+chemotherapy compared with ATRA+ATO. No spontaneous reporting of any AEs was done and no routine biochemistry testing was prespecified. Grading of following limited list of AEs was done after course 1 and 2: nausea; vomiting; alopecia; oral symptoms; diarrhea; cardiac function; liver function AST, ALT and bilirubin; renal function creatinine; proteinuria; hematuria; and sensory neuropathy. Likewise, AEs of special interest were checked for presence: QTc prolongation, other arrhythmias, sensory neuropathy, differentiation syndrome, tumor lysis syndrome, peak WBC, and secondary leukemias.

Patient exposure

Study APL0406

The original cohort of study APL0406 comprised a total of 162 patients recruited to September 2010 (6 of these patients were recruited but not treated) initially published with a median 34-month follow-up (Lo-Coco et al 2013a) and then with a median 53-month follow-up (Lo-Coco et al 2015).
An additional cohort of 114 patients was enrolled under the same protocol (recruited to January 2013). Results for the extended cohort, which comprises 276 patients (162+114) were initially published with a median follow-up of 36 months (Platzbecker et al 2014) and then with median 40.6 months follow-up (Platzbecker et al 2016).
Overall, across the original and extended cohorts, 129 patients were treated with the ATRA-ATO regimen in study APL0496

Study AML17

A total of 235 patients with APL were randomized in study AML17 and 116 patients were allocated to the ATRA-ATO arm. However, only 115/116 (99%) patients received the allocated treatment in course 1. One patient assigned to ATRA-ATO received ATRA+chemotherapy because of prolonged QT interval.
Results have been published with a median 30.5-month follow-up (Burnett et al 2015). Twenty-eight of the 30 high-risk patients in the ATRA-ATO group also received gemtuzumab ozogamicin (the other 2 high-risk patients were given an anthracycline as there was no gemtuzumab ozogamicin available at their site pharmacy) and 7 low- or intermediate- risk patients were given gemtuzumab ozogamicin for a rising WBC count.

Expected ATO exposure

In the currently approved Trisenox SmPC for treatment of relapsed/refractory APL, the recommended dose for ATO in induction is 0.15 mg/kg daily until remission or day 50, followed by consolidation (using the same dose) for 5 days per week for a maximum of 5 weeks (total of 25 days).
This equates to a maximum cumulative dose of 11.3 mg/kg.

The ATRA-ATO regimen for newly diagnosed patients as used in the APL0406 study involved induction treatment with 0.15 mg/kg/day ATO and 45 mg/m^2 ATRA until CR or up to a maximum of 60 days. This is followed by consolidation treatment (using the same doses) for 5 days a week, 4 weeks on and 4 weeks off, for a maximum of 4 cycles (i.e., 80 days). Therefore, the maximum exposure to ATO treatment in this study was 140 days at a dose of 0.15 mg/kg (i.e., maximum cumulative exposure of 21 mg/kg).

The AML17 study used a different dosing schedule. For patients in the ATRA-ATO group, the first course comprised ATRA 45 mg/m^2 until remission or day 60, and ATO at 0.3 mg/kg on day 1-5, and then at 0.25 mg/kg twice weekly in weeks 2-8. For courses 2 to 5, the same regimen of ATRA was used (45 mg/m^2 on days 1-15) and the same dose of ATO was given but treatment stopped at week 4 (rather than week 8). The maximum cumulative exposure for ATO in this study is 25 days at 0.3 mg/kg and 38 days at 0.25 mg/kg (i.e., maximum cumulative dose of 17 mg/kg). This equates to a maximum exposure for 113 days at the dose of 0.15 mg/kg.

The proposed regimen for treatment of newly diagnosed APL is the same dose regimen as used in the APL0406 study.

Adverse events

In study APL0406 a comparison of the incidence of haematological and non-haematological toxicity episodes during treatment (NCI-CTCAE grading, version 3.0) was a secondary endpoint of the study. Adverse events (AEs) were defined in accordance with the Good Clinical Practice (GCP) definitions (2001/20/EC). Adverse events and/or adverse drug reactions (ADRs) were recorded according to the NCI CTCAE, version 3.0.

In Study AML17, after course 1 and 2, only a grading of the following AEs was done: nausea; vomiting; alopecia; oral symptoms; diarrhoea; cardiac function; liver function (aspartate transaminase [AST], alanine transaminase [ALT] and bilirubin); renal function creatinine; proteinuria; haematuria; and sensory neuropathy. After course 1 and 2, the following AEs of special interest were also checked for presence: QTc prolongation, other arrhythmias, sensory neuropathy, differentiation syndrome, tumour lysis syndrome, peak white blood cells (WBC), secondary leukaemia's. No spontaneous reporting of any AEs was done. Toxicity was recorded using the NCI-CTCAE version 3.0.

Non-haematological toxicities in study APL0406 are summarised in Table 12.

Table 12: Non-Hematologic Toxicities in Study APL0406, Extended Cohort, 40.6-month Follow-up

Toxicity	ATRA+ATO N=129	ATRA+CHEMO N=137	P-value
Cardiacfunction (Grade 3-4)			
Induction	0	5 (4%)	0.06
1st consolidationcycle	0	0	
2nd consolidationcycle	0	0	
3rd consolidationcycle	0	0	
Neurotoxicity			
Induction	1 (1%)	0	0.48
1st consolidationcycle	5 (4%)	0	0.02
2nd consolidationcycle	6 (5%)	0	0.01
3rd consolidationcycle	7 (6%)	0	0.006
Gastrointestinaltoxicity (Grade 3-4)			
Induction	3 (2%)	25 (18%)	<0.0001

Toxicity	ATRA+ATO N=129	ATRA+CHEMO N=137	P-value
1st consolidationcycle	0	1 (1%)	1
2nd consolidationcycle	0	6 (5%)	0.03
3rd consolidationcycle	0	0	1
Hypercholesterolemia			
Induction	14 (10%)	12 (9%)	0.55
1st consolidationcycle	19 (16%)	12 (10%)	0.13
2nd consolidationcycle	19 (16%)	12 (10%)	0.14
3rd consolidationcycle	16 (14%)	11 (9%)	0.27
Hypertrigliceridemia			
Induction	29 (22%)	29 (22%)	0.76
1st consolidationcycle	22 (18%)	19 (15%)	0.49
2nd consolidationcycle	17 (14%)	10 (8%)	0.12
3rd consolidationcycle	16 (14%)	13 (11%)	0.5

Source: Platzbecker et al 2016 Table 3
ATO=arsenic trioxide, ATRA=all-trans retinoic acid, CHEMO=chemotherapy, ITT=intent-to-treat, QTc=corrected QT.
Notes: Data are presented for ITT analysis set with evaluable data

The incidence of non-haematological AEs for Study AML17 is shown in Tables 13 and 14.

Table 13: Study AML17: Incidence of Non-Haematological Adverse Events Following Course 1 of Treatment

	ATRA+ATO				ATRA+chemotherapy			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	38/110 (35%)	19/110 (17%)	0/110	0/110	36/115 (31%)	20/115 (17%)	5/115 (4%)	0/115
Alopecia	10/95 (11%)	2/95 (2%)	3/95 (3%)	2/95 (2%)	16/98 (16%)	24/98 (24%)	13/98 (13%)	10/98 (10%)
Diarrhoea	25/109 (23%)	9/109 (8%)	1/109 (1%)	0/109	27/115 (23%)	39/115 (34%)	7/115 (6%)	0/115
Oral	18/109 (17%)	10/109 (9%)	1/109 (1%)	0/109	24/115 (21%)	27/115 (23%)	17/115 (15%)	5/115 (4%)
Cardiacevents	13/107 (12%)	7/107 (7%)	1/107 (1%)	1/107 (1%)	3/110 (3%)	1/110 (1%)	5/110 (5%)	1/110 (1%)
Raisedliver ALT	25/109 (23%)	25/109 (23%)	22/109 (20%)	5/109 (5%)	33/108 (31%)	17/108 (16%)	9/108 (8%)	2/108 (2%)
Raisedliver AST	8/46 (17%)	6/46 (13%)	2/46 (4%)	0/46	5/51 (10%)	2/51 (4%)	2/51 (4%)	0/51
Hyperbilirubinaemia	15/110 (14%)	6/110 (5%)	1/110 (1%)	0/110	24/114 (21%)	11/114 (10%)	6/114 (5%)	2/114 (2%)
Raised creatinine	21/110 (19%)	3/110 (3%)	1/110 (1%)	0/110	20/114 (18%)	10/114 (9%)	0/114	1/114 (1%)
Proteinuria	3/82 (4%)	1/82 (1%)	0/82	0/82	1/87 (1%)	3/87 (3%)	0/87	1/87 (1%)

	ATRA+ATO				ATRA+chemotherapy			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haematuria	5/82 (6%)	2/82 (2%)	0/82	0/82	4/90 (4%)	4/90 (4%)	0/90	1/90 (1%)

Source: Burnett et al 2015 Table 3
ALT=alanine aminotransferase, AST=aspartate aminotransferase, ATO=arsenic trioxide, ATRA=all-trans retinoic acid. ITT=intent-to-treatNote: The denominators differ for the various toxic effects because of variations in the total numbers of patients returning data foreach effect.

