Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Arsenic trioxide

Proprietary Product Name: Phenasen

Sponsor: Phebra Pty Ltd

First Round CER report: 19 November 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
6MP	6-mercaptopurine
ADR	Adverse drug reaction
AE	Adverse event
AIDA	all trans retinoic and idarubicin
ALLG	Australasian Leukaemia and Lymphoma Group
ALT	Alanine amino transferase
AML	Acute myelogenous leukemia
APL	Acute promyelocytic leukaemia (also APML)
APLDS	APL differentiation syndrome
APML3,APML4	ALLG APML trial codes, 3rd and 4th trials
AST	Aspartate amino transferase
ATO	Arsenic trioxide, As_2O_3
ATRA	All-trans retinoic acid
BaCT	Centre for Biostatistics and Clinical Trials
CI	Confidence interval
CNS	Central nervous system
CR	Complete remission
CSR	Clinical study report
CT	chemotherapy
CTCAE	Common terminology criteria for adverse events
D	Daunorubicin
DFS	Disease free survival
DMSC	Data Management and Safety Committee
EC	Ethics committee

Abbreviation	Meaning
ECG	Electrocardiogram
EFS	Event-free survival
FAB	French-American-British, classification system
FFS	Failure Free Survival
FLT3	FMS-like tyrosine kinase-3
GCP	Good clinical practices
GGT	Gamma glutamine transferase
GI	Gastrointestinal
H	Homoharringtinone
HCR	Haematological complete remission
IDA	Idarubicin
ITT	Intention-to-treat
iv	Intravenous
mRNA	Messenger ribonucleic acid
MTX	Methotrexate
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ND	Not done
OS	Overall survival
PML-RARα	Promyelocytic leukaemia – retinoic acid receptor alpha fusion gene
PP	Per protocol
QTc	QT interval
RCT	Randomised controlled trial
RFS	Relapse free survival
RT-PCR	Reverse transcriptase-polymerase chain reaction

Abbreviation	Meaning
SAE	Serious adverse event
TE	Thromboembolism
TGA	Therapeutic Goods Administration
TTR	Time to relapse
VZV	Varicella Zoster Virus
WBC	White blood count
WCC	White cell count

1. Introduction

1.1. Submission type

This is a Category 1 Type-C submission for extension of indications.

1.2. Drug class and therapeutic indication

Phenasen (ATO) is an antineoplastic agent (ATC code L01XX27: Antineoplastic and immunomodulating agents – Other antineoplastic agents).

The approved indication is: 'For the induction of remission and consolidation in patients with acute promyelocytic leukaemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression.'

The proposed {additional/replacement} indication is:

> '*For the induction of remission and consolidation in patients with previously untreated Acute promyelocytic leukaemia (APL) in combination with all-trans retinoic acid (ATRA) and chemotherapy unless ATRA and/or chemotherapy is contraindicated*.'

1.3. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

PHENASEN (Arsenic trioxide) injection 10 mg/10 mL) is presented in 10 mL vials in cartons of 10.

No new dosage forms or strengths are proposed.

1.4. Dosage and administration

The recommended dose is 0.15 mg/kg/day diluted with 100 - 250 mL of 5% glucose injection or 0.9% sodium chloride injection and administered intravenously (IV) over two hours.

Cycles of treatment are given to achieve complete remission, defined as the complete disappearance of all leukemic myeloblasts and promyelocytes and < 5% overall myeloblasts by morphological examination of the marrow. After induction of remission, consolidation cycles may be given, and maintenance therapy considered. Phenasen may be given in combination with all-trans retinoic acid (ATRA) and/or chemotherapy, or as single agent treatment.

In patients with newly diagnosed APL, combination treatment induction is initiated on Day 1 with ATRA 45 mg/m^2/day (orally in divided doses) for a maximum of 36 days, plus idarubicin (IV) on Days 2, 4, 6 and 8. The idarubicin dose is age-dependent: 12 mg/m^2 if age ≤ 60, 9 mg/m^2 if age 61 - 70, and 6 mg/m^2 if age ≥ 71 years. Phenasen 0.15 mg/kg/day (IV) is commenced on Day 9 and continued to Day 36. It is strongly recommended that during induction patients are treated with prednisone (or prednisolone); 1 mg/kg/day for at least 10 days. Aggressive platelet and plasma should also be considered to maintain haemostatic targets. Where unacceptable toxicity or features of APLDS occur, the doses of ATRA and Phenasen can be reduced (to 25 mg/m^2/day and 0.08 mg/kg/day respectively) or ceased depending on clinical severity.

After a break of 2 - 3 weeks, 2 cycles of consolidation therapy, ATRA and Phenasen are then given:

- in the first consolidation cycle ATRA 45 mg/m^2/day and Phenasen 0.15 mg/kg/day are given every day for 28 days
- in the second consolidation cycle the drugs are given on an intermittent schedule: ATRA 45 mg/m^2/day on days 1 - 7, 15 - 21 and 29 - 35 (7 days on, 7 days off); Phenasen 0.15 mg/kg/day on days 1 - 5, 8 - 12, 15 - 19, 22 - 26 and 29 - 33 (5 days on, 2 days off).

A break of 3 - 4 weeks is recommended between the consolidation cycles, and before maintenance therapy is commenced.

For patients in CR after the 3 cycles of induction/consolidation, maintenance consisting of ATRA (45 mg/m^2/day) from Day 1 – 14, followed by 6MP (from 50 mg/m^2/day) and MTX (from 5 mg/m^2 once weekly) both from Day 15 - 90 (each cycle 3 months) may then be administered for 24 months.

In patients with newly diagnosed APL, as a single agent If ATRA and/or chemotherapy is contraindicated, the proposed dosage regimen for induction is Phenasen 0.15 mg/kg/day (IV) given for 28 days. After a break of 3 - 4 weeks this cycle is repeated as the first consolidation cycle (28 days); however in the second consolidation cycle (again after a 3 - 4 week break) Phenasen is given intermittently for 5 days a week (5 days on, 2 days off) for 5 weeks.

In patients refractory to, or relapsed from retinoid and anthracycline therapy (previously approved indication) For induction, a daily infusion of 0.15 mg/kg/day is continued until bone marrow remission is obtained. If bone marrow remission is not obtained by day 60, dosing must be discontinued.

Consolidation Treatment Therapy

An additional course beginning consolidation of treatment may begin 3 - 4 weeks after completion of the induction cycle. The dose is the same as for induction, except that 25 daily doses over a period of up to 5 weeks are given. There are no data on the use of arsenic trioxide in patients with renal and hepatic impairment. Caution is recommended in renal impairment since renal excretion is the main route of elimination of arsenic trioxide. Caution is also required in hepatic impairment since the liver is the major site of detoxification of arsenic trioxide.

Evaluator's Comments: No change is proposed in dosage for currently approved indication in relapsed/refractory APL.

2. Clinical rationale

Acute Promyelocytic Leukaemia (APL) is a rare disease, accounting for 5 - 15% of all the acute myelogenous leukemia in adults. APL has an incidence of 1,000 to 1,500 newly diagnosed patients a year in the United States and 700 to 800 in the European Union. There are less than 100 cases of APL diagnosed in Australia each year. APL has equal incidence in men and women.

The majority of APL patients enter complete remission (CR) when treated with ATRA, which induces terminal differentiation of the leukaemic clone and simultaneously corrects the coagulopathy. However, ATRA therapy is associated with a potentially fatal capillary leak syndrome (retinoic acid syndrome or APL differentiation syndrome (APLDS). Furthermore, ATRA-induced remissions are not durable, and continuous ATRA maintenance therapy is followed by the emergence of ATRA resistance. Randomised studies have confirmed the benefits of simultaneous ATRA and CT; the combined approach affords reciprocal protection against both coagulopathy aggravated by CT and the retinoic acid syndrome. The overall survival of APL patients prior to the introduction of ATRA was approximately 35% at 3 years, whereas it now exceeds 80% with combination therapy.

APL is uniquely associated with a t (15;17) reciprocal translocation, and disruption of the PML and RARα genes. Clinically the disease shows a propensity for life-threatening haemorrhage

that is aggravated by cytotoxic chemotherapy (CT), and sensitivity to both ATRA and to ATO. Both ATRA and ATO exert their therapeutic activity through their action on so-called Leukemia Initiating Cells, and in particular to therapy induced degradation of the PML-RARα oncoprotein. As ATRA and ATO target distinct moieties of the PML/RARα fusion and as the degradation pathways are non-cross resistant, there is a synergistic activity of ATRA and ATO in this setting which provides a rationale for their use in combination.

Evaluator's Comments: No clear clinical rationale has been provided to justify proposed use of ATO as single agent in newly diagnosed, previously untreated APL.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The current dossier and application is a Mixed/hybrid Type Application (a combination of complete study reports of limited clinical studies carried out and supported with bibliographical references) to the Therapeutic Goods Administration (TGA). This application is based on ALLG Phase II clinical trial (APML4) as the pivotal study supported by the published literatures.

The literature search was performed at 3 different periods. Initial search was performed on 16 - 17 October, 2012 and updated searches in 3 - 4 September, 2013 and in 2 - 4 June 2014, the entire literature search output that was generated was reviewed against the inclusion and exclusion criteria. None of the additional literatures identified in 2 - 4 June 2014 were found suitable for inclusion in the dossier in support of the claimed indication. The sponsors confirm that the search strategy used to generate the search output for the application was in full accordance with the search strategy approved by the TGA.

The submission contained the following clinical information:

Module 5 of the submission includes a Phase II study (APML4) of clinical efficacy in support of the proposed extended indication for use in patients with previously untreated Acute promyelocytic leukaemia (APL) in combination with ATRA and chemotherapy unless ATRA and/or chemotherapy is contraindicated.

All of the other clinical efficacy data is from published studies, including 4 controlled trials with ATO in combination treatment; 5 open, uncontrolled trials, in combination treatment.; 7 studies using ATO as single agent including, 5 open, uncontrolled trials, with ATO as single agent treatment in adults and 2 in children; 1 meta-analysis of 5 trials and 1 historical control trial – APML3 – which is considered the 'control' for APML4 (Table 1).

Table 1: List of clinical studies providing efficacy data.

Study Identifier (Author)	Study Design	ATO dose and treatment regimen
As combination treatment		
Lo-Coco et al[3] 2013, module 5.3.5.1.1	RCT, active control, prospective multicentre study, noninferiority	0.15 mg/kg/day intravenously (iv) during induction and consolidation
Shen et al[6], 2004 , module 5.3.5.1.2	RCT, active control, prospective multicentre study	0.16 mg/kg/day iv, during induction and maintenance
Powell et al[5], 2010, module 5.3.5.1.3	RCT, active control, prospective multicentre study	0.15 mg/kg/day iv, for post-remission treatment (prior to consolidation)
Dai et al[4], 2009 module 5.3.5.1.4	Non-randomised, active control, prospective single centre study	10 mg/day iv for 28 days, during induction and for 10-14 days during consolidation/maintenance.
ALLG APML4[1] module 5.3.5.2.1	Open, uncontrolled, prospective multicentre study; in CSR APML3 is active control	0.15 mg/kg/day iv during induction, and intermittent cycles in consolidation
Iland et al[2] 2012, ALLG APML3 module 5.3.5.4.1	Open, uncontrolled, prospective multicentre study - historical control for APML4	No ATO regimen
Ravandi et al[7] 2009 module 5.3.5.2.2	Open, uncontrolled, prospective single centre study	0.15 mg/kg/day iv, during both induction and maintenance
Lou et al[8] 2012 module 5.3.5.2.3	Open, uncontrolled, retrospective single centre study	10 mg/day iv, during both induction and maintenance
Pei et al[9] 2012 module 5.3.5.2.4	Open, uncontrolled, prospective single centre study	0.16 mg/kg/day iv, during induction and 10 mg/day iv 10 mg/m2/day iv for 14-21 days in 3rd month during maintenance for 6–8 courses over approximately 3 years
Gore et al[10] 2010 module 5.3.5.2.5	Open, uncontrolled, prospective multicentre study	0.15 mg/kg/day iv, on weekdays from Day 8 for 30 doses. during consolidation only
Meta-analysis		
Wang et al[18] 2011 module 5.3.5.3.1	Meta-analysis – includes 5 trials* in newly diagnosed APL	0.16 mg/kg/day iv in Shen et al 2004, Li et al 2008, and Su et al 2006. 10 mg/day iv in Bai et al 2007 and Wang et al 2004

*Of the trials in the meta-analysis, 1 was identified in the literature search and included (Shen et al., 2004); but the other 4 were excluded during the literature sorting phase-primarily on the basis of being single centre trails, reported in Chinese language journals.

Table 1 continued; List of clinical studies providing efficacy data

Study Identifier (Author)	Study Design	ATO dose and treatment regimen
As single agent treatment		
Ghavamzadeh et al[11] 2006 module 5.3.5.2.6	Open, uncontrolled, prospective single centre study	0.15 mg/kg/day iv, for induction (Bk); and 6 days/week for 28 days during consolidation. No maintenance treatment was given.
Ghavamzadeh et al[12] 2011 module 5.3.5.2.7	Open, uncontrolled, prospective single centre study	0.15 mg/kg/day iv, for induction (Bk), and 6 days/week for 28 days during consolidation, for up to 4 courses. Additional consolidation courses at 1 and 2 years
Mathews et al[13] 2006 module 5.3.5.2.8	Open, uncontrolled, prospective single centre study	ATO 10 mg/day iv.in induction until CR (to max 60-75 days), 28 days break then, ATO (same dose) for consolidation for 4 weeks, 28 day break, ATO (same dose) as maintenance for 10 days/month, every 4 weeks, for 6 months while subjects remained in remission.
Mathews et al[14] 2010 module 5.3.5.2.9	Open, uncontrolled, prospective single centre study	No treatment – long term follow-up of Mathews et al 2006
Alimoghaddam et al[15] 2006 module 5.3.5.2.10	Open, uncontrolled, prospective study	Induction ATO 0.15 mg/kg/day until CR Consolidation ATO (same dose as induction) for 28 days daily (after a 4 week break, post CR) No maintenance treatment.
As single agent treatment in children		
George et al[16] 2004 module 5.3.5.2.11	Open, uncontrolled, prospective single centre study	0.15 mg/kg/day iv, during induction (Bk), 28 days daily for consolidation (Bk), then 6 cycles of maintenance 10 days every month.
Zhou et al[17] 2010 module 5.3.5.2.12	Open, uncontrolled, prospective single centre study	Induction: 0.16 (patients aged above 6 years of age) or 0.20 (patients aged 4 to 6 years of age) mg/kg/day iv, with a maximum daily dose of 10 mg. ATO given daily until Haematological CR or to a maximum of 60 doses, with a 28 days (Bk) then, Maintenance: 14 days every month in 1st year, every 2 months in 2nd year, every 3 months in 3rd year.

'Bk' – indicates a 4 week break after induction when CR achieved, or a 4 week break between consolidation treatment and maintenance.

3.2. Paediatric data

The submission did not include specific clinical studies in paediatric patients and no formal paediatric development plan has been prepared for Phenasen in this proposed indication. However, there is limited clinical data with the use of arsenic trioxide in paediatric population. All trials except Lo-Coco et al (2013) and Gore et al (2010) included adolescent patients (age 14 - 18 years). The APML4 study, Ghavamzadeh et al (2006) and Mathews et al (2006) also included children. Two published papers using ATO as single agent in newly diagnosed APL (George et al, 2004 and Zhou et al, 2010) were conducted only in paediatric (< 12 years) and adolescent patients (12 - 15 years)[1]. Efficacy and safety in paediatric patients below the age of 5 years has not been studied.