Table 14: Study AML17: Incidence of Non-Hematological Adverse Events Following Course 2 of Treatment

	ATRA+ATO				ATRA+chemotherapy			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	26/93 (28%)	8/93 (9%)	0/93	0/93	11/101 (11%)	7/101 (7%)	1/101 (1%)	0/101
Alopecia	12/77 (16%)	0/77	0/77	2/77 (3%)	6/89 (7%)	28/89 (31%)	11/89 (12%)	14/89 (16%)
Diarrhoea	10/93 (11%)	3/93 (3%)	1/93 (1%)	0/93	5/101 (5%)	3/101 (3%)	1/101 (1%)	0/101
Oral	10/94 (11%)	0/94	0/94	0/94	9/101 (9%)	5/101 (5%)	0/101	0/101
Cardiac events	5/92 (5%)	2/92 (2%)	3/92 (3%)	0/92	0/99	0/99	0/99	0/99
Raised liver ALT	6/38 (16%)	0/38	0/38	0/38	5/48 (10%)	0/48	0/48	0/48
Raised liver AST	26/93 (28%)	9/93 (10%)	2/93 (2%)	0/93	23/98 (23%)	10/98 (10%)	2/98 (2%)	0/98
Hyperbilirubinaemia	6/93 (6%)	0/93	0/93	0/93	4/101 (4%)	1/101 (1%)	0/101	0/101
Raised creatinine	9/93 (10%)	0/93	0/93	0/93	8/101 (8%)	2/101 (2%)	0/101	0/101
Proteinuria	3/82 (4%)	1/82 (1%)	0/82	0/82	0/73	0/73	0/73	0/73
Haematuria	1/67 (1%)	0/67	0/67	0/67	0/76	0/76	0/76	0/76

Source: Burnett et al 2015 Table 4
ALT=alanine aminotransferase, AST=aspartate aminotransferase, ATO=arsenic trioxide, ATRA=all-trans retinoic acid, ITT=intent-to-treatNote: The denominators differ for the various toxic effects because of variations in the total numbers of patients returning data foreach effect.

Serious adverse event / deaths / other significant events

Serious adverse events (SAEs)

Study APL0406

Overall, 95 SAEs were reported in 65 patients: 43 SAEs in the ATRA+ATO group and 52 in the ATRA+chemotherapy group.

Tables 15 summarises the SAEs reported in study APL0406 by preferred term and decreasing order of frequency and by system organ class (SOC) and preferred term.

Table 15: Serious Adverse Events in Study APL0406 Extended Cohort by System Organ Class and Preferred Term

System Organ Class	Preferred term	ATRA+ATO (N=129)	ATRA+chemotherapy (N=137)
Blood and lymphatic system disorders	**TOTAL**	**0**	**10 (7.3%)**
	Febrile neutropenia	0	8 (5.8%)
	Bone marrow failure	0	1 (0.7%)
	Neutropenia	0	1 (0.7%)
Cardiac disorders	**TOTAL**	**3 (2.3%)**	**7 (5.1%)**
	Pericarditis	1 (0.8%)	2 (1.5%)
	Acute myocardial infarction	1 (0.8%)	1 (0.7%)
	Cardiac failure	0	1 (0.7%)
	Ejection fraction decreased	0	1 (0.7%)
	Myocardial ischemia	0	1 (0.7%)
	Syncope	1 (0.8%)	0
	Tachyarrhythmia	0	1 (0.7%)
Eye disorders	**TOTAL**	**1 (0.8%)**	**0**
	Diplopia	1 (0.8%)	0
Gastrointestinal disorders	**TOTAL**	**1 (0.8%)**	**5 (3.6%)**
	Anal haemorrhage	0	1 (0.7%)
	Diarrhoea	0	1 (0.7%)
	Dyspepsia	1 (0.8%)	0
	Emesis	0	1 (0.7%)
	Inguinal hernia	0	1 (0.7%)
	Pancreatitis acute	0	1 (0.7%)
General disorders	**TOTAL**	**1 (0.8%)**	**5 (3.6%)**
	Mucosal inflammation	0	2 (1.5%)
	Pyrexia	1 (0.8%)	2 (1.5%)
	Fever in aplasia	0	1 (0.7%)
Hepatic disorders	**TOTAL**	**4 (3.1%)**	**0**
	Hepatotoxicity	1 (0.8%)	0
	Hypertransaminasemia	1 (0.8%)	0
	Hepatic failure	1 (0.8%)	0
	Cholelithiasis	1 (0.8%)	0
System Organ Class	**Preferred term**	**ATRA+ATO (N=129)**	**ATRA+chemotherapy (N=137)**
Injury, poisoning and procedural complications	**TOTAL**	**1 (0.8%)**	**1 (0.7%)**
	Maternal exposures before pregnancy	1 (0.8%)	1 (0.7%)

Infections and infestations	**TOTAL**	**6 (4.7%)**	**10 (7.3%)**
	Pneumonia	2 (1.6%)	2 (1.5%)
	Bronchopneumonia	0	2 (1.5%)
	Catheter site infection	2 (1.6%)	0
	Infection	0	2 (1.5%)
	Sepsis	0	2 (1.5%)
	Febrile infection	1 (0.8%)	0
	Herpes zoster	1 (0.8%)	0
	Bacteraemia	0	1 (0.7%)
	Urinary tract infection	0	1 (0.7%)
Investigations	**TOTAL**	**7 (5.4%)**	**2 (1.5%)**
	Electrocardiogram QT prolonged	2 (1.6%)	0
	ALT increased	2 (1.6%)	0
	AST increased	1 (0.8%)	0
	Hepatic enzyme increased	1 (0.8%)	0
	C-reactive protein increased	1 (0.8%)	0
	Hyperglycaemia	0	1 (0.7%)
	Transaminases increased	0	1 (0.7%)
Nervous system	**TOTAL**	**4 (3.1%)**	**1 (0.7%)**
	Cerebrovascular accident	1 (0.8%)	0
	Cerebral haemorrhage	1 (0.8%)	0
	Depression	1 (0.8%)	0
	Hydrocephalus	1 (0.8%)	0
	Ischaemic stroke	0	1 (0.7%)
Psychiatric disorders	**TOTAL**	**1 (0.8%)**	**0**
	Confusional state	1 (0.8%)	0
Reproductive system and breast disorders	**TOTAL**	**1 (0.8%)**	**0**
	Endometriosis	1 (0.8%)	0
Respiratory, thoracic and mediastinal disorders	**TOTAL**	**10 (7.8%)**	**7 (5.1%)**
	Retinoic acid syndrome	1 (0.8%)	3 (2.2%)
	Respiratory failure	2 (1.6%)	2 (1.5%)
	APL differentiation syndrome	3 (2.3%)	0
	Dyspnoea	3 (2.3%)	0
	Acute respiratory distress syndrome	0	1 (0.7%)
	Pneumonia	1 (0.8%)	0
	Pulmonary embolism	0	1 (0.7%)
Skin and subcutaneous	**TOTAL**	**1 (0.8%)**	**0**

tissue disorders	Leucocytoclastic vasculitis	1 (0.8%)	0
Vascular disorders	**TOTAL**	**1 (0.8%)**	**4 (2.9%)**
	Extradural haematoma	0	1 (0.7%)
	Intracranial aneurysm	1 (0.8%)	0
	Pulmonary embolism	0	1 (0.7%)
	Shock haemorrhagic	0	1 (0.7%)
	Thrombosis	0	1 (0.7%)

Source: Platzbecker et al 2016 Appendix 1
APL=acute promyelocytic leukemia, ALT=alanine transaminase, AST=aspartate transaminase, ATO=arsenic trioxide, ATRA=all-trans retinoic acid, ITT=intent-to-treat
Note: Data are presented for ITT analysis set with evaluable data

Table 16: Serious Adverse Events in Study APL0406 Extended Cohort by Preferred Terms and Order of Frequency

Preferred term	**ATRA+ATO (N=129)**	**ATRA+chemotherapy (N=137)**
Febrile neutropenia	0	8 (5.8%)
Pneumonia	3 (2.3%)	2 (1.5%)
Pyrexia	1 (0.8%)	2 (1.5%)
Respiratory failure	2 (1.6%)	2 (1.5%)
Retinoic acid syndrome	1 (0.8%)	3 (2.2%)
APL differentiation syndrome	3 (2.3%)	0
Dyspnoea	3 (2.3%)	0
Pericarditis	1 (0.8%)	2 (1.5%)
Acute myocardial infarction	1 (0.8%)	1 (0.7%)
ALT increased	2 (1.6%)	0
Bronchopneumonia	0	2 (1.5%)
Catheter site infection	2 (1.6%)	0
Electrocardiogram QT prolonged	2 (1.6%)	0
Infection	0	2 (1.5%)
Mucosal inflammation	0	2 (1.5%)
Pulmonary embolism	0	2 (1.5%)
Sepsis	0	2 (1.5%)
Acute respiratory distress syndrome	0	1 (0.7%)
Anal haemorrhage	0	1 (0.7%)
AST increased	1 (0.8%)	0
Bacteraemia	0	1 (0.7%)
Bone marrow failure	0	1 (0.7%)
Cardiac failure	0	1 (0.7%)
Cerebral haemorrhage	1 (0.8%)	0
Cerebrovascular accident	1 (0.8%)	0

Cholelithiasis	1 (0.8%)	0
Confusional state	1 (0.8%)	0
C-reactive protein increased	1 (0.8%)	0
Depression	1 (0.8%)	0
Diarrhoea	0	1 (0.7%)
Diplopia	1 (0.8%)	0
Dyspepsia	1 (0.8%)	0
Ejection fraction decreased	0	1 (0.7%)
Emesis	0	1 (0.7%)
Endometriosis	1 (0.8%)	0
Extradural haematoma	0	1 (0.7%)
Fever in aplasia	0	1 (0.7%)
Febrile infection	1 (0.8%)	0
Fracture	1 (0.8%)	0
Hepatic enzyme increased	1 (0.8%)	0
Hepatic failure	1 (0.8%)	0
Hepatotoxicity	1 (0.8%)	0
Herpes zoster	1 (0.8%)	0
Hyperglycaemia	0	1 (0.7%)
Hydrocephalus	1 (0.8%)	0
Hypertransaminasemia	1 (0.8%)	0
Intracranial aneurysm	1 (0.8%)	0
Inguinal hernia	0	1 (0.7%)
Ischaemic stroke	0	1 (0.7%)
Leucocytoclastic vasculitis	1 (0.8%)	0
Maternal exposures before pregnancy	1 (0.8%)	1 (0.7%)
Myocardial ischemia	0	1 (0.7%)
Neutropenia	0	1 (0.7%)
Pancreatitis acute	0	1 (0.7%)
Shock haemorrhagic	0	1 (0.7%)
Syncope	1 (0.8%)	0
Tachyarrhythmia	0	1 (0.7%)
Thrombosis	0	1 (0.7%)
Transaminases increased	0	1 (0.7%)
Urinary tract infection	0	1 (0.7%)

Source: Platzbecker et al 2016 Appendix 1

ALT=alanine transaminase, APL= acute promyelocytic leukemia, AST=aspartate transaminase, ATO=arsenic trioxide, ATRA=all-trans retinoic acid.

Table 17: Serious Adverse Events Considered Related to Study Treatments in Study APL0406 Extended Cohort by Preferred Terms and Order of Frequency

Preferred term	ATRA+ATO (N=129)	ATRA+chemotherapy (N=137)
Febrile neutropenia	0	7 (5.1%)
Retinoic acid syndrome	1 (0.8%)	3 (2.2%)
Pneumonia	1 (0.8%)	2 (1.5%)
ALT increased	2 (1.6%)	0
APL differentiation syndrome	2 (1.6%)	0
Bronchopneumonia	0	2 (1.5%)
Electrocardiogram QT prolonged	2 (1.6%)	0
Infection	0	2 (1.5%)
Mucosal inflammation	0	2 (1.5%)
Pericarditis	0	2 (1.5%)
Pyrexia	0	2 (1.5%)
Respiratory failure	1 (0.8%)	1 (0.7%)
Acute respiratory distress syndrome	0	1 (0.7%)
Anal haemorrhage	0	1 (0.7%)
AST increate	1 (0.8%)	0
Bacteraemia	0	1 (0.7%)
Bone marrowfailure	0	1 (0.7%)
Cardiac failure	0	1 (0.7%)
Cerebrovascular accident	1 (0.8%)	0
Cerebral haemorrhage	1 (0.8%)	0
C-reactive protein increased	1 (0.8%)	0
Cholelithiasis	1 (0.8%)	0
Dyspepsia	1 (0.8%)	0
Dyspnoea	1 (0.8%)	0
Febrile infection	1 (0.8%)	0
Fever in aplasia	0	1 (0.7%)
Hepatic enzyme increased	1 (0.8%)	0
Hepaticfailure	1 (0.8%)	0
Hepatotoxicity	1 (0.8%)	0
Herpes zoster	1 (0.8%)	0
Hydrocephalus	1 (0.8%)	0
Hypertransaminasemia	1 (0.8%)	0
Ischaemic stroke	0	1 (0.7%)
Myocardial ischemia	0	1 (0.7%)
Neutropenia	0	1 (0.7%)

Sepsis	0	1 (0.7%)
Thrombosis	0	1 (0.7%)

Source: Platzbecker et al 2016 Appendix 1
ALT=alanine transaminase, APL= acute promyelocytic leukemia, AST=aspartate transaminase, ATO=arsenic trioxide, ATRA=all-trans retinoic acid.

Deaths

Study APL0406

In the original cohort of study APL0406 with 34-month follow-up (n=156 patients), there were fewer deaths reported in the ATRA-ATO group overall than in the ATRA+chemotherapy group (1 vs. 7). One patient in the ATRA-ATO group died from bronchopneumonia associated with H1N1 virus infection during consolidation therapy (Lo-Coco 2013). With the extended follow-up period (median 53 month) no additional deaths were reported in the ATRA-ATO group (Lo-Coco 2015).

In the ATRO+chemotherapy group, 4 patients died during induction therapy (2 from the differentiation syndrome, 1 from ischemic stroke, and 1 from bronchopneumonia) and 3 patients died during consolidation therapy (1 each from haemorrhagic shock, pulmonary embolism, and bronchopneumonia) (Lo-Coco 2013). With the extended follow-up period, post-remission events reported in the ATRA+chemotherapy group included 5 deaths in remission (1 of which was due to secondary leukaemia) (Lo-Coco 2015).

In the extended cohort study, no additional deaths were reported in the induction phase in either of the of the treatment arms (Platzbecker et al 2016). Likewise, no additional deaths in remission were reported compared with the original cohort. This was maintained after a median follow-up of 40.6 months (n=266 patients). The number of deaths in remission therefore was 1 in the ATRA+ATO group (due to H1N1 bronchopneumonia) and 5 in the ATRA+chemotherapy group (1 due to haemorrhagic shock, 1 to pulmonary embolism, 2 to bronchopneumonia, 1 to secondary leukaemia).

Overall, 9 SAEs with a fatal outcome were reported for the extended cohort (1 in the ATRA+ATO group and 8 in the ATRA+chemotherapy group). The patient who died in the ATRA+ATO group had a SAE of pneumonia, which was considered unrelated to either study treatment.
In the ATRA+chemotherapy group, 7 of the 9 patients who died had fatal SAEs reported (1 death due to bronchopneumonia and the death due to secondary MDS were not reported as SAEs):

- 1 case of acute respiratory distress syndrome (ARDS) related to ATRA and idarubicin
- 1 case of respiratory failure and retinoic acid syndrome related to ATRA and idarubicin
- 1 case of ischemic stroke related to ATRA and idarubicin
- 1 case of bronchopneumonia considered related to ATRA
- 1 case of bronchopneumonia considered related to methotrexate
- 1 case of haemorrhagic shock considered unrelated to study treatment
- 1 case of pulmonary embolism considered unrelated to study treatment.

Other significant events

Differentiation syndrome

APL differentiation syndrome is also a well-known side effect of ATO, as indicated in the current SmPC (which reports that 27% of patients treated with ATO have experienced symptoms similar to the APL differentiation syndrome). The SmPC of ATRA (Vesanoid) also reports that differentiation syndrome has

been reported in APL patients in up to 25% in some centres.

Study APL0406

In the original cohort of the APL0406 study, differentiation syndrome, including moderate and severe forms, developed in 15 patients in the ATRA-ATO group (19%) and in 13 patients in the ATRA+chemotherapy group (16%, p-value 0.62). Severe differentiation syndrome occurred in 10 patients (5% to 6% in each group, p-value 0.99) and was fatal in 2 patients assigned to ATRA+chemotherapy (Lo-Coco et al 2013a).

In the extended cohort moderate and severe differentiation syndrome was reported in 16 (13%) and 5 (4%) patients, respectively, in ATRA-ATO group, and in 9 (7%) and 8 (6%) patients in the ATRA+chemotherapy group (p-value 0.38). There were 2 fatal cases in the ATRA+chemotherapy group; these patients were in the original cohort also. In addition there were 4 cases of indeterminate differentiation syndrome in each group (Platzbecker et al 2016).

In the APL0406 study, during the induction phase all patients received prophylactic treatment to prevent differentiation syndrome with prednisone, 0.5 mg/kg/day from day 1 until the end of induction. At the earliest manifestations of suspected differentiation syndrome (e.g., unexplained respiratory distress), and prior to development of a fulminant syndrome, the following measures were to be immediately undertaken:

• temporary discontinuation of ATRA-ATO treatment.

•prompt initiation of dexamethasone 10 mg intravenously (IV) 12-hourly until disappearance of symptoms and signs, and for a minimum of 3 days.

•furosemide when clinically required.

As soon as the signs and symptoms had resolved, treatment with ATRA and/or ATO was to be resumed at 50% of the previous dose during the first 7 days in APL0406 (4 days in AML17). Thereafter, in the absence of worsening of the previous toxicity, ATRA and/or ATO was to be resumed at full dosage.