[1] George et al 2004 (11 patients in the age range 6-14) and Zhou et al 2010 (19 patients under 15 years in age).

3.3. Good clinical practice

The APML4 study was conducted in compliance with GCP guidelines. All other published studies were also conducted in compliance with Declaration of Helsinki and ICH guidelines.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

No new pharmacokinetic data was provided in this submission.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

No new pharmacodynamic data was provided in this submission.

The precise molecular and cellular mechanisms underlying the pharmacodynamics of arsenic trioxide in acute promyelocytic leukaemia (APL) are uncertain. Arsenic trioxide can induce partial differentiation and apoptosis of leukemic cells in vitro. There is also evidence that its other known pharmacological effects (degradation of specific APL fusion transcripts, antiproliferation, inhibition of angiogenesis) may contribute to efficacy in APL.

6. Dosage selection for the pivotal studies

No new data was submitted.

7. Clinical efficacy

7.1. For extended indication

'For the induction of remission and consolidation in patients with previously untreated Acute promyelocytic leukaemia (APL) in combination with ATRA and chemotherapy unless ATRA and/or chemotherapy is contraindicated.'

A tabular listing of all clinical studies providing efficacy data for the new proposed indication of newly diagnosed APL is provided in Table 1. The published studies in combination treatment Lo-Coco et al 2013, Dai et al, 2009 and the CSR for the open, uncontrolled Phase II APML4 study (which includes comparison to the APML3 study as control group) are considered the primary efficacy trials which support the proposed indication for Phenasen in newly diagnosed APL (with ATO in induction and consolidation). These studies are discussed in section 7.1.1 below.

All of the other clinical efficacy data is from published studies, including 4 controlled trials, 5 publications of open, un-controlled trials, in combination treatment (Iland, 2012[2], Ravandi 2009, Lou 2013, Pei 2012 and Gore 2010), 7 publications to support use as single agent therapy (5 in adults and 2 paediatric studies) and 1 published meta-analysis of 5 trials (Wang et al, 2011) (Table 1). These have been evaluated and discussed in section 7.1.2. The historical control trial – APML3 – which is considered the 'control' for APML4 is discussed in section 7.1.2.3.

[2] The interim analysis of APML4, superseded by the clinical study report (CSR).

7.1.1. Pivotal efficacy studies

7.1.1.1. Study APML4

7.1.1.1.1. Study design, objectives, locations and dates

The APML4 clinical trial, initiated by the Australasian Leukemia and Lymphoma Group (ALLG) and the Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG) was a single-arm, open-label, Phase II study with a target accrual of 125 newly diagnosed APL patients. Protocol treatment consisted of triple induction with ATRA, idarubicin and ATO, followed by 2 consolidation cycles of ATRA and ATO without chemotherapy and then maintenance with ATRA, oral methotrexate (MTX), and 6-mercaptopurine (6MP) for 24 months. All patients were followed for a minimum of 2 years[3] after commencement of maintenance therapy.

The primary objectives were to evaluate in a group of patients with newly diagnosed APL, the effect of a chemotherapy protocol consisting of arsenic trioxide (ATO) added to standard induction (all-trans retinoic acid (ATRA) plus intensive idarubicin (IDA)) and 2 cycles of consolidation (ATRA plus ATO) on time to relapse and to assess the effect of obligatory use of prednisone (or prednisolone) and aggressive haemostatic support, during induction on early death rate.

The secondary objectives were to assess the safety of the chemotherapy protocol in these patients, to evaluate the effect of the chemotherapy protocol on the complete remssion rate, disease-free survival, event-free survival, overall survival and on the cumulative incidences of treatment failure, relapse and death.

The study was conducted from Nov 2011 to March, 2012 at 27 study centres in Australia.

Evaluator's Comments: The study design was a non-randomised, non-comparative, open, Phase II trial. There was no concurrent control group, although the study was powered for a direct comparison with the APML3 maintenance cohort as a historical control group (refer section 7.1.2.3, for details of APML3 study).

The ALLG APML4 protocol was designed for newly diagnosed APL patients with 3 broad principles in mind: (1) to capitalise on the previous ALLG APML3 study which achieved a low early death rate, a high CR rate and excellent OS with a treatment regimen combining ATRA and intensive IDA; (2) to minimise short and long term toxicity by reducing the reliance on anthracycline chemotherapy; and (3) to improve the molecular relapse free survival rate by the inclusion of ATO as an antileukaemic therapy that is more specific for APL.

7.1.1.1.2. Inclusion and exclusion criteria

Patients (aged > 1 year) were eligible for enrolment if they were diagnosed with de novo acute promyelocytic leukaemia and met the following inclusion criteria:

- Morphological diagnosis of de novo APL, either classical FAB-M3 or variant FAB-M3v.;
- Demonstration of PML-RARα fusion transcripts by reverse transcriptase polymerase chain reaction (RT-PCR), to effectively exclude other APL variants, which respond poorly to ATRA;
- In the event that PML-RARα transcripts could not be demonstrated, inclusion required unequivocal evidence of a t(15;17) translocation.

[3] All patients who remained alive and on study, were followed for a minimum of 2 years from their commencement of maintenance therapy. At the completion of maintenance treatment, patients continued to be followed every 3 months for 1 year and then every 6 months thereafter until study closure.

- ECOG performance status 0 - 3.
- Normal left ventricular ejection fraction (LVEF), according to institutional criteria (prior to the start of treatment with IDA on Day 2).
- ECG showing sinus rhythm and QTc interval < 500 ms.
- Written informed consent must have been given by each patient or parent/guardian prior to commencement of treatment with ATRA, unless the patient was deemed by the local investigator to be at immediate risk of life-threatening haemorrhage; Registration completed before the first dose of idarubicin on Day 2;

The main exclusion criteria were: previous history of preleukaemia, myelodysplasia or a myeloproliferative disorder; Failure to confirm the diagnosis of APL (by molecular or cytogenetic techniques); ECOG performance status > 3.; Age < 1 year.; previous history of serious cardiac, pulmonary, hepatic or renal disease or a history of grand mal seizures; serum creatinine > 200µmol/L or serum bilirubin > 50 µmol/L (unless medically correctable); Clinical cardiac impairment and/or a history of significant cardiac disease; ECG showing prolongation of QTc due to medication or electrolyte disturbance (unless corrected before registration); Previous treatment for APL; history of cancer (other than basal cell skin cancer, or carcinoma of cervix in situ); Contraindication to use of any of the study drugs; Pregnancy, in females of child-bearing age.

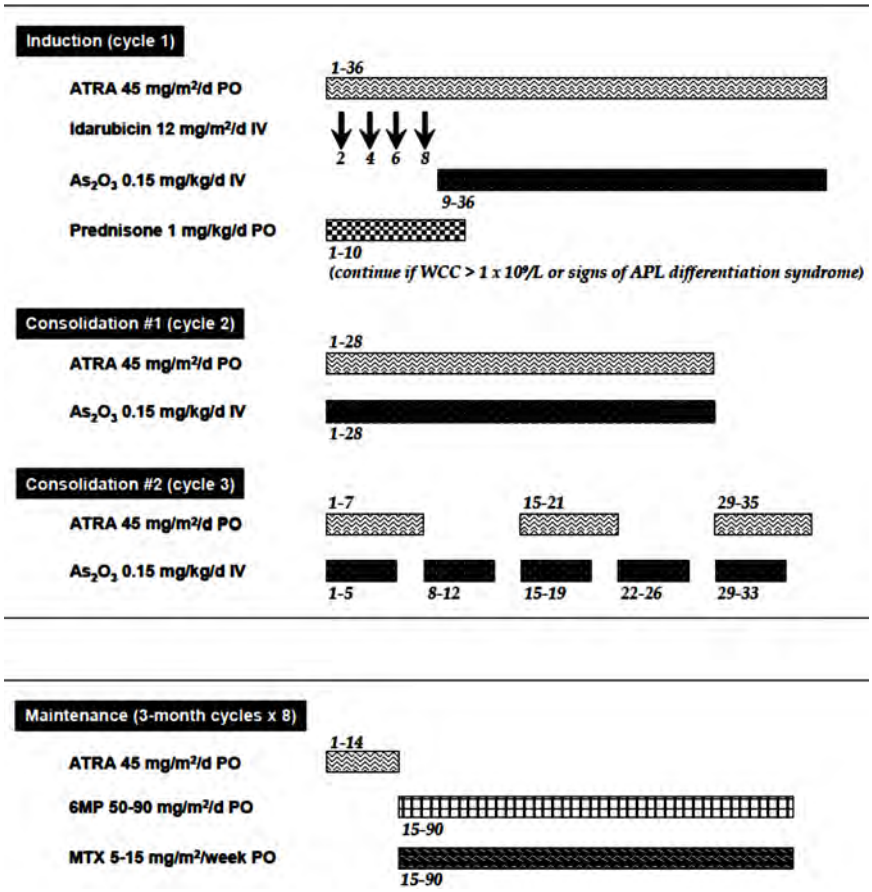
Evaluator's Comments: The study population was selected to specifically evaluate efficacy/safety in untreated patients with APL with no contraindications to treatment with ATRA or chemotherapy.

7.1.1.1.3. Study treatments

Arsenic trioxide 0.15 mg/kg/day intravenous infusion was given in 500 mL 5% dextrose or normal saline over 2 hours. The treatment regimen consisted of triple induction with ATRA, IDA[4] and ATO, followed by 2 consolidation cycles of ATRA and ATO without chemotherapy, and then maintenance with ATRA, oral methotrexate (MTX), and 6-mercaptopurine (6MP) for 24 months. All patients were followed for a minimum of 2 years after commencement of maintenance therapy. The remission induction strategy involved an induction cycle (IND) of ATRA plus IDA combined with ATO which commenced on Day 9 followed by 2 cycles of consolidation therapy (CON1 and CON2). In the second cycle of treatment, IDA was replaced by ATO. ATRA and ATO were repeated in the third cycle of treatment, but both were given on an intermittent schedule to facilitate outpatient treatment (Figure 1 below).

[4] The IDA dose was age-dependent: 12 mg/m^2 on days 2,4,6,8 if age ≤ 60, 9 mg/m^2 on days 2,4,6,8 if age 61-70 inclusive, and 6 mg/m^2 on days 2,4,6,8 if age ≥ 71

Figure 1: Pivotal Phase II Study APML4. Protocol Schema



In an attempt to reduce the number of early deaths due to APL differentiation syndrome (APLDS) and haemorrhage, the induction cycle included 2 additional components: (a) prednisone (or prednisolone) was mandatory for all patients, for the first 10 days and (b) aggressive platelet and plasma support[5] was administered to all patients so that specified haemostatic targets were achieved.

For patients in CR after the 3 cycles of induction/consolidation, triple maintenance (consisting of ATRA, 6MP and MTX) was then administered for 24 months. Patients with evidence of persistent disease immediately prior to starting maintenance were deemed treatment failures and taken off study. Further therapy was at the discretion of individual investigators. Details of study drugs administered during the induction, consolidation and maintenance treatment phases were provided.

Evaluator's Comments: With the exception of ATO all of the study drugs were registered and marketed in Australia at the time the study was conducted. ATO was approved for treatment of relapsed APL (Phenasen, Phebra Pty Ltd) in May 2009. However, it is considered an unapproved drug for the treatment of de novo (untreated) APL in Australia. For the duration of the APML4 trial, ATO was provided under Schedule 5A of the Therapeutic Goods Act and Regulations: supplied under contract between a public or private hospital (the site) and a licensed manufacturer (Phebra Pty Ltd, previously known as Pharmalab Pty Ltd) in accordance with a specified formulation.

[5] Aggressive haemostatic support with Cycle 1 included:-- Platelets 4 units (1 pooled pack) twice daily if platelet count < 30 x 10^9/L -- FFP and/or cryoprecipitate to maintain fibrinogen > 1.5 g/L, normal PT and APTT

7.1.1.1.4. Efficacy variables and outcomes

The following assessments were performed throughout the study in order to determine whether response or relapse definitions had been achieved:- Signs and symptoms relating to leukaemia; PB absolute neutrophil count and differential – to identify abnormal cells; Platelet count; BM aspirate – to identify abnormal promyelocytes, hypergranular cells, Auer rods, abnormal blast cells, PML-RARα transcripts.

The primary endpoints were 'Early death' and 'Time to relapse'. Early death was defined as any death that occurred either within the first 36 days after commencing ATRA treatment, or during IND therapy (if IND therapy continued beyond 36 days due to treatment delays or interruptions).

The secondary endpoints were:

1. The incidence and worst grade of adverse events reported during each treatment cycle
2. Durations of neutropenia and thrombocytopenia during induction and consolidation treatment cycles
3. The achievement of CR, DFS, EFS, OS
4. The cumulative incidences of competing events such as treatment failure, relapse and death.

Secondary endpoints were adjusted as part of the second protocol amendment to reflect definitions in line with current terminology and methods in the medical literature for other trials in APML.

Evaluator's Comments: All efficacy and safety assessments were considered standard (widely used and generally recognised as reliable, accurate and relevant). During the second protocol amendment actions were taken to ensure definitions for efficacy time-to-event endpoints were aligned with the definitions in current use by other cooperative groups in the medical literature (specifically with the US Intergroup definitions of EFS and treatment failure).

7.1.1.1.5. Randomisation and blinding methods

The study design was a non-randomised, non-comparative, open Phase II trial. Apart from age-related dose reductions for IDA, all patients received the same dose of the study product(s) with their final dose calculated based on body weight or body surface area (BSA). Dose adjustments were made based on toxicity. The study did not involve blinding of either study medication or assessments.

7.1.1.1.6. Analysis populations

All eligible patients registered in Study APML4 were included in the primary toxicity and efficacy analyses. Ineligible patients for whom the diagnosis of APL could not be confirmed by cytogenetics or RT-PCR demonstration of PML-RARα fusion transcripts were excluded from the primary analyses.

7.1.1.1.7. Sample size

Patient accrual to the APML4 clinical trial was continued until 125 eligible patients were registered. The target accrual of 125 patients was justified based on the following considerations:

- an accrual duration of 5 years and 1 year of follow-up,
- the anticipated CR rate of 90% providing an expected 112 patients evaluable for calculation of the 2 year relapse-free rate,

- an estimated 2 year relapse-free rate following CR in the maintenance phase of APML3 (available at the time of the original sample size calculation) of 80% from 57 patients who had achieved CR.

To demonstrate with 80% power that the 2 year relapse-free rate is statistically significantly greater than 80% required the true 2 year relapse-free rate in APML4 to be approximately 87.5%. Alternatively, allowing for the error in the APML3 rate, the study had approximately 80% power to detect an improvement of 15% in the 2 year relapse-free rate of APML4 compared with that in the maintenance phase of APML3 (for example, 95% versus 80%).

7.1.1.1.8. Statistical methods

Baseline characteristics and toxicity grades were summarized using descriptive statistics. The percentage of patients achieving complete remission was calculated for all eligible patients with a 95% confidence interval based on the exact values of the binomial distribution. All deaths occurring in the 36 days immediately following the date of commencement with ATRA therapy (Day 1) were classified as early deaths and a 95% confidence interval for the early death rate was based on the exact values of the binomial distribution. Overall, disease-free, and failure-free survival curves, as well as time to relapse and time to molecular relapse curves were estimated using the Kaplan-Meier product limit method. The statistical significance of potential prognostic factors including baseline pre-transfusion WCC, Sanz risk stratification and FLT3 mutation status were investigated using the log-rank test and Cox proportional hazards regression models; hazard ratios (HR) and associated 95% CIs were reported.