Study AML17

In Study AML17, differentiation syndrome was reported in 21% (38/178) of low- and intermediate-risk patients (23 patients in the ATRA+ATO group and 15 patients in the ATRA+chemotherapy group) and in 30% (17/57) of patients of the high-risk group (7 patients in the ATRA-ATO group and 10 patients in the ATRA+chemotherapy group). The difference between treatment groups was not significant (p-value 0.38).

No prophylaxis was administered for differentiation syndrome in Study AML17.

QTc Prolongation and cardiac toxicity

QTc prolongation is a well-documented side effect of ATO that can lead to potentially fatal torsade de pointes-type ventricular arrhythmia. In clinical trials, 40% of patients treated with ATO experienced at least 1 QTc interval prolongation greater than 500 milliseconds. Prolongation of QTc was observed between 1 and 5 weeks after ATO infusion, and then returned to baseline by the end of the 8 weeks after ATO infusion.

The current SmPC notes that ATO can cause QT interval prolongation and complete atrioventricular block. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging medicinal products, a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics or amphotericin B, or other conditions that result in hypokalaemia or hypomagnesaemia. According to the current SmPC, a 12-lead ECG is recommended prior to initiating ATO, and serum electrolytes and creatinine must be assessed. Patients with risk factors of QTc prolongation or risk factors of torsade de pointes should be monitored by continuous cardiac ECG monitoring. During therapy with ATO, serum potassium should be kept above 4

mEq/L and magnesium above 1.8 mg/dL.

Study APL0406

In the original cohort of the APL0406 study, prolonged QTc interval occurred in 12 patients in the ATRA-ATO group (16%) and in none of the patients in the ATRA+chemotherapy group (p-value <0.001) (Lo-Coco et al 2013).

In the extended cohort of the APL0406 study, there were 4 additional cases of prolonged QTc interval meaning overall prolonged QTc interval occurred in 15 patients in the ATRA-ATO group (11%) and 1 in the ATRA+chemotherapy group (0.8%) (p-value <0.0001) (Platzbecker et al 2016).

As shown in Table 18, QTc prolongation is primarily observed during the induction phase:

Table 18: QTc Prolongation in Study APL0406 Extended Cohort by Cycle

Toxicity	**ATRA+ATO N=129**	**ATRA+CHEMO N=137**	**P-value**
QTcprolongation[a]			
Induction	11 (9%)	1 (1%)	0.002
1st consolidationcycle	3 (2%)	0	0.11
2nd consolidationcycle	3 (2%)	0	0.11
3rd consolidationcycle	2 (2%)	0	0.23

Source: Platzbecker et al 2016, Table 3

[a] QTc prolongation was defined according to the NCI-CTCAE as an increase of >450 msec in males and >460 msec in females.

ATO=arsenic trioxide, ATRA=all-trans retinoic acid, CHEMO=chemotherapy, ITT=intent-to-treat, QTc=corrected QT

Note: Data are presented for ITT analysis set with evaluable data

There was no single case reported with life-threatening cardiac arrhythmias. In 1 of 15 patients with prolonged QTc interval, ATO was permanently discontinued and the patient went off protocol. QTc prolongation is essentially seen during the induction phase. No information on the outcome of individual patients with QTc interval prolongation in the APL0406 study is available.

Study AML17

In Study AML-17, QTc prolongation was not reported separately from cardiac toxicity (Burnett et al 2015). Grade 3 or 4 cardiac toxicity was more common in patients treated with ATRA+chemotherapy during course 1 (induction), but overall cardiac toxicity was higher in the ATRA-ATO treatment group.

Hepatotoxicity

Study APL0406

In the original cohort of the Study APL0406, ATRA-ATO was associated with a higher proportion of patients with raised liver transaminases (Lo-Coco et al 2013a). Grade 3 or 4 increases in liver enzymes were significantly more frequent in the ATRA-ATO group than for the ATRA chemotherapy group, reported for 63% of patients treated with ATRA-ATO (43/68) and 6% treated with ATRA+chemotherapy (4/69). There were no cases of acute hepatic failure or mortality attributable to hepatic toxicity. The increases in liver enzymes was in only a minority of cases associated with either bilirubin or alkaline phosphatase increase and resolved in all cases with temporary discontinuation of ATO, ATRA, or both, or with temporary discontinuation of chemotherapy during the maintenance phase.

Significant Grade 3-4 elevations of liver function tests were significantly more frequent in the ATRA-ATO group (44%) compared with the ATRA+chemotherapy group (3%) (p-value ≤0001) across all treatment cycles.

In the extended cohort, resolution of the hepatic toxicity was confirmed in all cases upon temporary discontinuation of ATO and/or ATRA or of low-dose chemotherapy during maintenance (Platzbecker et al 2016). Grade 3-4 increase in liver transaminases occurred in 44% of the ATRA-ATO group and in 3% of the ATRA+chemotherapy group (p-value <0.0001) across all treatment cycles. Grade 3-4 hepatotoxicity was essentially seen during the induction phase in the ATRA-ATO group (40%), while no cases were reported anymore during the last consolidation cycle (see Table 19).

Table 19: Hepatic Toxicity in Study APL0406 Extended Cohort by Cycle

Toxicity	ATRA+ATO N=129	ATRA+CHEMO N=137	P-value
Hepatictoxicity			
Induction	51 (40%)	4 (3%)	<0.0001
1st consolidationcycle	5 (4%)	1 (1%)	0.11
2nd consolidationcycle	1 (1%)	0	0.49
3rd consolidationcycle	0	0	

Source: Platzbecker et al 2016 Table 3
[a] QTc prolongation was defined according to the NCI-CTCAE as an increase of >450 msec in males and >460 msec in females.
ATO=arsenic trioxide, ATRA=all-trans retinoic acid, CHEMO=chemotherapy, ITT=intent-to-treat, QTc=corrected QT.
Note: Data are presented for ITT analysis set with evaluable data

AML17

Also in the AML17 study, the ATRA-ATO group showed an increase in Grade 3 and 4 transaminases while no similar increase was noted with regard to bilirubin (Burnett et al 2015). After course 1 in Study AML17, Grade 3 or 4 raised ALT was reported for 25% of patients in the ATRA-ATO group (27/109) compared with 10% in the ATRA+chemotherapy group (11/108). Grade 3 or 4 raised AST was reported for 4% of patients in each group (2/46 for ATRA-ATO 2/51 for ATRA+chemotherapy) and Grade 3 or 4 raised bilirubin was more frequent in the ATRA+chemotherapy group than in the ATRA+ATO group, reported for 1% of patients in the ATRA+ATO group (1/110) compared with 7% in the ATRA+chemotherapy group (8/114). After course 2, no Grade 3 or 4 raised ALT or bilirubin was reported. Grade 3 or 4 raised AST was reported for 2% of patients in each group (2/93 for ATRA+ATO and 2/98 for ATRA+chemotherapy).

In conclusion, ATRA+ATO leads to increase in Grade 3 and 4 transaminases without an increase in bilirubin. In all cases this liver toxicity was reversible with temporarily discontinuation of ATRA, ATO or both, and no cases of hepatic failure or death due to hepatic toxicity were reported.
The MAH sought Expert Review Regarding Hepatotoxicity with ATO from Professor Minotti Professor of Clinical Pharmacology, University Campus Bio-Medico of Rome. A summary of the report's conclusions are provided below.
• Mechanism of hepatotoxicity is multifactorial and only in part understood, but oxidative stress plays an important role.
•Hepatotoxicity from a single agent shows noticeable interindividual variability that is most probably related to genetic polymorphism.
•The higher prevalence of Grade 3-4 liver enzyme increases in the ATRA+ATO treatment group in the APL0406 study suggests that ATO and ATRA engage in some kind of toxic synergism causing more oxidative stress.
•However, discontinuing drug and re-introducing it does not result in recurring increase in liver enzymes which may be the result of continued consumption of retinoid stores by ATO.
•The reversibility and rechallengeability of APL patients with ATRA+ATO suggests that arsenic accumulation and fixation of hepatic damage is unlikely.

Secondary Leukaemias and MDS

No cases of secondary leukemia have been reported in either study with ATRA-ATO.

In the extended cohort of the APL0406 study, after a median follow-up of 40.6 months, there were no cases of secondary leukaemias in the ATRA-ATO group while there were 2 cases in the ATRA+chemotherapy group (Platzbecker et al 2016).

In Study AML17, there were no reports of treatment-related MDS or AML in the ATRA-ATO group compared with 3% in the ATRA+chemotherapy group (HR 0.15 [95% CI: 0.003 to 7.48] p-value 0.34) (Burnett et al 2015).

Hyperleukocytosis

Hyperleukocytosis (WBC count $\geq 10\times10^9$/L) is also a well-known side effect of ATO as mentioned in the current SmPC for treatment of relapsed/refractory APL.

In the original cohort of Study APL0406, WBC count $>10\times10^9$/L developed during induction therapy in 47% (35/74) of patients in the ATRA-ATO group. As expected the incidence of hyperleukocytosis in the ATRA+chemotherapy group was lower (24% (19/79) (p-value 0.007) (Lo-Coco et al 2013).

For the extended cohort with 40.6 months median follow-up, hyperleukocytosis was reported for 43% of patients in the ATRA-ATO group. All cases were managed with hydroxyurea.In study APL0406, in fact, hydroxyurea was permitted in patients who developed a WBC count > 10 $x10^9$/L after initiation of therapy. Hydroxyurea was discontinued when WBC count returned to <10 $x10^9$/L.