The comparison of RDC% values from the paired bone marrow and peripheral blood samples were based on the calculation of a correlation coefficient for the pairs of values or a suitable variance-stabilising transformation (such as the log transformation) of the values.[6] Informal comparisons of the results from the maintenance cohort of the APML3 clinical trial with the results from this APML4 trial were performed using Fisher's exact test for the comparison of rates and the log-rank test for the comparison of time-to-event curves. For TTR and DFS, the APML4 subsidiary endpoints measured from documented HCR were used as these are consistent with the definitions used in APML3. These comparisons were considered exploratory only as it was not possible to separate any effects due to the different therapies from 'trial effects'. In addition, the rate of early deaths in comparison to APML3, as well as a comparison of the causes of early death were compared with the incidences of these events in the APML4 study to assess whether the obligatory use of corticosteroids and the aggressive haemostatic support during induction had had any impact on the incidence of fatal APLDS, cerebral and pulmonary haemorrhages'.

Evaluator's Comments: No adjustments were made for demographic/baseline measurements or concomitant therapy, however a number of potential baseline prognostic factors including pre-transfusion WCC, Sanz risk stratification and FLT3 mutation status were identified and investigated for association with several of the study endpoints. For time-to-event endpoints, patient dropouts or those who were lost to follow-up prior to the closeout date were censored at the date of last contact. For other endpoints, there was no imputation of missing data. Missing data were minimised through extensive data checking and querying. If data were found to be truly missing, reasons were documented. Missing values and reasons (if known) were clearly reported in all data summaries in the final statistical report. As this was a Phase II single arm study, no adjustments for multiple

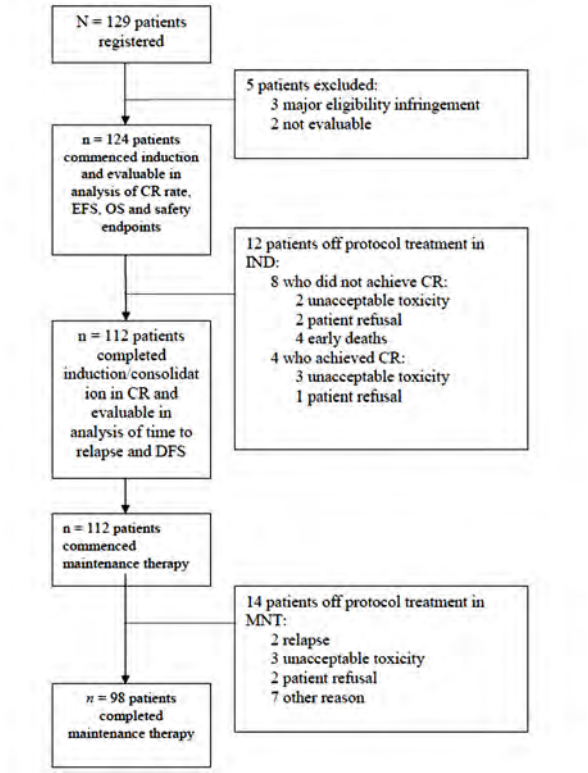
[6] Up to 11 paired samples will be available from each patient and a repeated measures analysis will also be performed on the RDC% values (or a transformation of them) to ascertain if there are linear and nonlinear trends common to all patients.

comparisons or interim analyses were made. The protocol, which was discussed extensively at ALLG meetings both before and during the trial, ensured consistent treatment, assessment and follow up of patients enrolled across the multiple Australian centres participating in the ALLG APML4 clinical trial. No adjustment for multiple centres was made in the analysis.

7.1.1.1.9. Participant flow

Of the 129 patients registered in the study, 5 patients were excluded from all analyses: 3 patients were found to be ineligible as the original diagnosis of APL was not confirmed either by cytogenetics or by RT-PCR demonstration of PML-RARα fusion transcripts; 1 patient was identified as a minor eligibility infringement and 1 patient withdrew consent prior to commencing protocol treatment. Of the remaining 124 patients who commenced treatment on study: 112 patients completed IND treatment, 8 patients discontinued during IND and did not achieve CR while a further 4 patients who discontinued during IND had a subsequent response assessment where CR was confirmed). The 12 patients who were taken off protocol during IND were not evaluable for the CR duration endpoints of TTR and DFS (Figure 2). All 112 patients who completed IND and commenced CON1 treatment achieved molecular CR by the end of CON2 and proceeded to MNT therapy. Of these 112 patients, 98 completed all 8 cycles (24 months) of MNT therapy. The number (proportion) of patients completing the trial according to the protocol was 98 (79%) of the 124 eligible patients, whereas 26 (21%) eligible patients discontinued treatment. The most frequent reason for discontinuing treatment was unacceptable toxicity, experienced by 9 patients (7%), this occurred for 6 patients in induction and 3 patients in MNT therapy. Other reasons included: patient refusal in 5 patients, death in 3 patients, relapse in 2 patients and was recorded as 'other' in 7 patients.

Figure 2: Patient flow chart



7.1.1.1.10. Major protocol violations/deviations

Of the 124 patients commencing induction, the delivery of the ATRA dose was subject to protocol deviations in 65 patients (52%), the ATO dose in 73 patients (59%) and IDA dose in 53

patients (43%). Similarly during the consolidation cycles ATRA dose delivery was recorded as a protocol deviation in 18 patients (16%) in CON1, 13 patients (12%) in CON2, and the ATO dose in 36 patients (32%) in both CON1 and CON2.

Majority of the 112 patients commencing MNT treatment received 80-110% of their protocol prescribed dose of ATRA each cycle. For ATRA this was an (average) median dose of 44.4 mg/m^2 per day (range 23.3-51.3), the median duration per cycle was 14 days (range 9-28) and no change in dose occurred for more than 96% of patients (the greatest number of changes in dose occurred in MNT cycle 2 due to toxicity). Treatment with 6-MP and MTX showed more variation over the 8 MNT cycles. Overall protocol deviations during maintenance occurred in at least 38 patients (37%) per cycle.

Evaluator's Comments: Throughout the study formal routine monitoring visits by an independent monitor were not conducted and there was no formal record of protocol deviations occurring at the site, other than those captured in the case report form (CRF). The CRF captured protocol deviations mainly related to treatment delivery, including dose delays, dose errors and missed doses.

7.1.1.1.11. Baseline data

Patients had a median age of 44 years (range 3-78), and majority of patients were adults; 1 child (3 years old) and 3 adolescents (ages 15, 16 and 17) were the only patients under 18 years of age enrolled in the study. There were equal number of males and females. Majority of patients had ECOG classification of 0 (52%) or 1 (35%), with FAB classification of M3 (80%), had standard t(15:17) cytogenetics (66%) with intermediate (54%) to high (19%) Sanz risk stratification. Bone marrow was positive for PML-RARα transcripts for 85% of the patients; in the remaining 15% of patients in the APML4 cohort, the presence of PML-RARα transcripts was unknown in the bone marrow but positive in the blood.

Evaluator's Comments: It is important to note that majority of patients had ECOG PS of 0 or 1 (87%). Hence, there is inadequate evaluation of efficacy and safety in newly diagnosed patients with higher ECOG PS (only 9% had ECOG of 2 and 5% had ECOG PS of 3).

Most patients received at least 80% of the protocol specified doses of ATRA, ATO and IDA in each cycle and only small percentages of patients received less than the minimum acceptable dose. Of the 124 eligible patients, 112 completed induction and went on to 2 cycles of consolidation treatment. Most patients received at least 80% of the protocol specified doses of ATRA and ATO in each cycle. Only 3 patients in CON1 and 1 patient in CON2 received less than the minimum acceptable dose. Of the 124 eligible patients commencing induction, 123 (99%) received blood product support (1 patient died on Day 0 and did not receive any blood products). The median (range) number of units of fresh frozen plasma (FFP), cryosupernatant, cryoprecipitate and platelets were 4.0 (0 - 40), 0.0 (0-20), 16.0 (0 - 232) and 13.0 (0 - 100) respectively. Of the 124 patients commencing induction, 35 (29%) received prednisone and 87 (71%) received prednisolone. The median total dose was 10.0 mg/kg (range 1.0 - 51.8) and the median duration was 10 days (range 1 - 56); 71 patients (58%) received at least the minimum acceptable dose (1.0 mg/kg/day for 10 days) and only 2 patients did not receive either prednisone or prednisolone.

7.1.1.1.12. Results for the primary efficacy outcome

Early death rate: The early death rate was 3.2% (4/124; 95% CI: 1.1% – 7.6%); the 4 early deaths occurred on Days 0, 2, 6 and 29 (where Day 0 represented the start of ATRA therapy) and 2 of the 4 early deaths were due to intracerebral haemorrhage. The relationships between early death and both age and baseline WCC were analysed. Early death was associated with age > 70 years (age ≤ 70 years: 2/117 (2%) versus age > 70years: 2/7 (29%); OR = 21.2; 95% CI: 1.30 – 350; P-value = 0.02), but not with WCC greater than 10 x 10^9/L at baseline (WCC ≤ 10 x

10^9/L: 2/101 (2%) versus WCC > 10 x 10^9/L: 2/23 (9%); OR = 4.63; 95% CI: 0.32 – 67.3; P-value = 0.16).

Evaluator's Comments: Interpretation of above results of increased risk of early death in patients aged > 70 years and with baseline WCC > 2.5 x 10^9/L should be interpreted with caution due to smaller sample sizes in these subgroups.

Time to relapse (and duration of CR): Of the 124 patients eligible and evaluable for assessment of the HCR and the CR rate, 118 patients (95.2%, 95% CI: 89.9% – 97.9%) had HCR documented at the response assessment conducted after IND. The median duration between start of ATRA therapy and achievement of HCR after induction was 53 days (range 34 – 83 days).

Additionally, 116 of the 124 evaluable patients (93.5%; 95% CI: 87.9% – 97.2%) achieved CR by the end of consolidation (CON2). Four of these 116 patients were withdrawn from protocol treatment during induction but achieved documented CR at the subsequent post-induction response assessment. The remaining 112 patients commenced consolidation at a median of 6.5 days (range 0 – 28 days) after documented HCR or CR post-induction and all 112 were in CR by the end of CON2. Therefore 112 patients were evaluable for analyses of CR duration endpoints. The median potential follow-up time to the closeout date for CR duration endpoints was 3.7 years (range 3 months to 6.9 years) from response assessment at the end of CON2 and 4.0 years (range 6 months to 7.2 years) from the date of documented HCR.

Cytogenetics and PML-RARα in induction and consolidation: Results of cytogenetic and PML-RARA from BM aspirates were used to confirm molecular response (MCR) and showed that 87-88% of patients had normal karyotype during induction and consolidation treatment phases; the PML-RARAα transcript was negative for 65% of patients at induction and increased to 93-94% of patients after consolidation treatment phases. Five of the 112 evaluable patients suffered relapse. Four were molecular relapses and 1 was a haematological relapse. The observed annual relapse-free rates measured from the end of CON2 were as follows: 1 and 2 years 97.3% (95% CI: 91.8% – 99.1%); 3, 4 and 5 years 95.4% (95% CI: 89.3% – 98.1%). Median TTR from end of CON2 was not estimable.

No statistically significant associations were identified between TTR from CON2 and baseline prognostic factors (WCC pre-transfusion, Sanz risk stratification and FTL3 mutation status).

7.1.1.1.13. Results for other efficacy outcomes

7.1.1.1.13.1. Disease free survival (DFS):

Analyses of DFS were identical to those of TTR. Two of the evaluable patients died; both following molecular relapse.

7.1.1.1.13.2. Overall survival (OS):

Of the 124 evaluable patients, 7 deaths were observed prior to the closeout date. Deaths occurred on Days 0, 2, 6, 29, 90, 414 and 725 where Day 0 represented the start of ATRA therapy. The observed annual overall survival rates were as follows: 1 year 96.0% (95% CI: 90.6% –98.3%); 2, 3, 4 and 5 years 94.3% (95% CI: 88.5% – 97.3%). Median overall survival was not estimable. No statistically significant associations were identified between overall survival and baseline prognostic factors (WCC pre-transfusion, Sanz risk stratification and FTL3 mutation status).

7.1.1.1.13.3. Event-free survival (EFS):

Of the 124 evaluable patients, 17 were classified with 'failure events'; that is the treatment was considered to have failed, the patient relapsed, or died. The failure events (first events) included: early death for 3 patients, treatment failure due to unacceptable toxicity or patient refusal (withdrawal of consent) for 9 patients and relapse for 5 patients. Three patients withdrew consent during induction and these were all considered to be treatment failures as

withdrawal was considered to be related to the treatment[7]: The observed annual EFS rates were as follows: 1 year 88.7% (95% CI: 81.7% – 93.1%); 2 years 87.9% (95% CI: 80.7% – 92.5%); 3, 4 and 5 years 86.1% (95% CI: 78.6% – 91.1%). Median EFS was not estimable. The assessment of associations between the baseline prognostic factors WCC pre-transfusion, Sanz risk stratification and FTL3 mutation status and EFS were evaluated in a series of log-rank tests and univariate Cox proportional hazards regression analyses; Only a trend for Sanz risk stratification category was identified as marginally statistically significant (Table 2).

Table 2: Associations of prognostic factors with event-free survival

Factor	*N*	Observed events	Expected events	HR	95% CI	*P*-value	2yr EFS	5yr EFS
WCC pre-transfusion								
≤ 10 x 10^9/L	101	12	14.1				90%	88%
> 10 x 10^9/L	23	5	2.9	2.02	(0.71, 5.73)	0.18	78%	78%
Sanz risk stratification								
Low	33	1	4.7			0.09	97%	97%
Intermediate	67	11	9.3	5.61	(0.72, 43.4)	(trend 0.03)	87%	83%
High	23	5	2.9	8.09	(0.95, 69.3)		78%	78%
FLT3 mutation status								
Negative	66	10	9.6				86%	85%
Positive	52	7	7.5	0.90	(0.34, 2.36)	0.83	89%	87%

Using an alternative definition for EFS, unacceptable toxicity during induction or withdrawal of consent during induction (9 patients) was no longer considered treatment failure. Two of these 9 patients subsequently died and are therefore included as events in the EFS analysis using the alternative definition. Of the remaining 7 patients, 2 withdrew without subsequent documentation of HCR, and are also included as events. The remaining 5 were no longer considered as treatment failures as 4 of these patients achieved CR and 2 patients achieved HCR following induction but did not proceed to consolidation therapy, either due to unacceptable toxicity (n = 5) or patient refusal (n = 1). The observed annual EFS rates were as follows: 1 year 92.7% (95% CI: 86.5% – 96.1%); 2 years 91.9% (95% CI: 85.5% – 95.6%); 3, 4 and 5 years 90.2% (95% CI: 83.3% – 94.3%).

The cumulative incidences, prior to the closeout date, of treatment failure, relapse and death without prior failure from start of ATRA therapy are summarised in Table 3. The cumulative incidences of haematological relapse, molecular relapse and death in remission from the end of consolidation therapy (from CON2) are summarised in Table 4.

[7]One patient no longer wanted to receive ATO therapy due to required daily attendance at the Hospital; another patient refused to continue with protocol treatment on 23 February 2007 following the onset of an SAE (increased respiratory distress) on 9 February 2007, and the third patient withdrew consent on 15 December 2004 following the onset of an SAE (HSV type 1 infection) on 23 November 2004.