No data are available regarding hyperleukocytosis in AML17 although it is reported that 7 low- or intermediate- risk patients were given gemtuzumabozogamicin for a rising WBC count.

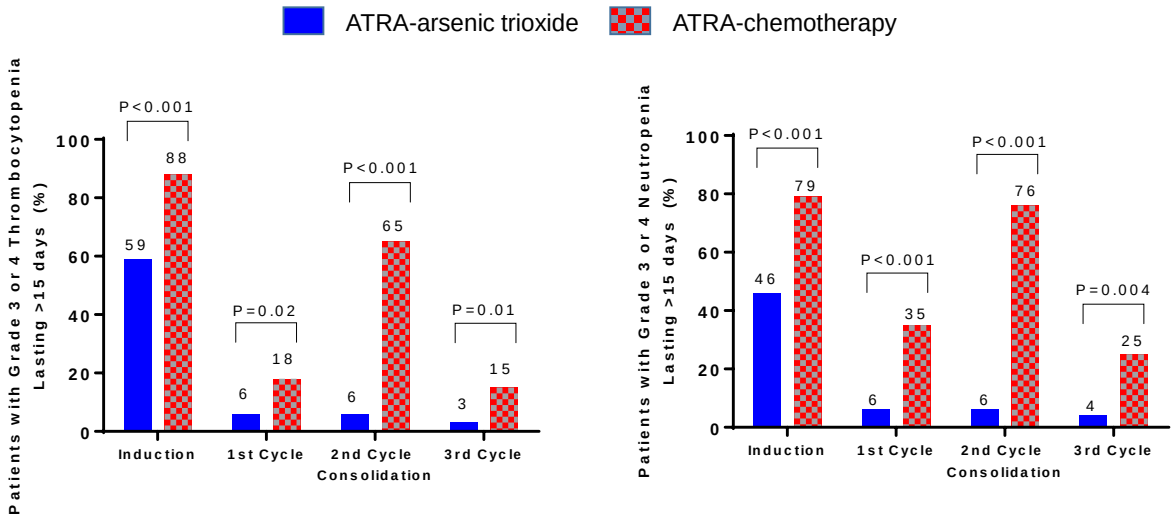
Myelosuppression

In Study APL0406 the dose of ATO and/or ATRA was to be reduced in the event of significant myelosuppression defined as: absolute neutrophil count (ANC) <1x10^9/L and/or platelets <50 x109/L for >5 weeks after the start of a course. During the maintenance phase, the doses of methotrexate and 6-mercaptopurine had to be modified as a function of the peripheral blood counts as follows:

- WBC between 2.5 and 3.5x10^9/L: dose reduction by 50%.
- WBC <2.5 x 10^9/L: temporary discontinuation of maintenance.

Myelosuppression was significantly reduced in the ATRA-ATO group compared with the ATRA+chemotherapy group in Study APL0406. In the original cohort of Study APL0406 (Lo-Coco et al 2013) and the extended cohort (Platzbecker et al 2016), Grade 3 or 4 neutropenia lasting >15 days and Grade 3 or 4 thrombocytopenia lasting >15 days were significantly more frequent both during induction therapy and after each consolidation course in the ATRA+chemotherapy group than in the ATRA-ATO group (see Figure 14).

Figure 14: Study APL0406: Haematological Toxic Effects in Original Cohort, 34-month Follow-up



Source: Lo-Coco et al 2013 Figure 4
ATRA=all-trans retinoic acid.

No data are available regarding neutropenia/thrombocytopenia in AML17, however, patients in the ATRA-ATO group had significantly less requirement for most aspects of supportive care than did those in the ATRA+chemotherapy group. Over the first 2 courses of treatment, ATRA-ATO was associated with an average of 7.4 fewer days in the hospital, 4.5 fewer units of blood, 4.3 fewer units of platelets, and 10.7 fewer days of IV antibiotics. A summary of the supportive care required is presented in Table 20.

Table 20: Study AML17: Summary of Supportive Care Required by Treatment Course and Treatment Group

Type of Supportive Care	Course	ATRA+ATO	ATRA+CHEMO	p-value
Blood (meanunits)	1	5.9	9.5	<0.0001
	2	0.1	1.0	<0.0001
Platelets (meanunits)	1	8.8	12.8	<0.0001
	2	0	0.3	0.0001
Antibiotics (meandays)	1	9.3	19.2	<0.0001
	2	0.9	1.7	0.4
Hospitalization (meandays)	1	27.3	33.3	<0.0001
	2	6.5	7.9	0.01
Hospitalization (mediandays)	1	25	34	ND
	2	1	5	ND

Source: Burnett et al 2015 Table 5
ATO=arsenic trioxide, ATRA=all-trans retinoic acid, CHEMO=chemotherapy, ND=not determined

Laboratory findings

Not available

Safety in special populations

Age

In the original cohort of Study APL0406, 35 patients aged between 60 and <71 years received treatment; 16 were assigned to ATRA+ATO and 19 to ATRA+chemotherapy. No patients died in the group receiving ATRA+ATO. In the group receiving ATRA+chemotherapy, 3 patients died (1 during induction from the differentiation syndrome and 2 during consolidation from pulmonary embolism and bronchopneumonia) (Lo-Coco et al 2013b).

No description of older patients was included in the AML17 publication (Burnett et al 2015).

Special Populations from the Literature

Only 1 study was identified in patients aged ≤15 years with newly diagnosed APL. This study reported leukocytosis (68%) as the most common ATO-related toxicity, with other ATO-related toxicities being minimal and transient. Two early deaths occurred from intracranial haemorrhage. Post-remission ATO therapy continued for 3 years; the most common side effect was ATO-induced neutropenia. No chronic arsenic toxicity or second malignancies were found during the follow-up period, and arsenic retention was not significant in patients off treatment more than 24 months (Zhou et al 2010).

Based on a study in newly diagnosed APL patients aged≥60 years, Zhang et al 2013 reported that single-agent ATO was particularly suitable for elderly APL patients who are not tolerant to conventional chemotherapy. The side effects of ATO were mild and manageable, even for elderly patients with antecedent cardiac, hepatic, and/or renal diseases. Also, as a result of the absence of myelosuppressive effects during post-remission therapy, ATO treatment could not only shorten the duration of hospitalization but also avoid deaths from infection in HCR, prolonging the survival time of the elderly patients.

Safety related to drug-drug interactions and other interactions

Not available

Discontinuation due to adverse events

In Study APL0406, 1 patient in the ATRA-ATO group was taken off protocol during induction due to medical decision and 1 after induction therapy owing to a toxic effect (repetitive tachycardia). In the ATRA+chemotherapy group, 1 patient did not receive consolidation therapy because of a cardiac toxic effect and loss to follow-up. Another patient went off protocol after consolidation therapy owing to withdrawal of consent, major protocol violation, and a toxic effect and 2 patients did not complete maintenance therapy because of prolonged myelosuppression (>50 days).

In the extended cohort of APL0406, for 1 patient who started induction in the ATRA+ATO group the assigned treatment was terminated early due medical decision (detection of severe QTc prolongation and electrolytes abnormalities at day+3). Likewise 1 patient in the ATRA+chemotherapy group had induction treatment discontinued due to medical decision (unknown reason).

Four patients in the ATRA-ATO group went off protocol before the bone marrow assessment after third consolidation due to toxicity and medical decision. In the ATRA+chemotherapy group, 6 patients did not undergo bone marrow evaluation after third consolidation because toxicity.

No information is available from Study AML17 on the numbers of patients discontinuing ATRA+ATO due to safety reasons although it was noted that 1 patient withdrew from the trial during course 1 of treatment because of fungal chest complications and during course 2, 2 patients in the ATRA+ATO arm were not given ATO because of QTc prolongation. No information is available with regard to the risk category of

these patients (high-, intermediate- or low-risk APL).

Both study protocols required modification to study drugs in the event of differentiation syndrome, pseudotumour cerebri, QT prolongation, and hepatotoxicity. Additionally, in Study APL0406, dose modifications were recommended in the event of other non-haematological toxicities of Grade 2 and above, and myelosuppression. Any Grade 3-4 toxicity unresponsive to dose reduction was grounds for treatment-withdrawal in Study APL0406, and in Study AML17 severe neurological toxicity required study drug discontinuation.

No details were available regarding the numbers of patients requiring dose modification or delays for Study APL0406.

During Course 1 in study AML17, a higher proportion of patients in the ATRA-ATO group had treatment modifications compared with the ATRA+chemotherapy group. During course 2 in Study AML17, 9 patients on ATRA+chemotherapy had treatment modifications or delays, including 1 who switched to ATRA-ATO (clinician's decision), whereas 18 patients in the ATRA-ATO group had dose modifications or delays, including 6 who switched to idarubicin (clinician's decision). Two patients in the ATRA-ATO group were not given ATO because of QTc prolongation.

Post marketing experience

Arsenic trioxide (TRISENOX) has been approved in the US since 25 September 2000 and in Europe (EU; centralized procedure) on 5 March 2002 for the treatment of relapsed/refractory APL. At the time of this MAA products containing active substance ATO have been registered by the MAH in 46 countries globally.

The MAH has received reports containing 2048 adverse reactions from post-marketing reporting sources, including non-serious solicited reports.

Throughout the marketing experience of ATO, the most common adverse reactions of greater than 5% frequency in patients with relapsed or refractory APL are from the following MedDRA SOCs: Investigations (18.3%), General Disorders and Administration Site Conditions (8.6%), Blood and Lymphatic system Disorders (8.8%), Respiratory, Thoracic, and Mediastinal Disorders (7.7%), Nervous System Disorders (6.6%), Cardiac Disorders (6.2%), and Gastrointestinal Disorders (5.6%).

Significant ADRs that require special mention to prescribers include QT prolongation, APL differentiation syndrome, leukocytosis, anaemia, thrombocytopenia, neutropenia, gastrointestinal reactions (nausea, vomiting, diarrhoea, and abdominal pain), fatigue, oedema, dyspnoea, cough, rash, itching, AST increased, peripheral neuropathy, and headaches.

Systematic Literature Review of Safety

A systematic literature review was conducted with the objective of identifying all published clinical studies in first-line APL, where ATO was included in any phase of the treatment regimen (see the Analysis performed across trials Section above for additional details).

Two studies involved high- and low-risk APL patients treated with ATRA-ATO (Estey et al 2006 and Ravandi et al 2009). In the Estey study, elevations in ALT or AST were seen in 17 patients, all asymptomatic and unaccompanied by rises in serum bilirubin. In none of these 17 patients was ATRA or ATO discontinued. Five patients had toxicity that led to discontinuation of ATO, 3 with arrhythmias, 1 with QTc prolongation, and 1 with peripheral neuropathy. In the Ravandi study, 2 out of 82 patients had Grade 3 increase in liver enzymes and 3 patients had Grade 3 cardiac arrhythmias. One patient had a Grade 4 myocardial infarction. Both ATRA+ATO studies included low- as well as high-risk patients. The number of patients included in the studies is low. Safety results are in line those of the APL0406 and the AML17

studies.

All other studies involved single agent ATO. Amongst the studies using ATO alone there were 2 studies including children (Zhou et al 2010 conducted a study in 19 paediatrics and Aznab et al 2015 studied paediatrics and adults, they reported that 60% of their patients were aged 12 to 24 years. Both of these studies report long-term follow-up information with no long-term toxicity nor secondary malignancies.

One study was conducted in patients aged 60 years and above (Zhang et al 2013). Side effects were not different with 21% of patients showing liver toxicity and 36% QTc prolongation. All non-hematologic AEs such as ECG abnormalities, GI reactions, liver dysfunction, and oedema were all manageable and reversible. Other non-hematologic AEs were all transient and mild, and no further management was required

Multiple studies (Alimoghaddam et al 2006, Ghavamzadeh et al 2011, Mathews et al 2006a, Mathews et al 2006b) showed liver toxicity to a variable extent. In all cases it concerned essentially increase in liver transaminases without increase in bilirubin. In most cases the liver toxicity was reversible. There was 1 patient in the Mathews study who developed Grade 2 hepatotoxicity during maintenance who had persistent asymptomatic Grade 1 transaminitis 6 months after completion of therapy.

These studies confirmed the fact that hepatotoxicity concerns elevation of transaminases alone that is reversible in all cases. It also confirmed the low cardiotoxicity rate.

Finally, the Eghtedar et al 2015 publication compared retrospectively the incidence of secondary leukemias in patients who received either ATRA+chemotherapy or ATRA+ATO (17% versus 2%, respectively). They concluded that treatment of patients with APL using the non-chemotherapy regimen of ATRA+ATO was not associated with a higher incidence of secondary cancers adjusted for unit time of exposure vs ATRA+chemotherapy regimen.

2.5.1. Discussion on clinical safety

Trisenox has been approved in the EU for the single-agent treatment of relapsed/refractory acute promyelocytic leukemia (APL) since 2002. Its safety profile, based on the results from the clinical studies conducted in the relapsed/refractory APL clinical program and on the post-marketing data obtained by the MAH since 2000, is well characterised. Overall, the main toxicity associated with ATO treatment is: leukocytosis and DS, QT prolongation and arrhythmias (often exasperated by concomitant electrolytic alterations), peripheral neuropathy, hepatotoxicity (mainly in the form of transaminitis), myelosuppression and gastrointestinal disorders (i.e. diarrhoea and nausea).

On the contrary, safety information regarding the proposed ATRA-ATO combination for the first line treatment of APL is currently limited, and due to the potential synergistic toxicity of ATRA and ATO (i.e. on hepatotoxicity), no direct extrapolation of safety data observed with single-agent ATO is considered adequate.

Safety data and information regarding the overall exposition to the proposed ATRA-ATO combination, the actual adverse events (AEs) incidence profile, the toxicity profile and, most of all, the long-term toxicity of ATRA-ATO is very limited. In this regard, if only those patients actually exposed to the same ATRA-ATO regimen as the one proposed for MA are considered, the safety database would comprise only 129 subjects (i.e. the patients who received ATRA-ATO across all study APL0406 cohorts). A post-authorisation long term safety cohort study in APL patients treated with Trisenox will conducted by the MAH in order to explore further the long-term safety of ATRA+ATO in newly diagnosed low to intermediate risk APL patients in a real-world clinical practice setting (see Risk Management Plan).

In study APL040695 SAEs were reported, 43 for the ATRA-ATO arm and 52 for the ATRA+chemotherapy

arm. Overall, the safety profile of the ATRA-ATO combination, as reflected by the provided SAEs, is consistent with the specific toxicities of ATRA and ATO.

Compared with ATRA+chemotherapy, an advantage with ATRA-ATO is mainly observed in the lower rates of infections/infective complications. In fact, despite a similar rate of pneumonia+bronchopneumonia, febrile neutropenia, fever and pyrexia were observed in 11 vs. 3 subjects with ATRA+chemotherapy and ATRA-ATO respectively. Moreover, bacteraemia and sepsis were only reported for patient treated with the AIDA regimen.

ATRA-ATO was also superior to the AIDA regimen with respect to other common chemotherapy-related symptoms (as supported by the lower rates of SAEs in the GI and general disorders SOCs observed with ATRA-ATO and the lower myelotoxic potential).

Moreover, considering the biologic characteristics of APL, the reduced rates of haemorrhagic (1 haemorrhagic SAE reported with ATRA-ATO vs. 3 SAEs with the AIDA regimen) and thromboembolic events (1 vs. 4 thromboembolic SAEs reported for ATRA-ATO and AIDA, respectively) further support the better disease control achieved with ATRA-ATO.

Safety data regarding on-study deaths and deaths in remission from study APL0406 also favoured the ATRA-ATO regimen. Only 1 patient experienced a fatal AE during treatment with ATRA-ATO (H1N1 pneumonia), while 4 subjects died during induction in the ATRA+chemotherapy arm. Most interestingly, with the exception of 1 patient who experienced a fatal AE of bronchopneumonia (which is an expected complication of cytotoxic treatments in leukaemia), the other induction deaths observed in the AIDA arm (2 patients died because of differentiation syndrome related complications, and 1 of ischemic stroke) might suggest an inferior disease control with chemotherapy. Deaths in remission data, as emerge from study APL0406 (1 death in remission in the ATRA-ATO arm vs. 5 in the AIDA arm, respectively), also support the overall favourable safety profile of ATRA-ATO.

In both studies APL0406 and AML17, the incidence of DS was higher in the ATRA-ATO group compared to patients treated with AIDA (i.e. in the extended cohort of study APL046 the DS rates were 13% and 7% for ATRA-ATO and ATRA+chemotherapy, respectively). However, the overall incidence of DS in the provided trials (19% in study APL0406 and 21% in AML17, respectively) was within the ranges expected with chemotherapy regimens in the first line-treatment (maybe because of the additional preventive measures employed in the APL0406 study [i.e. prophylactic corticosteroids] and the exclusion of high-risk patients), and no significant differences were observed with respect to severe DS rates. Overall, it was concluded that, with the mandatory prophylaxis with corticosteroids as employed in study APL0406 (SmPC, section 4.4.) no concerns for a significant increase in the incidence or severity of DS with ATRA-ATO are present.

QTc prolongation is also a well-documented side effect of ATO that can lead to potentially fatal torsade de pointes-type ventricular arrhythmia. The available data clearly showed that the risk of QTc prolongation is significantly higher with the ATRA-ATO combination. On the other hand, the combination with ATRA was confirmed not to increase or modify in any way the known risk of QTc prolongation with ATO. In fact, approximately 11-16% of patients treated with ATRA-ATO in pivotal study APL0406 presented a QTc prolongation, mainly during induction, and no patient developed severe arrhythmias. Moreover, rates of ischemic disease and cardiac failure events were higher in the ATRA+chemotherapy arms.

Although hepatotoxicity is common with ATO (included in SmPC), the combination with ATRA seems to significantly increase its frequency and severity: a grade 3-4 transaminases increase was observed in 44% of the patients who received ATRA-ATO in study APL0406 compared to 3% of patients treated with ATRA+chemotherapy. However, the absence of cases of acute hepatic failure or mortality attributable to ATRA-ATO induced hepatic toxicity is reassuring. Moreover, hepatotoxicity proved to be reversible if ATRA and/or ATO are discontinued. As a safety measure, information on Grade 3-4 hepatotoxicity has been included in section 4.4 of the SmPC.