Table 3: Summary of cumulative incidences (prior to the closeout date) of failure from start of ATRA therapy for the whole patient cohort and by Sanz risk stratification category.

	Observed events	1 year Cumulative	2 years Cumulative	3 years Cumulative
From start of ATRA therapy				
Original definition of treatment failure				
All patients				
Treatment failure	9	7.3 (± 2.3)	7.3 (± 2.3)	7.3 (± 2.3)
Relapse	5	1.6 (± 1.1)	2.5 (± 1.4)	4.2 (± 1.8)
Death	3	2.4 (± 1.4)	2.4 (± 1.4)	2.4 (± 1.4)
Low Sanz risk				
Treatment failure	1	3.0 (± 3.0)	3.1 (± 3.0)	3.0 (± 3.0)
Relapse	0	0	0	0
Death	0	0	0	0
Intermediate Sanz risk				
Treatment failure	6	9.0 (± 3.5)	9.0 (± 3.5)	9.0 (± 3.5)
Relapse	4	1.5 (± 1.5)	3.0 (± 2.1)	6.3 (± 3.0)
Death	1	1.5 (± 1.5)	1.5 (± 1.5)	1.5 (± 1.5)
High Sanz risk				
Treatment failure	2	8.7 (± 5.9)	8.7 (± 5.9)	8.7 (± 5.9)
Relapse	1	4.4 (± 4.3)	4.4 (± 4.3)	4.4 (± 4.3)
Death	2	8.7 (± 5.9)	8.7 (± 5.9)	8.7 (± 5.9)
Low & Intermediate Sanz risk				
Treatment failure	7	7.0 (± 2.6)	7.0 (± 2.6)	7.0 (± 2.6)
Relapse	4	1.0 (± 1.0)	2.0 (± 1.4)	4.2 (± 2.1)
Death	1	1.0 (± 1.0)	1.0 (± 1.0)	1.0 (± 1.0)
Alternative definition of treatment failure				
All patients				
Treatment failure	2	1.6 (± 1.1)	1.6 (± 1.1)	1.6 (± 1.1)
Relapse	5	1.6 (± 1.1)	2.5 (± 1.4)	4.2 (± 1.8)
Death	5	4.0 (±1.8)	4.0 (±1.8)	4.0 (±1.8)
Low Sanz risk				
Treatment failure	0	0	0	0
Relapse	0	0	0	0
Death	1	3.0 (± 3.0)	3.1 (± 3.0)	3.0 (± 3.0)
Intermediate Sanz risk				
Treatment failure	1	1.5 (± 1.5)	1.5 (± 1.5)	1.5 (± 1.5)
Relapse	4	1.5 (± 1.5)	3.0 (± 2.1)	6.2 (± 3.0)
Death	2	3.0 (± 2.1)	3.0 (± 2.1)	3.0 (± 2.1)
High Sanz risk				
Treatment failure	1	4.4 (± 4.3)	4.4 (± 4.3)	4.4 (± 4.3)
Relapse	1	4.4 (± 4.3)	4.4 (± 4.3)	4.4 (± 4.3)
Death	2	8.7 (± 5.9)	8.7 (± 5.9)	8.7 (± 5.9)
Low & Intermediate Sanz risk				
Treatment failure	1	1.0 (± 1.0)	1.0 (± 1.0)	1.0 (± 1.0)
Relapse	4	1.0 (± 1.0)	2.0 (± 1.4)	4.2 (± 2.1)

Table 4: Summary of cumulative incidences (prior to the closeout date) of failure from end of consolidation therapy for the whole patient cohort and by Sanz risk stratification category.

	Observed events	1 year CI	SE	2 years CI	SE	3 years CI	SE
From end of consolidation therapy							
HCR and MCR separately							
All patients							
Haematological relapse	1	0		0		0.9 (± 0.9)	
Molecular relapse	4	2.7 (± 1.6)		2.7 (± 1.6)		3.7 (± 1.8)	
Death in remission	0	0		0		0	
Low Sanz risk							
Haematological relapse	0	0		0		0	
Molecular relapse	0	0		0		0	
Death in remission	0	0		0		0	
Intermediate Sanz risk							
Haematological relapse	1	0		0		1.7 (± 1.7)	
Molecular relapse	3	3.4 (± 2.3)		3.4 (± 2.3)		5.2 (± 2.9)	
Death in remission	0	0		0		0	
High Sanz risk							
Haematological relapse	0	0		0		0	
Molecular relapse	1	5.3 (± 5.1)		5.3 (± 5.1)		5.3 (± 5.1)	
Death in remission	0	0		0		0	
Low & Intermediate Sanz risk							
Haematological relapse	1	0		0		1.1 (± 1.1)	
Molecular relapse	3	2.2 (± 1.6)		2.2 ± 1.6)		3.4 (± 1.9)	
Death in remission	0	0		0		0	
HCR and MCR combined							
All patients							
Relapse	5	2.7 (± 1.6)		2.7 (± 1.6)		4.6 (± 2.0)	
Death in remission	0	0		0		0	
Low Sanz risk							
Relapse	0	0		0		0	
Death in remission	0	0		0		0	
Intermediate Sanz risk							
Relapse	4	3.4 (± 2.3)		3.4 (± 2.3)		6.9 (± 3.3)	
Death in remission	0	0		0		0	
High Sanz risk							
Relapse	1	5.3 (± 5.1)		5.3 (± 5.1)		5.3 (± 5.1)	
Death in remission	0	0		0		0	
Low & Intermediate Sanz risk							
Relapse	4	2.2 (± 1.6)		2.2 (± 1.6)		4.5 (± 2.2)	
Death in remission	0	0		0		0	

7.1.1.1.13.4. Comparison of results from Study APML4 with historical Study APML3:

An informal comparison of patients enrolled on the APML4 study with the historical APML3 maintenance cohort allows exploration of whether the addition of ATO to standard chemotherapy in de novo APL patients improves efficacy by way of a reduction in early deaths and the relapse rate.

7.1.1.1.13.5. Early death:

In the APML3 maintenance patients, 5 of 70 (7.1%) patients died either within the first 36 days after commencing ATRA treatment, or during induction therapy (considered early deaths), compared with 4 early deaths in the 124 APML4 patients (3.2%); this difference was not statistically significant (OR = 0.44; 95% CI: 0.08, 2.10; P-value = 0.29). However, in the published report of APML3 (Iland et al 2012), it was noted that 8 of the full 101 patients (8%) eligible for both efficacy and safety analysis died within 30 days of study entry. The causes of death were usually multifactorial, including haemorrhage in 7 patients (4 intracerebral, 2 pulmonary and 1 gastrointestinal), sepsis in 3 patients, multi-organ failure in 3 patients and necrotising enteritis in 1 patient. APLDS was a major contributing factor in the deaths of 2 patients. The WCC at diagnosis was strongly associated with increased risk of early death; no deaths occurred among the 55 patients with a WCC ≤ 2.5 x 10^9/L, whereas 8 of 46 patients (17%) with a WCC > 2.5 x 10^9/L died within 30 days (P < 0.002). The cause of death in 2 of the 4 early deaths in APML4 was haemorrhage. In 7 of the 8 early deaths in APML3 haemorrhage was a major contributing factor to the cause of death. Therefore there appears to be a smaller number of deaths linked to haemorrhage in APML4, in which obligatory corticosteroids and

aggressive haemostatic support were provided during the induction phase. However this difference does not reach statistical significance (2/124 versus 7/101; p = 0.08).

The results of a series of unadjusted log-rank tests and univariate Cox proportional hazards regression analyses assessing differences between the APML4 cohort and the APML3 maintenance cohort in terms of TTR, DFS[8], OS and EFS are summarised in Table 5. Results show highly statistically significant improvements in APML4 compared with APML3 with respect to all 5 endpoints. For TTR and DFS, the APML4 subsidiary endpoint definition measured from documented HCR was used, as this was consistent with the definition used in APML3. The 2-year relapse-free rate was significantly higher in the APML4 study compared with the APML3 study both at 2-years (97% versus 87%) and at 5 years (95% versus 80%) (Figure 3). Similar results were observed for disease-free survival rate (2 years: 97% versus 86% and 5 years: 95% versus 79%) (Figure 4), overall survival rate (2 years: 94% versus 90% and 5 years: 94% versus 83%) (Figure 5), event-free survival using original protocol-specified definition (2 years: 88% versus 74% and 5 years: 86% versus 68%) (Figure 6) and event-free survival using alternative definition (2 years: 92% versus 78% and 5 years: 90% versus 72%) (Figure 7).

Table 5: Time-to-event endpoints-comparison of APML4 with APML3 maintenance cohort

Endpoint	*N*	Observe	Expecte	HR	95% CI	*P*-	2yr	5yr
Time to relapse								
ALLG APML4	112	5	11.0	0.23	(0.08, 0.64)	0.002	97	95
ALLG APML3	64	12	6.0	-	-	-	87	80
Disease-free survival								
ALLG APML4	112	5	11.7	0.21	(0.07, 0.59)	0.001	97	95
ALLG APML3	64	13	6.3	-	-	-	86	79
Overall survival								
ALLG APML4	124	7	11.6	0.35	(0.14, 0.91)	0.02	94	94
ALLG APML3	70	11	6.4	-	-	-	90	83
Event-free survival								
ALLG APML4	124	17	25.3	0.42	(0.22, 0.78)	0.005	88	86
ALLG APML3	70	22	13.7	-	-	-	74	68
Event-free survival (alternative definition)								
ALLG APML4	124	12	20.2	0.34	(0.16, 0.69)	0.002	92	90
ALLG APML3	70	19	10.8	-	-	-	78	72

[8] For TTR and DFS, the APML4 subsidiary endpoint definition measured from documented HCR was used, as this was consistent with the definition used in APML3.

Figure 3: Comparison of AALG APML4 with ALLG APML3 in terms of time to relapse (from documented HCR)

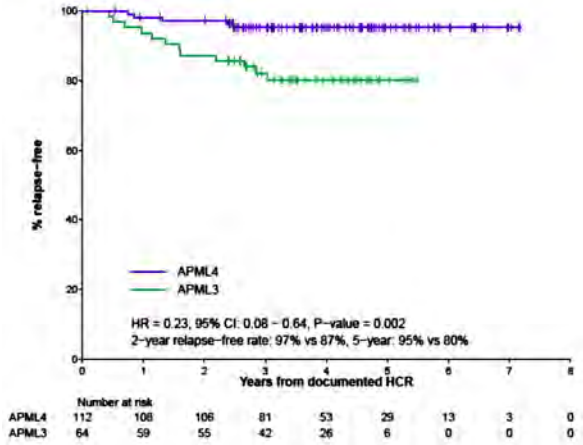


Figure 4: Comparison of AALG APML4 with ALLG APML3 in terms of disease-free survival (from documented HCR)

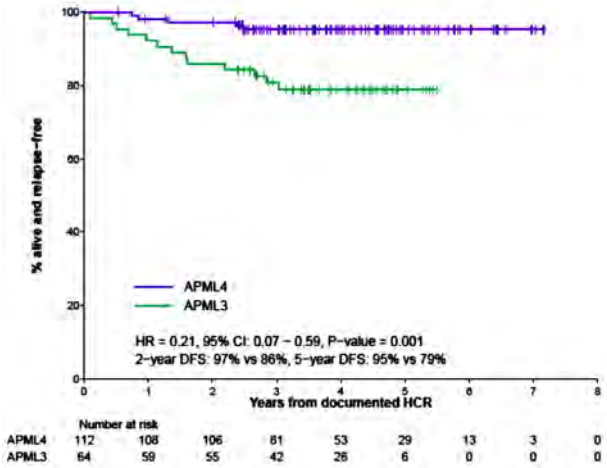


Figure 5: Comparison of AALG APML4 with ALLG APML3 in terms of overall survival

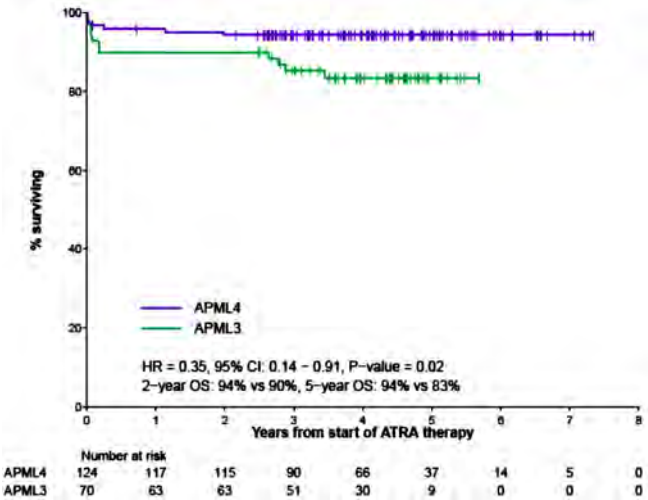


Figure 6: Comparison of AALG APML4 with ALLG APML3 in terms of event-free survival (original protocol-specified definition)

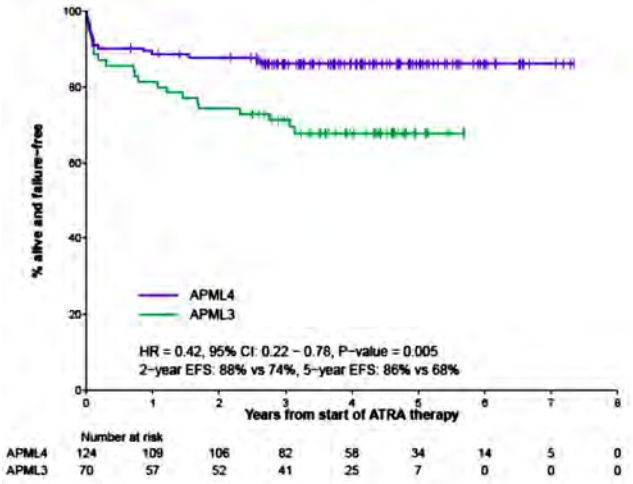
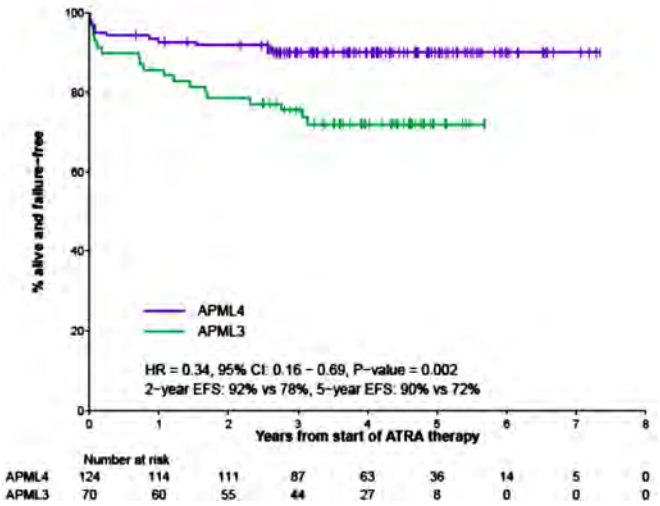


Figure 7: Comparison of AALG APML4 with ALLG APML3 in terms of event-free survival (alternative definition)



Evaluator's Comments: In the APML4 study addition of ATO to the IND phase, with obligatory use of corticosteroids and aggressive haemostatic support, resulted in 4 early deaths reported from a population of 124 patients (3.2%). This rate was not statistically significantly different to the number of early deaths reported in the maintenance group of the APML3 study (5 early deaths in 70 patients; 7.1%); however when compared to the 8 early deaths from the full 101 patients (8%) in Study APML3, there appeared to be fewer deaths attributed to haemorrhage (2 versus 7). In the APML4 study, ATO was also used in consolidation, effectively substituting for the second cycle of IDA that had been used in APML3. The results of analyses of time to event endpoints show statistically significant improvements in APML4 compared with APML3 with respect to TTR, DFS, OS and EFS. As the main difference to the treatment protocol from APML3 was the addition of ATO, in this report ATO is considered as the 'study drug'. Although the intensity of induction was greater in Study APML4 than Study APML3 (three drugs versus two drugs), the CR rate was at least as good, and the time to event outcomes were all statistically significantly better. The

superiority of APML4 over APML3 appears to be due to a combination of improved supportive care resulting in fewer deaths during induction, and better anti-leukemic therapy resulting in significantly fewer relapses. However, comparison of results between APML4 and earlier Study APML3 must be interpreted with caution due to exploratory nature of the analysis.

7.1.1.2. Lo-Coco, et al. 2013.

7.1.1.2.1. Study design, objectives, locations and dates

This was a prospective, randomised, open-label, Phase III, comparative, multi-centre, non-inferiority trial; designed to show that the difference in the 2 groups (with respect to event-free survival rate at 2 years from diagnosis) was not greater than 5%. The objective was to compare the efficacy and toxicity of standard all-trans-retinoic acid (ATRA) plus chemotherapy with ATRA plus arsenic trioxide (ATO) in patients with newly diagnosed, low to intermediate-risk APL. Enrolment of the pre-specified 162 patients was started in October 2007 and was completed in September 2010. The present analysis was performed in November 2012, with a median follow up of 34.4 months (range, 0.5 to 55.8).

7.1.1.2.2. Inclusion and exclusion criteria

Patients with newly diagnosed APL confirmed either by detection of the promyelocytic leukaemia-retinoic acid receptor (PML-RARα) fusion gene by real-time quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) analysis, demonstration of the t(15; 17) translocation (by karyotyping or fluorescence in situ hybridisation (FISH)), or evidence of microspeckled PML pattern (by direct immunofluorescence assay) were eligible and were randomised if they also satisfied the inclusion criteria: WHO performance status score of ≤ 2; creatinine level of 3.0 mg/dL or lower (≤ 265 μmol/L); bilirubin level of 3.0 mg/dL or lower (≤ 51 μmol/L); morphological diagnosis according to French-American-British (FAB) criteria; age 18 to 71 years.

7.1.1.2.3. Study treatments

Patients were randomised to either the test group receiving ATRA + ATO for induction and consolidation therapy, or the reference group receiving standard ATRA + idarubicin induction therapy, followed by 3 cycles of consolidation therapy with ATRA + chemotherapy (CT), and maintenance therapy with low-dose CT and ATRA.

Patients were administered induction therapy from Day 1 until complete remission (CR). As prophylaxis for APL differentiation syndrome (APLDS), prednisone at 0.5 mg/kg/day was administered from Day 1 until the end of induction. At the earliest signs of APLDS, ATO or ATRA or both were temporarily discontinued and intravenous (IV) dexamethasone administered at 10 mg every 12 hours (h) until disappearance of signs of APLDS for a minimum of 3 days. Guidelines for the prevention and management of coagulopathy, hyperleukocytosis, prolongation of QTc interval, and haematologic and non-haematologic toxicities were predefined in the protocol.

The doses of ATRA, ATO, and the CT agents; and the frequency of dosage in the different treatment phases are summarised in Figure 8.

Figure 8: Lo-Coco, 2013. Treatment regimen

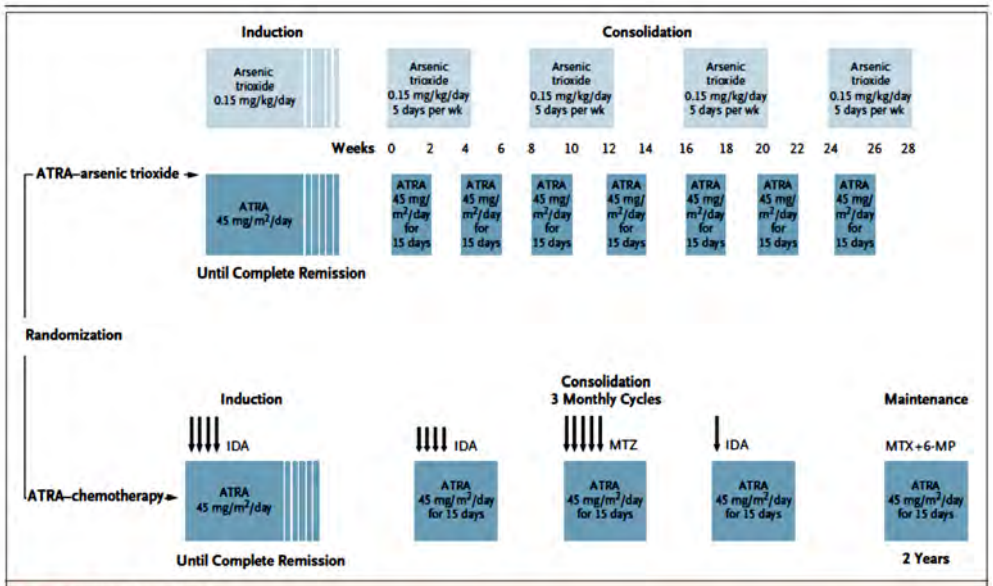


Figure 1. Treatment Groups

In the all-*trans* retinoic acid (ATRA)–chemotherapy group, the chemotherapy regimen was as follows: idarubicin (IDA) at a dose of 12 mg per square meter of body-surface area per day on days 2, 4, 6, and 8 of the induction phase; IDA at a dose of 5 mg per square meter per day on days 1 through 4 of the first cycle of consolidation therapy; mitoxantrone (MTZ) at a dose of 10 mg per square meter per day on days 1 through 5 of the second cycle of consolidation therapy; IDA at a dose of 12 mg per square meter per day on day 1 of the third cycle of consolidation therapy; and intramuscular or oral methotrexate (MTX) at a dose of 15 mg per square meter per week and oral 6-mercaptopurine (6-MP) at a dose of 50 mg per square meter per day, alternating with ATRA at a dose of 45 mg per square meter per day, for 15 days every 3 months for 2 years. The vertical lines in the induction-therapy boxes indicate variability in the duration of remission-induction therapy. The arrows indicate the approximate timing and doses of the different chemotherapeutic agents.

7.1.1.2.4. Efficacy variables and outcomes

The primary study end point was event-free survival (EFS) at 2 years after diagnosis. Treatment failure was defined as any of: haematological CR not achieved after induction therapy; molecular CR not achieved after 3 courses of consolidation; molecular relapse; haematological relapse; death.

Secondary endpoints included: the rate of haematologic CR after induction, the probability of overall survival (OS), the cumulative incidence of relapse, toxicity (using NCI CTCv3 for adverse events (AEs)), and the kinetics of minimum residual disease. Disease free survival (DFS) was defined as the time from achievement of haematologic CR to relapse (either molecular or haematologic), persistence of PCR positivity after consolidation therapy, or death, whichever occurred first.

7.1.1.2.5. Randomisation and blinding methods

Patients were enrolled in the study from multiple centres. Randomisation was centralised, and stratified according to the institution. There was no blinding as it was an open-label study.

7.1.1.2.6. Analysis populations

All efficacy analyses were based on the intention-to-treat (ITT) principle comparing groups according to the randomly assigned treatment. For the primary efficacy analysis for non-inferiority, a per-protocol (PP) analysis, which included patients who received protocol treatments as scheduled was conducted.

7.1.1.2.7. Sample size

The expected EFS rates in the reference and test groups were 85% and 95% respectively. It was determined, that evaluation of 73 patients per group would allow a determination that ATRA + ATO was not more than 5% inferior to ATRA + CT, with a type I error probability of 5% and

power of 92%. The target sample size was increased to 162 patients to allow for an expected rate of loss of 10%.

7.1.1.2.8. Statistical methods

Non-inferiority was assessed by estimating the 2-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%.

7.1.1.2.9. Participant flow

The pre-specified 162 patients were enrolled by September 2010, however genetic tests ruled out a diagnosis of PML-RARα–positive APL in 3 patients. Three of 159 patients with genetically confirmed APL did not start the assigned treatment (1 withdrew consent, and 2 had major protocol violations). Therefore, the ITT analysis included 156 patients who all received at least one dose of the assigned therapy after randomization (Figure 9).

Figure 9: Participant flow

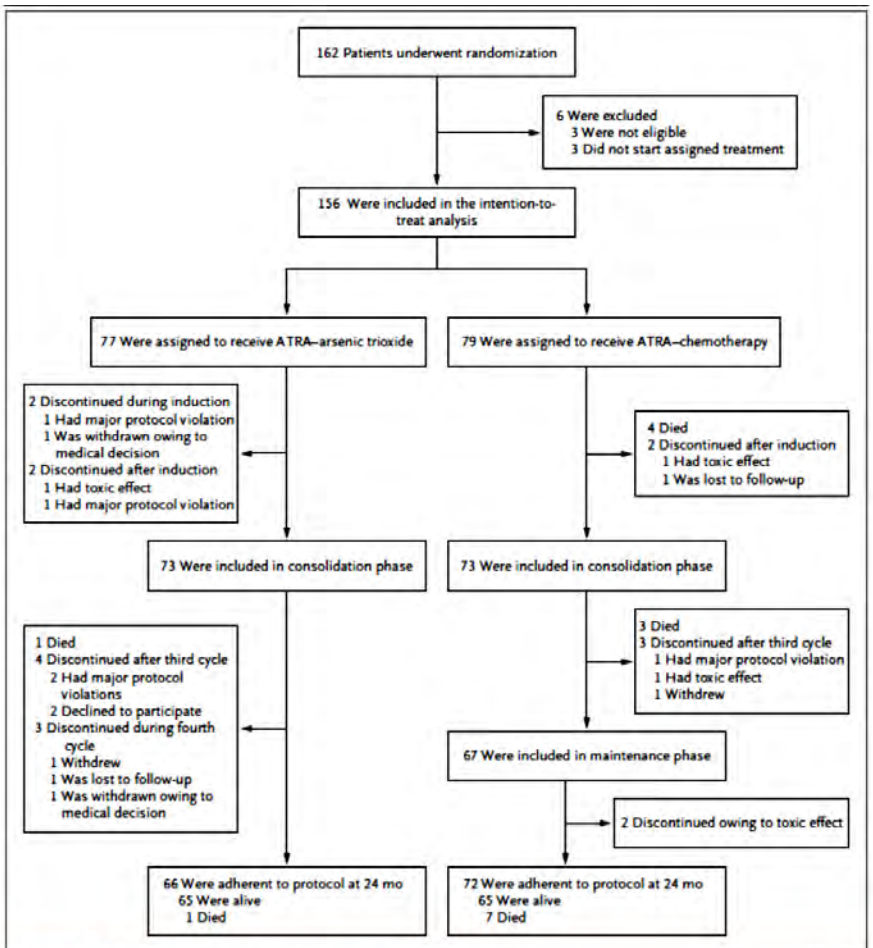


Figure 2. Study Enrollment, Randomization, and Retention.
In the ATRA–arsenic trioxide group, both the patients who did not complete induction therapy and the patient who discontinued treatment after induction therapy owing to a major protocol violation could be evaluated for postconsolidation polymerase-chain-reaction status and event-free survival at 2 years and thus were included in the intention-to-treat analysis. Two patients in the ATRA–arsenic trioxide group (one who withdrew from the study and one who was lost to follow-up during the fourth cycle of consolidation therapy) and one patient in the ATRA–chemotherapy group (who withdrew from the study after the third cycle of consolidation therapy) could not be evaluated for the primary end point owing to insufficient follow-up.

7.1.1.2.10. Baseline data

The median age was 45 years and there were equal number of female and male patients. The ATRA+ATO group had slightly lower proportion of patients with intermediate risk level

compared with the ATRA+CT group (57% versus 66%); other baseline disease characteristics such as median white cell count, platelet count, PML-RARα and FLT3-ITD mutation were similar across the 2 treatment groups.

7.1.1.2.11. Results for the primary efficacy outcome

7.1.1.2.11.1. Event-free survival (Primary end point)

Seven patients had a relapse during follow-up (2 in the ATRA + ATO group, at 22 and 27 months after diagnosis, and 5 in the ATRA + CT group, at 8, 14, 16, 21, and 35 months). In 2 of the 7 patients with disease recurrence, a relapse was detected at the molecular level before detection of the hematologic relapse, leading to early administration of salvage therapy. Of 156 patients in the ITT population, 6 (4%) could not be evaluated at 24 months for the primary analysis (3 from each group) because a molecular evaluation was not performed after the third consolidation cycle, or follow-up was insufficient. Of the remaining 150 patients, 97% in the ATRA + ATO group (72 of 74 patients) were alive and free of events at 24 months, as compared with 86% in the ATRA + CT group (65 of 76 patients) (difference, 11% 95% CI: 2 to 22). Since the lower bound of the 95% confidence interval for the difference in EFS rates was not lower than -5%, the non-inferiority of ATRA + ATO was confirmed (P < 0.001). Furthermore, the log-rank test for the difference in EFS curves indicated the superiority of ATRA + ATO (P = 0.02). In the PP population, the EFS rates were 97% in the ATRA – ATO group (64 of 66 patients) versus 85% in the ATRA–CT group (61 of 72) (difference: 12%; 95% CI, 2 to 23; P < 0.001 for non-inferiority).

7.1.1.2.12. Results for other efficacy endpoints

7.1.1.2.12.1. Secondary end points

Overall survival, disease-free survival, and cumulative incidence of relapse

The 2-year OS probability was 99% (95% CI: 96 to 100) in the ATRA + ATO group and 91% (95% CI: 85 to 97) in the ATRA + CT group (P = 0.02). The 2-year DFS rate was 97% (95% CI: 94 to 100) in the ATRA + ATO group and 90% (95% CI: 84 to 97) in the ATRA + CT group (P = 0.11). The 2-year cumulative incidence of relapse was 1% (95% CI: 0 to 4) in the ATRA + ATO group and 6% (95% CI: 0 to 11) in the ATRA + CT group (P = 0.24).

7.1.1.2.12.2. Induction therapy

All 77 patients in the ATRA + ATO group and 79 patients in the ATRA + CT group could be evaluated for a response to induction therapy. Hematologic CR was achieved in all patients in the ATRA + ATO group (100%) and in 75 of the 79 patients in the ATRA + CT group (95%) (P = 0.12). The median time to hematologic CR was 32 days (range 22 - 68) in the ATRA + ATO group and 35 days (range 26 - 63) in the ATRA+CT group (P = 0.61).

Four patients in the ATRA + CT group died during induction therapy: 2 from the APLDS, 1 from ischemic stroke, and 1 from bronchopneumonia. Induction therapy was terminated early in 2 patients in the ATRA + ATO group: in 1 because of a major protocol violation and in the other because of severe prolongation of the QTc interval and electrolyte abnormalities on Day 3. However, both these patients could be evaluated for a molecular response after consolidation therapy was given off protocol; and they were included in the ITT analysis.