It is noted, however, that only 25% of patients treated in the ATRA-ATO arm of study AML17 developed a grade 3-4 hepatotoxicity, compared to 44% in study APL0406. These data could suggest that the alternative ATRA-ATO regimen employed in the supportive study might be better tolerated. It is acknowledged that, at present, efficacy and safety data are too limited to support the use of the AML17 ATRA-ATO regimen, however further data are requested to investigate the efficacy and safety profile of this alternative regimen. The MAH will obtain data from two pre-existing ongoing registries (the NAPOLEON registry from the German AML Intergroup and the French APL Study Group registry) to further evaluate the benefit/risk of different ATRA-ATO administration regimens (see risk management plan).

Leukocytosis is another well-known AE with ATO, and the higher rates of patients with WBC count > 10 $x10^9$/L after treatment initiation observed in the ATRA-ATO arm in study APL0406 is not therefore unexpected.

It has been noticed that the cumulative dose of ATO received in the ATRA-ATO regimen proposed for this application (21 mg/kg) is significantly higher than the one calculated for the already authorised relapsed/refractory use (11.3 mg/kg) or administered in the alternative ATRA-ATO regimen in study AML17 (17 mg/kg). Even though the differences between chronic and acute arsenic intake are acknowledged, the cumulative ATO exposure with the proposed ATRA-ATO regimen (i.e. 1470 mg for a 70 Kg adult man) is also significantly higher than the calculated annual intake of arsenic which is considered to be possibly harmful by the WHO (max 54.77 mg). The carcinogenic activity of ATO is already included as a potential risk in the RMP. Of note, the new few long-term data from both studies APL0406 and AML17 point toward a reduced risk of secondary leukaemia/MDS with ATRA-ATO. However, in light of the high cumulative ATO dose administered in the proposed first-line regimen, the MAH will investigate/control the long-term carcinogenic risk of ATO as part of the post-authorisation long term safety cohort study in APL patients treated with Trisenox designed to explore further the long-term safety of ATRA+ATO in newly diagnosed low to intermediate risk APL patients in a real-world clinical practice setting (see Risk Management Plan).

2.5.2. Conclusions on clinical safety

Overall, although the available safety data are limited, the toxicity profile of ATO in the proposed ATRA-ATO combination appears sufficiently characterized. All known ATO-specific toxicities are confirmed (i.e. differentiation syndrome, QTc prolongation and leukocytosis), and their incidence appears overall unmodified by the co-administration of ATRA.
Compared to ATRA+chemotherapy, an advantage was observed with ATRA-ATO in terms of myelotoxicity, infective risk and thromboembolic/haemorrhagic complications. Moreover, a positive trend toward a reduction in remission deaths and in the risk of secondary leukaemia/MDS has also been observed.
Hepatotoxicity, on the contrary, is increased with the ATRA-ATO combination due to a possible synergistic toxic effect of ATRA and ATO. However, the observed hepatic damage is reversible with the suspension of ATO and/or ATRA, and no additional safety measures beyond a warning on the SmPC are considered needed.
In conclusion, the toxicity of the proposed ATRA-ATO combination is considered manageable.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 1.0 (dated 03 March 2016) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report dated 17 June 2016.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the RMP version 1.3 (dated 11 October 2016) with the following content:

Safety concerns

Table 21*: Summary of the Safety Concerns*

Important identified risks	• Leukocyte Activation Syndrome (APL Differentiation Syndrome) • Blood dyscrasias (including hyperleukocytosis) • Electrocardiogram (ECG) Abnormalities such as QT/QTc interval prolongation and complete atrioventricular block • Liver enzyme elevation
Important potential risks	• Embryotoxic and teratogenic effect in pregnancy • Serious adverse reactions in nursing infants • Carcinogenicity
Important potential Drug Interaction	Potential interactions of arsenic trioxide with: • Drugs known to cause hypokalaemia or hypomagnesaemia • Drugs known to cause QT/QTc prolongation
Missing information	• Influence on fertility • Use in paediatric patients under the age of 4 years • Use in patients with renal impairment • Use in patients with hepatic impairment • Long-term safety

Pharmacovigilance plan

Table 22: On-going and Planned Additional PhV Studies / Activities in the Pharmacovigilance Development Plan

Study / Activity Type, Title and Category (1-3)	**Objectives**	**Safety Concerns addressed**	**Status (planned, started)**	**Date for Submission of Interim or Final Reports (planned or actual)**
PASS; Study Title: A post-authorisation long term safety cohort study in acute promyelocytic leukaemia (APL) patients treated with Trisenox (Category 3)	To assess the long-term safety of ATRA+ATO in newly diagnosed low to intermediate risk APL patients in a real-world clinical practice setting.	Long-term safety Carcinogenicity	Planned	Interim report 1: 4Q 2019 Interim report 2: 4Q 2021 Final report: 2Q 2023

Risk minimisation measures

Table 23: ***Summary table of the risk minimisation measures***

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT IDENTIFIED RISKS		
Leukocyte Activation Syndrome (APL Differentiation Syndrome)	Labelling information (SmPC Sections 4.4 and 4.8) and PIL. Prescription only medicine.	None
Blood dyscrasias (including hyperleukocytosis)	Labelling information (SmPC Sections 4.4 and 4.8) and PIL. Prescription only medicine.	None
Electrocardiogram (ECG) Abnormalities such as QT/QTc interval prolongation and complete atrioventricular block	Labelling information (SmPC Sections 4.4 and 4.8) and PIL. Prescription only medicine.	None
Liver enzyme elevation	Labelling information (SmPC Sections 4.2 and 4.8) and PIL. Prescription only medicine.	None
IMPORTANT POTENTIAL RISKS		
Embryotoxic and teratogenic effect in pregnancy	Labelling information (SmPC Section 4.6) and PIL. Prescription only medicine.	None
Serious adverse reactions in nursing infants	Labelling information (SmPC Section 4.6) and PIL. Prescription only medicine.	None
Carcinogenicity	Labelling information (SmPC Sections 4.4 and 5.3). Prescription only medicine.	None
Potential interactions of arsenic trioxide with: • Drugs known to cause hypokalaemia or hypomagnesaemia • Drugs known to cause QT/QTc prolongation	Labelling information (SmPC Section 4.5) and PIL. Prescription only medicine.	None
MISSING INFORMATION		
Influence on fertility	Labelling information (SmPC Section 4.6) and PIL. Prescription only medicine.	None
Paediatric patients < 4 years old	Labelling information (SmPC Sections 4.2 and 5.2) and PIL. Prescription only medicine.	None
Use in patients with renal impairment	Labelling information (SmPC Sections 4.2, 4.4 and 5.2). Prescription only medicine.	None
Use in patients with hepatic	Labelling information (SmPC Sections 4.2,	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
impairment	4.4 and 5.2). Prescription only medicine.	
Long-term safety	None proposed	None

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4., 4.8 and 5.1 of the SmPC have been updated. Particularly, a new warning with regard to hepatotoxicity has been added to the product information. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

• Changes to the PL were considered not affecting readability and changes have been written in very similar writing style and complexity as in the previously approved variation II/042 (approved 27th June 2012).

3. Benefit risk assessment

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH applied for the first line acute promyelocytic leukaemia (APL)

3.1.2. Available therapies and unmet medical need

Acute promyelocytic leukemia is a potentially life threatening rare subtype of acute myeloid leukemia (AML) characterized by the presence of the Promyelocytic Leukemia Retinoic Acid Receptor Alpha (PML-RARα) fusion transcript. The annual incidence of APL in the European Union (EU) is reported to be 0.14/100,000 (Sant et al 2010).

The disease is highly curable with improve treatment care. The treatment for APL as changed over the years and has progressively increased the CR. The first-line treatment of APL is currently based on the combination of all-trans retinoic acid (ATRA) with chemotherapy (mainly anthracyclines) during both treatment induction and consolidation (Lo-Coco et al 2010). Standard treatment currently provides a CR

of 90% and approximately 80% cures, but 9-10% of patients have an early death, 5% death in patients in CR, 5-10% patients relapse and 1-2% of patients developing MDS (myelodysplastic syndrome) and AML (acute myeloid leukemia). Patients having an early death or death in CR are mainly older patients because of their lower tolerability to chemotherapy.

3.1.3. Main clinical studies

The MAH has submitted the results from two clinical studies (pivotal phase III study APL0406 and supportive phase III study AML17) comparing the efficacy and safety of ATRA-ATO vs. an AIDA-like regimen in first-line low- to intermediate-risk APL patients.

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.

Efficacy results in low/intermediate risk patients (n=178) from the supportive study AML17 are consistent with those observed in the pivotal study (4-year EFS rate 92% vs. 71% in the ATRA-ATO and ATRA-chemotherapy groups respectively, HR=0.34, p=0.008; 4-year OS rate 95% vs. 90%, HR=0.47, p=0.17).

3.3. Uncertainties and limitations about favourable effects

Not applicable.