7.1.1.2.12.3. Consolidation therapy

A total of 146 of 152 patients in hematologic CR proceeded to consolidation therapy. Two patients in the ATRA + CT group did not receive consolidation therapy because of a cardiotoxic effect, and were lost to follow-up. Besides the 2 patients who went off protocol during induction therapy, 2 additional patients in the ATRA + ATO group were taken off protocol after induction therapy owing to a toxic effect (repetitive tachycardia) and a major protocol violation. However, the patient with the protocol violation could be evaluated for the primary end point. Four patients died during consolidation therapy (3 in the ATRA + CT group and 1 in the ATRA +ATO group). The 3 patients in the ATRA + chemotherapy group died from haemorrhagic shock,

pulmonary embolism, and bronchopneumonia. The patient in the ATRA + ATO group died from bronchopneumonia associated with H1N1 virus infection.

After the third consolidation cycle, molecular CR was achieved in all 145 patients who could be evaluated for a molecular response (75 in the ATRA + ATO group and 70 in the ATRA + CT group). Four patients in the ATRA + ATO group did not proceed to their fourth consolidation cycle (2 declined to continue treatment and 2 had major protocol violations), while 3 patients (in the ATRA + ATO group) did not complete the fourth consolidation course owing to withdrawal of consent, loss to follow-up, and the treating physician's decision.

7.1.1.2.12.4. Maintenance therapy

A total of 67 of the 70 patients who completed consolidation therapy in the ATRA + CT 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).

Evaluator's Comments: This study shows that a combination of ATRA and ATO given for induction and consolidation therapy is at least not inferior and is possibly superior to standard ATRA and anthracycline based CT for adults with newly diagnosed, low-to-intermediate-risk APL. The observed advantage in the 2-year event-free survival with ATRA + ATO appears to be due mainly to lower mortality from causes other than relapse, probably as a consequence of reduced severe hematologic toxicity together with similar antileukemic efficacy (Figure 10).

This study excluded patients with high-risk disease which was based on three main factors: (1) the results of ATO treatment with or without ATRA in these patients were reported to be significantly inferior to the results in low-to-intermediate-risk patients (Ghavamzadeh, 2011; Estey E, 2006; Matthews V, 2006; Ravandi F, 2009), (2) Prolonged event-free and overall survival was routinely achieved in high-risk patients with risk-adapted consolidation therapy that included cytarabine (Sanz MA, 2010, Lo-Coco F, 2010; Ades L, 2008) and (3) there was concern about a potential increase in cases of the differentiation syndrome.

Figure 10: Hematologic toxic effects

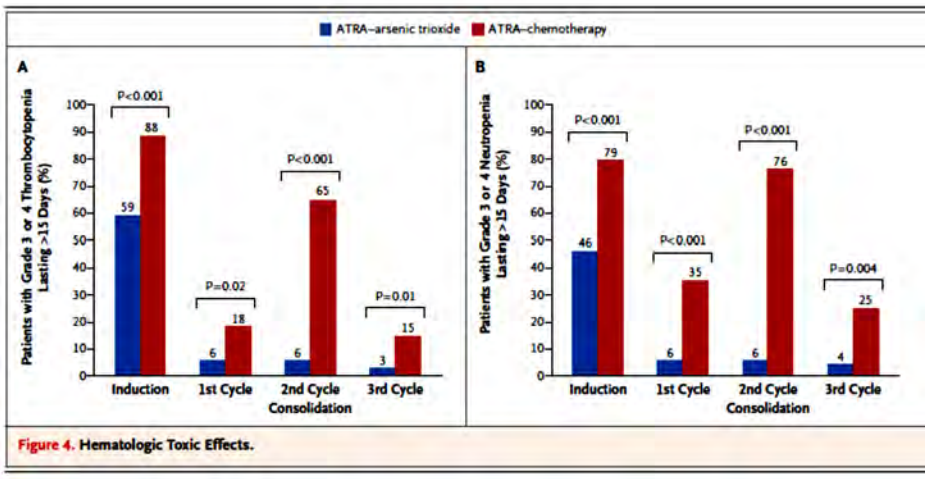


Figure 4. Hematologic Toxic Effects.

7.1.1.3. Dai et al, 2009.

7.1.1.3.1. Study Design and Methodology

In this, open-label, non-randomised, single-centre study , 90 patients with newly diagnosed acute promyelocytic leukemia (APL) were studied for all- trans retinoic acid (ATRA) and arsenic trioxide (As_2O_3) combination treatment in remission induction and post-remission therapy. In addition, 20 APL patients who had achieved complete remission (CR) with an ATRA-based regimen received ATRA/As_2O_3 combination for consolidation and maintenance. All enrolled patients were initially enrolled into 2 groups: Group A: 72 patients received an ATRA-based regimen for remission induction; group B: 90 patients received an ATRA plus As_2O_3 regimen for induction. Patients who achieved CR in Group A were further divided into 2 subgroups according to the different regimens for post-remission therapy: in Group A1, the post-remission regimen included As_2O_3 in addition to ATRA and CT; in Group A2, ATRA plus CT was used for consolidation and maintenance. Among group B, the patients who achieved CR (with the combination of ATRA and As_2O_3) constituted Group B1, in which the patients subsequently received ATRA and an As_2O_3-containing regimen for post-remission treatment (Figure 11).

Figure 11: Dai et al, 2009. Procedure of treatments.

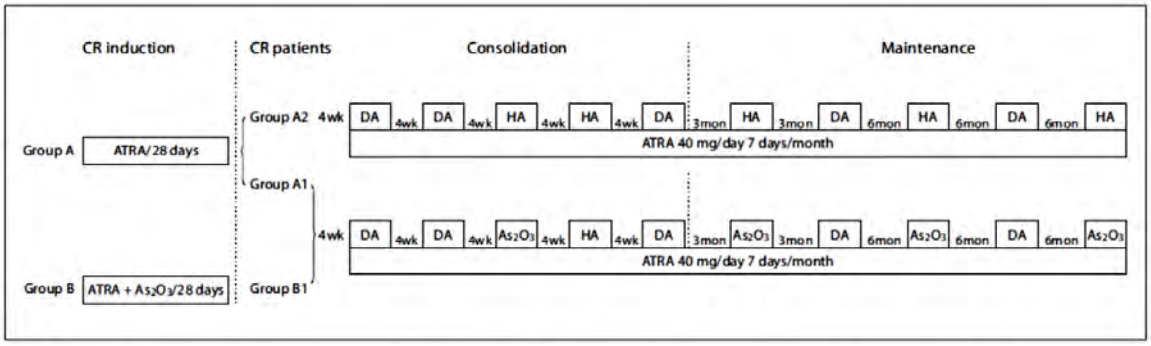


Fig. 1. Procedure of the treatments. During CR induction, ATRA and As_2O_3 was administrated for around 28 days. All CR patients took ATRA orally at a dose of 40 mg/day, 7 days per month for about 30 months for consolidation and maintenance. Besides, patients in group A2 received DA (daunorubicin 45/m^2/day for 3 days; Ara-C 150 mg/days for 5–7 days) and HA (homoharringtonine 2–4 mg/day for 3–5 days; Ara-C 150 mg/day for 5–7 days) regimens for consolidation (5 courses, with each interval of 4 weeks) and maintenance (5 courses, with the first 2 intervals of 3 months each; subsequently 3 intervals of 6 months each). For the patients in groups A1 and B1, DA, HA and As_2O_3 (10 mg/day for 10–14 days, intravenously) was administrated for postremission therapy in addition to ATRA, with the same courses and intervals as group A2.

7.1.1.3.2. Inclusion/ exclusion criteria:

Newly diagnosed patients with APL were included in the study. The diagnosis of APL was established according to clinical presentation and morphological criteria of the FAB classification, and was confirmed by cytogenic assay for t(15;17)(q22;q21) or RT-PCR analysis for PML-RARα transcripts. Patients with dysfunction of liver or kidney; any heart diseases or cardiac insufficiency; pregnant women; patient who rejected any antileukemic therapy or died before initiating the therapy were excluded from the study.

7.1.1.3.3. Study treatments:

7.1.1.3.3.1. Induction Regimens:

Group A received ATRA 45 mg/m^2/day orally for induction. Group B received combination ATO 10 mg iv per day for –28 days, and ATRA 45 mg/m^2/day for induction.

7.1.1.3.3.2. Consolidation/Maintenance regimens:

Both Group A1 and Group B1 received ATO 10 mg per day IV for 10 - 14 days as part of their regimen. The ATO was delivered as part of alternating courses of chemotherapy (DA or HA regimen). During consolidation and maintenance all 3 groups (A1, A2 and B1) received ATRA 40 mg/m^2/d orally for 7 days per month. A total of 5 courses were received for consolidation, with

intervals of 4 weeks between each course. The third course of the regimens was different: For patients in Groups A1 and B1: 2 courses of DA[9], were followed by 1 course of ATO, 1 course of HA[10] and 1 course of DA. For patients in Group A2: 2 courses of DA were followed by 2 courses of HA, and then 1 course of DA.

Patients then received 5 courses of maintenance therapy over approximately 24 months; with a 3-month interval for the first 2 courses and a 6-month interval for each of the remaining courses. For Groups A1 and B1: ATO and DA alternating. For patients in Group A2: the HA and DA regimens alternating (HA replacing the ATO course in the other regimen). Patients who achieved CR and subsequently relapsed were re-induced with ATO + ATRA combination therapy (Figure 11). Overall, the As_2O_3 was administered for 4 courses and the total dosage would be around 560 mg during the post-remission treatment for groups A1 and B1.

7.1.1.3.3.3. Supportive treatment:

If PT or PTT value was abnormal fresh frozen plasma (FFP) was infused. If PT was prolonged or fibrinogen level was <1 g/L cryoprecipitate fibrinogen was infused. Platelet transfusions were given to maintain a platelet count of more than 20 x 10^9/L and packed red cell transfusions were given to maintain a haemoglobin level higher than 7 g/dL. APLDS was treated with 45 mg methylprednisolone per day for 7 days. ATO was withdrawn immediately in cases of Grade 3 - 4 liver dysfunction.

7.1.1.3.4. Efficacy endpoints, statistical considerations:

Criteria for evaluation included the number of subjects and proportion achieving CR[11] and RFS[12], the time from achieving CR to last follow-up or relapse, or death.

Rates of CR were evaluated with contingency tables, X2 and Fisher's exact test. Differences of quantitative variables, such as age and peripheral BCC, were compared using one-way ANOVA method. Survival analyses were performed using the Kaplan-Meier estimate, and the log-rank tests for comparisons. Relapse free survival (RFS) was calculated from the date of CR. All P values of ≤ 0.05 indicated statistical significance.

7.1.1.3.5. Participant flow, baseline data

A total of 162 newly diagnosed APL patients were enrolled; Group A1 (with ATO) included 20 patients; A2 (not ATO) included 45 patients and Group B1 (with ATO) included 84 patients. The median age was 29 - 31 years (14 - 67years) and majority were males (n = 86, females = 63). Other baseline disease characteristics such as WBC count, platelet count, etc were similar in Groups A and B.

Evaluator's Comments: The baseline severity of disease (low/ intermediate or high risk) was not mentioned in this study.

7.1.1.3.6. Results:

Of the 162 evaluable patients, 149 (92.0%) entered CR; these included 65 (90.3%) of the 72 subjects in Group A and 84 (93.3%) of the 90 subjects in Group B. The difference in CR rates was not statistically significant between the 2 groups (P = 0.566). The remaining 13 patients, failed to achieve CR, due to early death (12 patients) or therapy resistance (1 patient). Nine early

[9] DA regimen – D 45 mg/m^2/day for 3 days; Ara-C 150 mg/day for 5 - 7 days
[10] HA regimen – H 2 - 4 mg/day for 3 - 5 days; Ara-C 150 mg/day for 5 - 7 days.
[11] Definition of CR required that clinical evidence of APL be absent, neutrophil count be higher than 1.5x10 [9] /liter, untransfused Hb be over 10 g/dl, an unsupported platelet count be more than 100x10 [9]/liter, and the bone marrow analysis show normocellularityto moderate hypocellularity with less than 5% blasts plus promyelocytes and absence of Auer rod-containing leukemic cells.
[12] RFS was calculated from time of achieving CR to last follow-up or relapse, death from any causes or censoring of the data on the patients, whichever occurred first.

deaths were attributable to cerebral haemorrhage, 2 were owing to infection and 1 was owing to pulmonary haemorrhage. The causes of death during induction were similar in both groups.

There was a statistically significant difference in the length of time to achieve CR between the 2 groups (P = 0.01), with the median time of 39 days (range 25 - 62 days) in Group A and 31 days (range 18 - 59) in Group B; The difference could not be attributed to the chemotherapy (hydroxyurea or homoharringtonine) added during remission induction, because no statistical differences were found in the frequencies of the chemotherapy administration between the 2 groups (p = 0.495). The APL differentiation syndrome (retinoic acid-like syndrome) was diagnosed in 5 patients (2 in Group A and 3 in group B), no patients died of this complication.

Of the 65 patients who entered CR from Group A, 20 (Group A1) received As_2O_3/ATRA/CT for postremission treatment, so did the patients of Group B1 (84 obtained CR with As_2O_3/ATRA regimen). In Group A2 (n = 45), in which the patients received ATRA and CT for postremission therapy, 10 of the 45 patients relapsed within 28 months. In Group A1, only 1 of the 20 patients relapsed within 1 year; in Group B1, 4 of the 84 patients relapsed within 29 months. The relapsed patients were re-induced with As_2O_3/ATRA combination therapy and 8 of the 10 relapsed patients in Group A2 and 3 of the 5 relapsed patients in Groups A1 plus B1 entered CR again.

The Kaplan-Meier RFS survival curves of the 3 groups are shown in Figure 12. There were statistically significant differences in the estimated survival curves between Groups A2 and B1 (p = 0.004) as well as between Groups A2 and A1 (p = 0.048). No statistical difference was observed between groups A1 and B1 (p = 0.992).

The 3-year Kaplan-Meier estimates for RFS:

Group A1: 93.8% +6.1% at a median follow-up of 30 months (range 2 – 59 months)

Group A2: 72.4 +7.6% at a median follow-up of 32 months (range 2 - 59 months)

Group B1: 92.6 +3.7% at a median follow-up of 30 months (range 1 – 58 months).

There were statistically significant differences in the estimated survival between Groups A2 and B1 (P = 0.004) and also between Groups A2 and A1 (P = 0.048) with both Groups A1 and B1 having longer survival than Group A2 (Figure 13).

Figure 12: Kaplan-Meier RFS survival curves

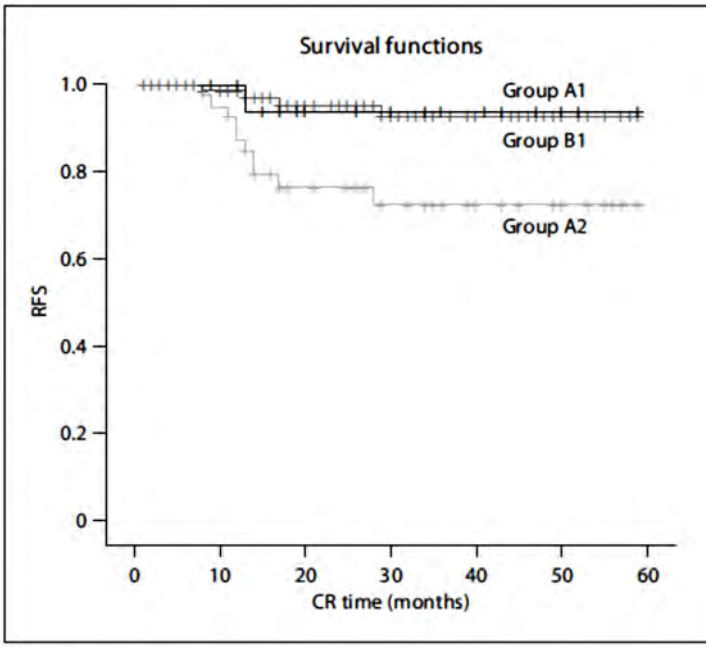


Fig. 2. Kaplan-Meier RFS survival curves. p = 0.004, group A2 vs. group B1; p = 0.048, group A2 vs. group A1; p = 0.992, group A1 vs. group B1.

Figure 13: Kaplan-Meier RFS survival curves

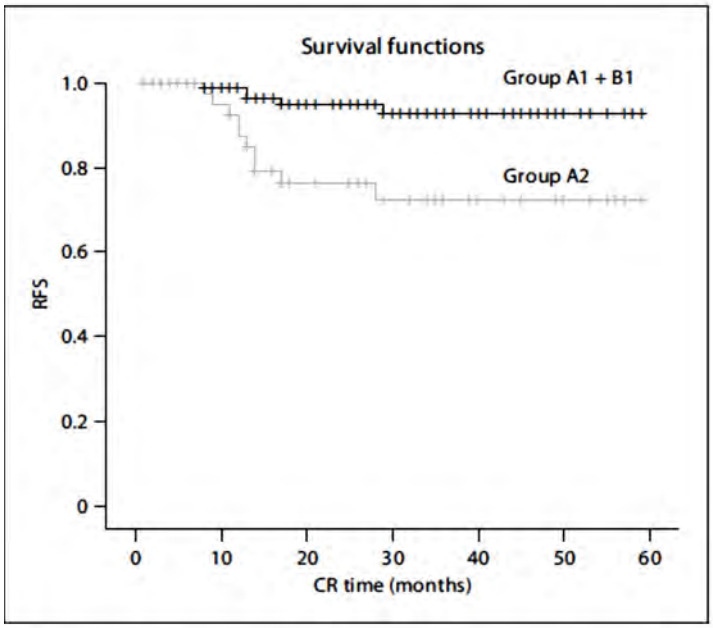


Fig. 3. Kaplan-Meier RFS survival curves. p = 0.002, group A2 vs. group A1+B1.

Evaluator's Comments: In this study, the ATRA-based regimen and ATRA plus As_2O_3 regimen were administered to induce remission for newly diagnosed APL patients. The results showed that both regimens yielded high CR rates (90.3 and 93.3%, respectively), with very low incidence of APLDS

(retinoic acid-like syndrome; 2.8 and 3.3%, respectively). The difference of the CR rates was not statistically significant; nevertheless, the median time to enter CR in group B (median: 31 days; range: 18 – 59 days) was significantly shorter than that in Group A (median: 39 days; range: 25 – 62 days; p = 0.01). This is consistent with the results reported by Shen et al. Furthermore, results indicated that the combination of ATRA and As_2O_3, as a synergistic therapy for remission induction and post-remission treatment, could yield a better clinical outcome than the ATRA/CT therapy, but interpretation was limited due to the following:

- The ATRA/CT regimen used in this study is not currently standard as ATRA was used alone for induction and CT (DA, HA and AR-c) only added during consolidation phase. Hence, it is not possible to draw any definite conclusions on comparisons between the ATRA/ As_2O_3 combination and the 'standard ATRA/CT regimen'.
- Assignment of treatment regimens was not randomised although several features of this study reduced the chance of bias as baseline clinical characteristics of the patients in various groups were nearly identical; the frequencies of chemotherapy administration during remission induction were not statistically different between the groups; the supportive measures were identically used only if the patients needed them.
- Baseline severity of disease (low/intermediate or high risk) was not provided.

Despite the above limitations, results of this study did suggest that newly-diagnosed APL patients may benefit from the early use of As_2O_3 in combination with ATRA both for induction as well as consolidation (post-remission).

7.1.2. Other efficacy studies (published studies)

7.1.2.1. Controlled studies with ATO in combination treatment

7.1.2.1.1. Shen, et al. 2004.

A randomised, open-label, Phase III, comparative, multi-centre, trial was designed to compare the effects of the combination of ATRA and ATO with the effects of ATRA or ATO as monotherapy in remission induction and maintenance therapy in 61 newly diagnosed patients with APL. The diagnosis of APL was established according to clinical presentation and morphological criteria of the FAB classification, and was confirmed by cytogenic assay for t(15;17)(q22;q21) and RT-PCR analysis for PML-RARα transcripts. CR was determined by haematological analysis, tumour burden was examined with real-time quantitative RT-PCR of the PML-RARα (promyelocytic leukemia-retinoic acid receptor) fusion transcripts, and side effects were evaluated by means of clinical examinations.

Patients were randomised into 3 groups: Groups 1, 2 and 3, for induction therapy (induction of remission), followed by consolidation therapy once they had achieved a CR, and finishing their treatment with 5 cycles of maintenance treatment. During induction Group 1 received ATRA (25mg/m^2/day), Group 2 received ATO (0.16 mg/kg/day) and Group 3 received both ATRA + ATO. All groups were administered CT as consolidation, consisting of 3 consecutive regimens: DA regimen (daunorubicin, 45 mg_m^2 per day for 3 days; Ara-C, 100 mg/m^2 per day for 7 days), Ara-C ''pulse'' regimen (Ara-C, 1.5–2.5 g/m^2 per day for 3 days), and HA regimen (homoharringtonine, 2–3 mg/m^2 per day for 3 days; Ara-C, 100 mg/m^2 per day for 7 days).

Patients then received a total of 5 maintenance therapy cycles (each lasting 60 - 90 days). For maintenance, the 3 groups received 30 days of ATRA, ATO or ATRA and ATO sequentially (each 30 days) according to their initial randomisation, followed by 30 days with either 6-mercaptopurine (6MP) or methotrexate (MTX)[13].

Criteria for evaluation included the rate and proportion of subjects achieving complete remission (CR)[14]. DFS was calculated, defined as the time from CR to relapse, death from any cause, or censoring of the data on the patients.

During induction treatment serial examinations of whole peripheral blood cell counts, BM morphological analysis, renal and hepatic function tests, fibrinogen, DD dimers, fibrin degradation product (FDP), prothrombin time (PT) and activated partial thromboplastin time (aPTT) were conducted. Patients whose white blood cell (WBC) counts were <10 x 10^9/L were given hydroxyurea (daily doses of 20 - 40 mg/kg) or a CT regimen containing idarubicin 6 mg/m^2 per day for 3 days and Ara-C: 100 mg/m^2 per day for 3 - 5 days (IA regimen). Hepatotoxicity was closely monitored and ATO was reduced to half the dose (0.08 mg/kg/day) and symptomatic therapy commenced for patients with grade 0 - 1 liver dysfunction. Patients with Grade 2 - 4 liver dysfunction were withdrawn from the study immediately.

Differences of quantitative variables, such as age, peripheral BCC, BM blast cell counts, and copy number, and reduction fold of PML-RARα fusion transcripts, were compared with Wilcoxon rank-sum test, whereas X2 (including Fisher's exact test) was used for categorical variables, including sex distribution, rate of toxic effects and relapse frequency. DFS using Kaplan-Meier curves.

The median age ranged from 30 to 39 years in the 3 treatment groups and majority of patients were males (45 - 60%). The baseline characteristics were generally similar across the 3 treatment groups (Table 6).

Out of a total of 61 subjects, only 4 failed to achieve CR during the trial. The 4 patients who failed to achieve CR died of intracerebral haemorrhage on day 1, 2, 8, and 15 respectively. CR rates were 95%, 90% and 95.2% in the ATRA, ATO and ATRA+ATO groups, respectively (Table 6).

However, subjects achieved CR fastest in Group 3, the combination ATRA + ATO group, with a median of 25.5 days to CR (range 18 - 35), while the medians in Groups 1 and 2 were 40.5 and 31 days respectively.

Five subjects in Group 1 relapsed within 13 months after achieving CR (26.3%). Three of these patients achieved second remission with ATO based re-induction therapy. The remaining 2 died of cerebral haemorrhage. Two subjects in Group 2 relapsed within 1 year after achieving CR (11.1%). One of these patients achieved second remission with ATO based re-induction therapy and the other achieved second remission with combined ATO and ATRA re-induction regimen. No patients in Group 3 had relapsed at the time the results were published. There was a statistically significant difference in relapse between Group 1 and Group 3 (P = 0.0202, Fisher's exact test).

[13] Maintenance treatments were different among the three groups, i.e., group 1 (ATRA, 25 mg_m2 per day for 30 days; then 6- mercaptopurine, 100 mg/day for 30 days or 15 mg of methotrexate once a week for 4 weeks), group 2 (As2O3, 0.16mg/kg per day for 30 days; then 6-mercaptopurine, 100 mg/day for 30 days or 15 mg of methotrexate once a week for 4 weeks), and group 3 (ATRA 25 mg/m^2 per day for 30 days; then As_2O_3 0.16 mg/kg per day for 30 days; then 6-mercaptopurine, 100 mg/day for 30 days or 15 mg of methotrexate once a week for 4 weeks).

[14] CR was defined as clinical evidence of absence of APL: untransfused haemoglobin >100 g/L, neutrophils >1.5 x 10^9/L, platelets >100 x 10^9/L, and bone marrow (BM) morphology revealing normocellularity with <5% promyelocytes and absence of Auer rod containing leukemic cells.

Table 6: Clinical data of the patients

	Treatment options (group)		
	ATRA (1)	As_2O_3 (2)	ATRA/As_2O_3 (3)
General data			
Cases	20	20	21
Sex (M/F)	12/8	9/11	12/9
Median age	30.5	39.5	34
(range, years)	(14–74)	(15–69)	(14–62)
Median WBC	3.0	2.7	2.1
(range, × 10^9/liter)	(1.2–49.4)	(0.9–40)	(0.5–52.6)
<2	6	8	7
2–10	10	8	8
>10	4	4	6
Median hemoglobin	77	76	81
(range, g/liter)	(43–123)	(34–105)	(53–120)
Median platelet	23	27	30
(range, × 10^9/liter)	(4–76)	(12–72)	(6–73)
Median % of blasts and promyelocytes in BM (range)	86 (31–94)	87.1 (38–95.5)	88.5 (70.5–96.5)
Treatment outcome			
CR (%)	19 (95%)	18 (90%)	20 (95.2%)
Median days to CR (range)	40.5 (25–65)	31 (28–38)*	25.5 (18–35)†‡
Accumulated dosage, mg			
Median(range) of ATRA	1,230 (750–1,950)		810 (578–1,200)
Median (range) of As_2O_3		290 (235–380)	210 (100–300)§
Chemotherapy administration (%)	11 (57.9%)	12 (66.7%)	14 (70%)
Side effects			
Skin reaction	4 (21%)	0	2 (10%)
Dysrhythmia	0	0	0
Gastrointestinal reaction	0	1 (5.6%)	1 (5%)
Dryness of mouth	11 (57.9%)	2 (11.1%)	12 (60%)
Headache	4 (21%)	1 (5.6%)	2 (10%)
Hyperleukocytosis	10 (52.6%)	12 (66.7%)	14 (70%)
Liver dysfunction			
Grade 1	4	7	8
Grade 2	0	2	3
Grade 3	1	2	2
Grade 4	0	0	0

*, $P = 0.0233$ vs. group 1; †, $P = 0.0003$ vs. group 1; ‡, $P = 0.002$ vs. group 2; §, $P = 0.046$ vs. group 2. The frequencies of side effects were calculated in patients who achieved CR.

Median DFS was 13 months in Group 1, 16 months in Group 2 and 20 months in Group 3.

Examination of whole peripheral blood cell counts revealed earlier recovery of normal platelets counts (>100x 10^9/liter) in group 3 (median, 22 days) over group 1 (median, 32 days, P 0.03) as well as group 2 (median, 33 days, P 0.031) whereas both the recovery time of Hb and that of white blood cell counts were found similar among three groups.

As expected, no marked differences of PML-RARα DoseN (the change of calibrated copy number by RT-PCR) were found among the three groups at diagnosis. When exposed to ATRA and/or As_2O_3 for 3 weeks (or shortly after CR), the median PML-RARα DoseN decreased quickly. The decrement was much stronger in the combination therapy group than that of the two monotherapy groups (Group 1 versus Group 3, P 0.0092; Group 2 versus Group 3, P 0.041), and Group 2 also differed statistically from Group 1 (P 0.013). After chemotherapy consolidation, the PML-RARα DoseN decreased further. Although the median level seemed lower in the combination therapy group than those of the other two groups, a statistically significant difference was observed only between Group 1 and Group 3 (P 0.0489) (Table 7). Of note, the PML-RARα DoseN increased for a short period in some patients during induction therapy, but the peaks of copy number coincided with the peak of hyperleukocytosis and then decreased quickly in parallel to white blood cell counts after further treatment. Finally, among the 7

patients who developed relapse during first CR, their PML-RARα DoseN all increased to a level above 1,000 before the clinical manifestations occurred. Therefore, these results confirm the previous report that PML-RARα DoseN can be considered as a useful tool to predict pending relapse.

Possible mechanisms of in vivo synergistic effects between ATRA and As_2O_3, were investigated in a series of in vitro studies. In situ terminal deoxynucleotidyltransferase labelling (TUNEL) results revealed more apoptotic cell percentage when NB4 cells or primary APL cells were exposed to the two drugs at the same concentrations for 6 to 10 days, as compared with those treated with As_2O_3 or ATRA alone (Table 8). BM smears from patients treated with different protocols revealed similar tendencies, in that significantly more apoptotic cells were found after 2 or 3 weeks of treatment in Group 3 than in the other two groups (Table 9).

Table 7: Results of quantitative real time RT-PCR

	Treatment options (group)		
Sample collection	ATRA (1)	As_2O_3 (2)	ATRA/As_2O_3 (3)
Pretreatment	$n = 19$	$n = 18$	$n = 20$
Median of copy number (range)	4,595.6 (1,305.6–531,249)	6,655.7 (1,777.2–681,692.1)	5,155.3 (1,111.2–618,050)
After CR	$n = 19$	$n = 18$	$n = 20$
Median of copy number (range)	793.5 (37.5–26,680)	286.3 (19.1–13,543)*	177.3 (0.7–389.9)†‡
Median of reduction fold (range)	6.7 (1.1–1152.7)	32.1 (2.4–993.5)§	118.9 (2.2–3,559.0)¶‖
After consolidation	$n = 14$	$n = 11$	$n = 14$
Median of copy number (range)	71.6 (0.39–481.2)	41.3 (0.39–362.5)	15.2 (0.03–252.4)**
Median of reduction fold (range)	369.5 (22.2–19683.4)	521.3 (18.1–46899)	800 (25.9–523008)††‡‡

*, $P = 0.013$ vs. group 1; †, $P = 0.0092$ vs. group 1; ‡, $P = 0.041$ vs. group 2; §, $P = 0.0001$ vs. group 1; ¶, $P = 0.0001$ vs. group 1; ‖, $P = 0.0079$ vs. group 2; **, $P = 0.0489$ vs. group 1; ††, $P = 0.018$ vs. group 1; ‡‡, $P = 0.036$ vs. group 2.