3.4. Unfavourable effects

Overall, the safety profile of the ATRA-ATO combination, as emerged from the available data, is consistent with the specific toxicities of ATRA and ATO. Moreover, safety data regarding on-study deaths and deaths in remission from study APL0406 are in favour of the ATRA-ATO regimen.

The incidence of differentiation syndrome (a potentially-lethal complication with differentiating agents) was higher in the ATRA-ATO group compared to patients treated with AIDA (in the extended cohort of study APL046 the DS rates were 13% and 7%, respectively); however no significant differences were observed with respect to severe DS rates.

QTc prolongation is also a well-documented side effect of ATO that can lead to potentially fatal arrhythmias. The available data clearly show that the risk of QTc prolongation is significantly higher with the ATRA-ATO combination. In fact, approximately 11-16% of patients treated with ATRA-ATO in pivotal study APL0406 presented a QTc prolongation, mainly during induction. On the other hand, the combination with ATRA was confirmed not to increase or modify in any way the known risk of QTc prolongation with ATO.

Leukocytosis is another well-known AE with ATO, and the in study APL0406 higher rates of patients with WBC count > 10 x109/L after treatment initiation were observed in the ATRA-ATO arm compared to ATRA+chemotherapy (47% vs. 24% in the original cohort). Hydroxyurea was needed in order to control leukocytosis.

Although hepatotoxicity is also known to be common with ATO, the combination with ATRA seems to significantly increased its frequency and severity: a grade 3-4 transaminases increase was observed in 44% of the patients who received ATRA-ATO in study APL0406 compared to 3% of patients treated with ATRA+chemotherapy. However, no cases of acute hepatic failure or mortality attributable to ATRA-ATO induced hepatic toxicity were observed, and hepatotoxicity proved to be reversible if ATRA and/or ATO are discontinued.

With respect to infections/infective complications a similar rate of pneumonia+bronchopneumonia was observed in the ATRA-ATO and ATRA+chemotherapy arms. However, febrile neutropenia, fever and pyrexia rates were higher with ATRA+chemotherapy than with ATRA+ATO (11 vs. 3 subjects). Moreover, bacteraemia and sepsis were only reported for patient treated with the AIDA regimen.

Overall, lower rates of SAEs in the GI and general disorders SOCs were observed with ATRA-ATO, and its myelotoxic potential was also reduced compared to ATRA+chemotherapy.

The rates of haemorrhagic (1 haemorrhagic SAE reported with ATRA-ATO vs. 3 SAEs with the AIDA regimen) and thromboembolic events (1 vs. 4 thromboembolic SAEs reported for ATRA-ATO and AIDA, respectively), which are common complications with APL; also support the possibility that a better disease control might be achieved with ATRA-ATO.

3.5. Uncertainties and limitations about unfavourable effects

The safety information regarding the proposed ATRA-ATO combination for the first line treatment of APL is limited. Indeed, no information regarding the actual adverse events (AEs) incidence profile, the toxicity profile in special populations and, most of all, the long-term toxicity of ATRA-ATO was available. A post-authorisation long term safety cohort study in APL patients treated with Trisenox will be conducted by the MAH in order to investigate the long-term safety of ATRA+ATO in newly diagnosed low to intermediate risk APL patients in a real-world clinical practice setting (see Risk Management Plan).

Only 25% of patients treated in the ATRA-ATO arm of study AML17 developed a grade 3-4 hepatotoxicity, compared to 44% in study APL0406. These data could suggest that the alternative ATRA-ATO regimen

employed in the supportive study might be better tolerated. Although, at present, data are too limited to support the use of the AML17 ATRA-ATO regimen, the possibility to further investigate the efficacy and safety profile of this alternative and better tolerated regimen should be evaluated. The MAH will obtain data from two ongoing registries (the NAPOLEON registry from the German AML Intergroup and the French APL Study Group registry) to further evaluate the benefit/risk of different ATRA-ATO administration regimens.

Although the carcinogenic activity of ATO is already included as a potential risk in the RMP, considering the higher cumulative dose in the first-line treatment and the limited long-term safety data with ATRA-ATO, the MAH will further investigate/control the carcinogenic risk of ATO (see risk management plan).

3.6. Effects Table

Table 24: **Effects Table for Trisenox in combination with ATRA versus standard ATRA and anthracycline-based chemotherapy (AIDA regimen) for the treatment of patients with newly diagnosed, non-high-risk acute promyelocytic leukaemia.**

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
2-year EFS	Rate	%	97	86		Discussion on clinical efficacy (CHMP AR)
HCR	Rate	%	100	95		
2-Year OS	Rate	%	99	91		
Unfavourable Effects						
Thrombocytopenia (grade 3-4) lasting >15 days Induction 1st Cycle 2nd Cycle Consolidation 3rd Cycle	Incidence	%	 59 6 6 3	 88 18 65 15	Limited data available	Discussion on clinical safety (CHMP AR)
Neutropenia (grade 3-4) lasting >15 days Induction 1st Cycle 2nd Cycle Consolidation 3rd Cycle	Incidence	%	 46 6 6 4	 79 35 76 25		
Fever of unknown origin or infection	Incidence	Number of episodes	26	59		
QTc prolongation	Incidence	%	15.6	0		
Hepatic toxicity (grade 3-4)	Incidence	%	63.2	5.8		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
GI toxicity (grade 3-4)	Incidence	%	4.4	9.9		
Oral toxicity	Incidence	%	0	19.4		

Abbreviations: AR: Assessment Report, EFS: Event-Free-Survival, GI: Gastrointestinal, HCR: Hematologic complete remission, OS: Overall survival

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy data in terms of primary and secondary endpoints demonstrated a clinical and statistical non-inferiority of ATRA/ATO combination therapy versus the active comparator (ATRA-chemotherapy combination), showing a clear benefit of ATRA/ATO combination therapy in the treatment of patients with low-to-intermediate-risk APL. The use of ATRA/ATO is associated with a similar rate of complete remission allowing the patients to go through the consolidation phase. These results are considered of important clinical relevance.

Overall, although the available safety data are limited, the toxicity profile of ATO in the proposed ATRA-ATO combination appears sufficiently characterized, and do not significantly differ from the known safety profile of ATO, with incidence of major AEs overall unmodified by the co-administration of ATRA.
Compared to the standard AIDA regimen, no cytotoxic agent is included in the proposed ATRA-ATO combination, and its clinical effect is mainly based on inducing the terminal differentiation of APL blasts. Moreover, no long-term maintenance is needed with ATRA-ATO; on the contrary, 2-year maintenance with MTX, 6-MP and ATRA is mandatory in the AIDA arm. Taking into account the possible impact of prolonged chemotherapy on quality of life, the absence of maintenance with ATRA-ATO can be considered an important favourable effect per se.

3.7.2. Balance of benefits and risks

Benefit-risk balance

Considered the clear therapeutic advantage associated with the ATRA-ATO combination therapy and the more favourable and overall manageable safety profile compared to ATRA+chemotherapy, the benefits of the combination in the claimed first-line indication overweigh the risks.

Discussion on the Benefit-Risk Balance

The benefits associated with the ATRA/ATO combination in the first-line setting of APL are widely recognised by the expert community, and the drug combination is included in most clinical guidelines and frequently used in the clinical practice. Thus a MA in in the first-line setting of APL is considered the natural consequence of what has become a recognised treatment regimen in this disease setting. The efficacy of the combination therapy is considered clearly demonstrated and the safety profile favorably compares with ATRA-chemotherapy regimens. It is concluded that the ATRA/ATO combination is confirmed as an important treatment option in the drug armamentarium for first-line treatment of APL.

3.7.3. Additional considerations on the benefit-risk balance

The MAH has submitted the results from two clinical studies (pivotal phase III study APL0406 and supportive phase III study AML17) in the format of bibliographic references.

This is considered acceptable considering the difficulty of conducting further clinical studies given the available results, the detailed study data reported in these comprehensive references, including short-term and long-term efficacy results, the quality of the design of the studies, the convincing treatment effect, the totality of the available data about the activity of ATO in APL, and the synergistic effect of the ATRA-ATO combination.

Regarding the safety information no information regarding the actual adverse events AEs incidence and the long-term toxicity of ATRA-ATO was available. Additional pharmacovigilance activities including a post-authorisation long term safety cohort study in APL patients treated with Trisenox in newly diagnosed low to intermediate risk APL patients and two ongoing registries (the NAPOLEON registry from the German AML Intergroup and the French APL Study Group registry) will address this safety issue and provide additional data on the safety profile of ATRA-ATO combination.

3.8. Conclusions

The overall B/R of Trisenox is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include induction of remission, and consolidation in adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) in combination with all trans retinoic acid (ATRA), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene for Trisenox.

As a consequence, sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated regarding the posology, efficacy and safety information and warnings. In addition, a Risk Management Plan (Version 1.3) is introduced. The Package Leaflet is updated in accordance.

This CHMP recommendation is subject to the following amended conditions:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include induction of remission, and consolidation in adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) in combination with all trans retinoic acid (ATRA), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene for Trisenox.

As a consequence, sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. A revised version of the RMP (version 1.3) has been approved as part of this application.

Summary

Please refer to the Scientific Discussion Trisenox-II-58.

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