Table 8: Percentages of TUNEL positive cells in cultured cells

	Treatment options (group)		
Time after treatment, days	ATRA (1)	As_2O_3 (2)	ATRA/As_2O_3 (3)
Cultured NB4 cells			
2	1.5 ± 1.0	1.5 ± 1.0	2.0 ± 0.9
4	2.0 ± 1.0	2.5 ± 1.3	3.5 ± 2.3
6	2.0 ± 1.5	8.5 ± 2.6*	14.5 ± 2.6†
8	4.5 ± 0.9	12.0 ± 2.2	20.5 ± 4.8‡
10	5.0 ± 1.7	14.5 ± 3.1§	28.0 ± 5.2¶‖
Cultured primary APL cells			
2	1.0 ± 0.5	1.0 ± 0.5	1.5 ± 0.9
4	1.3 ± 1.0	2.2 ± 1.2	3.8 ± 2.0
6	2.2 ± 0.8	5.8 ± 1.5	11.3 ± 3.5**
8	3.8 ± 0.8	8.9 ± 2.5	17.2 ± 3.4††
10	4.0 ± 1.3	12.7 ± 2.4‡‡	24.3 ± 5.7§§¶¶

*, $P = 0.025$ vs. group 1; †, $P = 0.001$ vs. group 1; ‡, $P = 0.001$ vs. group 1; §, $P = 0.024$ vs. group 1; ¶, $P < 0.0001$ vs. group 1; ‖, $P = 0.02$ vs. group 2; **, $P = 0.01$ vs. group 1; ††, $P = 0.002$ vs. group 1; ‡‡, $P = 0.026$ vs. group 1; §§, $P < 0.0001$ vs. group 1; ¶¶, $P = 0.035$ vs. group 2.

Table 9: Changes of bone marrow haematology and TUNEL-positive cells in APL patients.

Treatment options (group)	Cells	Time after treatment, days 0	13–16	19–23	30–35
ATRA (1)					
	TUNEL-positive cells, %	0	1.0 ± 0.5	0.5 ± 0.5	1.5 ± 1.0
	Cell type, %				
	Myeloblast	2.6 ± 1.6	0.5 ± 0.5	0.5	2.3 ± 1.8
	Promyelocyte	81.2 ± 11.4	9.8 ± 3.5	6.2 ± 6.4	6 ± 4.6
	Myelocyte	4.5 ± 2.2	27.7 ± 6.9	27.3 ± 15.6	11 ± 8.0
	Metamyelocyte	1.2 ± 0.8	20.8 ± 5.3	16.3 ± 11.0	10.5 ± 7.5
	Band	1.2 ± 0.8	3.5 ± 2.1	7.3 ± 2.4	10.2 ± 4.0
	Segmented		4.5 ± 2.8	9 ± 5.8	12.3 ± 10.8
	Erythroid lineage	3.5 ± 2.4	27.5 ± 11.5	21 ± 15.7	30.7 ± 5.9
	Lymphoid lineage	4.6 ± 1.5	7 ± 5.6	8.8 ± 9.4	9.3 ± 7.1
As_2O_3 (2)					
	TUNEL-positive cells, %	0	6.8 ± 2.2*	12.6 ± 3.7†	0.5 ± 0.5
	Cell type, %				
	Myeloblast	3.0 ± 1.5	0.5	1 ± 0.7	0.7 ± 0.3
	Promyelocyte	78.2 ± 9.7	8.7 ± 6.1	4.3 ± 2.2	3.6 ± 1.8
	Myelocyte	5.4 ± 2.7	18.5 ± 5.2	19.3 ± 2.2	11.8 ± 4.7
	Metamyelocyte	2.5 ± 1.4	11.5 ± 6.1	13.4 ± 4.4	8.2 ± 3.6
	Band	0.6 ± 0.5	8.5 ± 3.1	14.6 ± 4.8	12.2 ± 3.1
	Segmented		3.2 ± 1.3	13.4 ± 4.9	11.4 ± 9.5
	Erythroid lineage	4.5 ± 3.2	28.7 ± 4.3	25.3 ± 6.1	29.6 ± 10.6
	Lymphoid lineage	3.8 ± 2.2	14.2 ± 6.2	10.4 ± 6.1	15.6 ± 6.1
ATRA/As_2O_3 (3)					
	TUNEL-positive cells, %	0	16.3 ± 4.3‡§	25.4 ± 4.1‡¶	0.8 ± 0.5
	Cell type, %				
	Myeloblast	2.8 ± 1.4	2.6 ± 2.0	0.5	1 ± 0.4
	Promyelocyte	82.8 ± 9.1	6.3 ± 6.1	2.8 ± 1.8	3 ± 0.7
	Myelocyte	3.8 ± 1.5	33.9 ± 11.7	6.8 ± 1.8	10.3 ± 4.2
	Metamyelocyte	2.0 ± 0.8	19.5 ± 10.8	21 ± 20.8	9.4 ± 4.8
	Band	1.0 ± 0.8	4.3 ± 3.4	13.5 ± 6.3	12.9 ± 2.9
	Segmented		7.9 ± 8.9	6.7 ± 2.1	14.6 ± 2.8
	Erythroid lineage	2.2 ± 1.2	12.4 ± 9.4	36.8 ± 34.4	27.8 ± 3.5
	Lymphoid lineage	5.5 ± 3.6	8.4 ± 3.1	11.5 ± 9.3	16.2 ± 2.4

*, $P = 0.034$ vs. group 1;†, $P = 0.001$ vs. group 1; ‡, $P < 0.0001$ vs. group 1; §, $P = 0.036$ vs. group 2; ¶, $P < 0.0001$ vs. group 1; ‖, $P = 0.021$ vs. group 2.

Evaluator's Comments: CR rates in three groups were all high (>90%), but the time to achieve CR differed significantly, with the shortest time to CR observed in the ATRA+ATO combination group. Earlier recovery of platelet count was also found in this group. The disease burden as reflected by fold change of PML-RARα transcripts at CR decreased more significantly with combined ATRA+ As_2O_3 therapy compared with ATRA or As_2O_3 mono-therapy ($P < 0.01$). This difference persisted after consolidation ($P < 0.05$). Importantly, all 20 cases in the combination group remained in CR whereas 7 of 37 cases treated with mono-therapy relapsed ($P < 0.05$) after a follow-up of 8 – 30 months (median: 18 months). Synergism of ATRA and on apoptosis and degradation of PML-RAR oncoprotein might provide a plausible explanation for superior efficacy of combinative therapy in clinic. Overall, the ATRA+As_2O_3 combination of two selective differentiation-apoptosis inducers showed cooperative effect in a combined induction and consolidation therapy protocol in a reasonable sample size of newly diagnosed human leukemia and better results than either of the two drugs used alone in terms of the quality of CR and the status of the disease-free survival.

Some limitations of this study were:

- dose of ATRA (25mg/m^2/day) used was lower than proposed dose of 45mg/m^2/day and dose of As_2O_3 (0.16mg/kg/day) was slightly higher than proposed 0.15,g/kg/day.
- the severity of baseline disease (low, intermediate. high risk) was not specified.
- Follow-up was only up to 32 months.

7.1.2.1.2. Powell et al, 2010.

This study randomised 481 patients (>15 years) with untreated APL (stratified by age group: 15 - 60 years > 60 years) to standard induction and consolidation therapy with or without two 25 - day courses of As_2O_3 consolidation given after the standard induction and before the consolidation treatments (Figure 14). By study design children < 15 years of age were assigned to the standard non- As2O arm. Remission induction therapy used oral ATRA (45 mg/m^2/day, divided in twice-daily doses) beginning on day 1 and continuing until CR or day 90, cytarabine (200 mg/m^2 daily as a continuous intravenous infusion for 7 days) on days 3 through 9, and daunorubicin (50 mg/m^2 intravenously daily for 4 days) on days 3 through 6. Supportive care including management of coagulopathy15, transfusions, and antibiotics was at the discretion of the treating physician. Treatment of suspected APL differentiation syndrome was directed by the study and included dexamethasone 10 mg twice daily for 3 days and holding ATRA until symptoms resolved.

Figure 14: Powell et al, 2010. C9710 Treatment

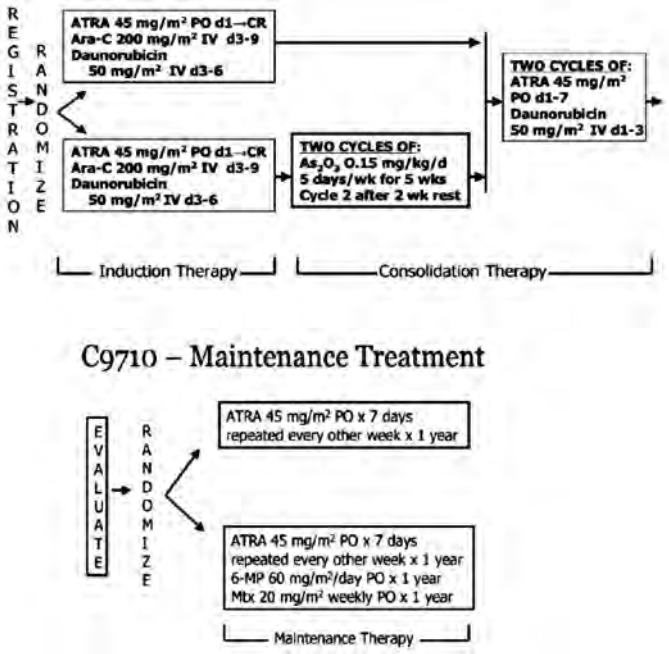


Figure 1: Treatment schema for C9710, a prospective randomized clinical trial evaluating As_2O_3 as early consolidation for adults with APL in first remission.

Consolidation therapy for both study arms began within 2 to 4 weeks of achievement of hematologic remission. Patients randomly assigned to the investigational arm received two 25-day courses of $As2O_3$ (0.15 mg/kg daily intravenously over 1 hour for 5 days each week for 5 weeks) with a 2-week interval between courses. All patients received standard consolidation with 2 courses of ATRA (45 mg/m^2 daily in divided doses for 7 days) plus daunorubicin (50 mg/m^2 intravenously daily on the first 3 days). Patients who remained in CR after completion of consolidation therapy were assigned by a second randomization (stratified by consolidation arm and by age group: 15 - 60 and > 60 years) to one year of ATRA maintenance (45 mg/m^2 daily in divided doses for 7 days repeated every other week), with or without oral 6-mercaptopurine (60 mg/m^2 daily) and oral methotrexate (20 mg/m^2 weekly). Maintenance therapy began 2 to 4 weeks after recovery from the final course of consolidation therapy. The initial 50 patients were randomized to maintenance ATRA or observation. When preliminary results from other trials suggested a benefit from maintenance therapy, this study was amended to the randomized treatments described above.

15 Study requirements included coagulation tests at least 3 times per week until normal and use of heparin was discouraged.

The primary endpoint for the randomized comparison of the 2 consolidation arms was EFS, defined as the time from study entry to first event. An event was defined as failure to achieve a CR, relapse after achieving a CR, or death. Disease-free survival (DFS) was defined as the time from attainment of a CR to relapse or death. Overall survival was defined as the time from study entry to death. Response and relapse were defined by 1990 NCI criteria.18 Toxicity was graded using the NCI Common Toxicity Criteria version 2.X. Risk status was defined as low or intermediate for WBC count < 10 x 10^9/L and high for WBC count > 10 x 10^9/L. Interim analyses were conducted semiannually by the independent CALGB Data and Safety Monitoring Board (DSMB) using the guidelines by Friedlin et al, and compared EFS, DFS, and survival using log-rank tests. Kaplan-Meier estimates were used for comparison of EFS, DFS, and survival at 3 years. All analyses were based on intention-to-treat and included all patients who had a confirmed diagnosis of APL and any available data, independent of the amount of therapy received or compliance with protocol therapy and follow-up.

Overall, 518 adults (15 - 79 years) with untreated APL were enrolled of whom 37 did not have confirmation of PML-RARα by RT-PCR, were ineligible and were not included in the analyses.

Patient characteristics of the 481 patients randomized to the standard arm and to the As_2O_3 investigational arm were very similar. Majority of patients were aged 15 - 60 years (85%), White (80%) with ECOG PS of 0 or 1 (75%) and belonged to low (28%) or intermediate (48%) risk group (only 23% were high risk).

The participant flow during the induction, consolidation and maintenance therapy were summarised in Figure 15.

Figure 15: CONSORT Flow Diagram

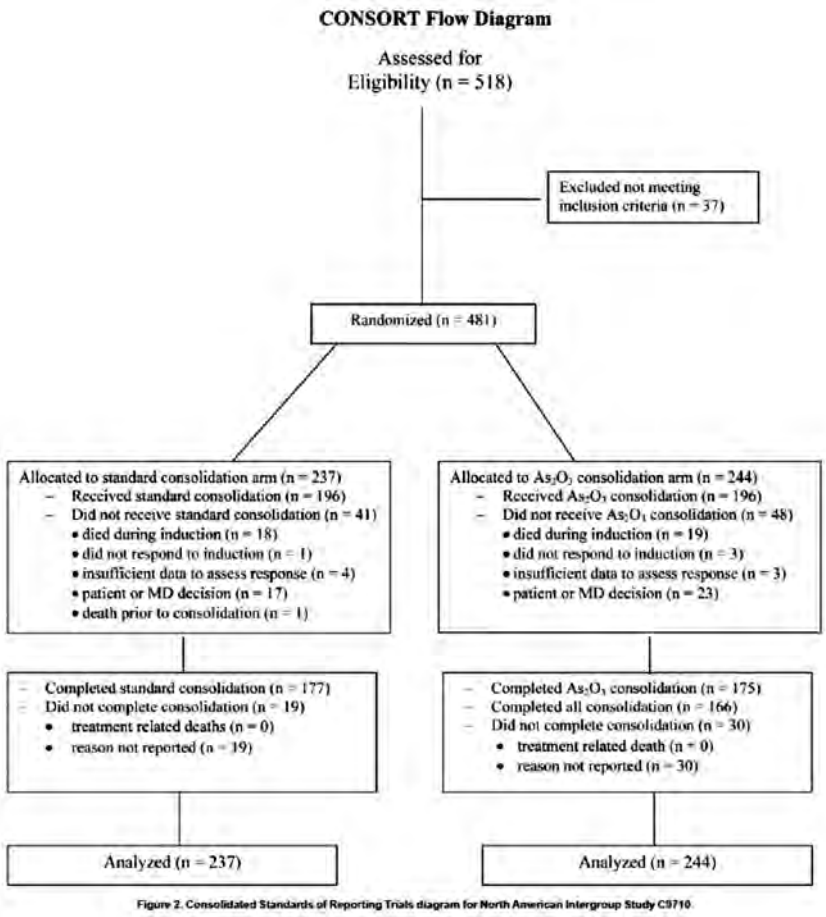


Figure 2. Consolidated Standards of Reporting Trials diagram for North American Intergroup Study C9710

Induction therapy was identical for both arms and yielded similar response rates of 90%: 213 of 237 and 219 of 244, respectively. Nineteen patients (8%) on each arm died during induction.

One patient on the standard arm and 3 on the As_2O_3 arm had persistent leukemia reported. Four and 3 patients, respectively, had insufficient data to evaluate response. The APL differentiation syndrome was reported in 177 (37%) patients and 162 received dexamethasone.

Of 213 responding patients on the standard arm, 196 (92%) received consolidation therapy, and 177 of 196 (90%) completed the planned consolidation therapy. Of the 219 responding patients randomized to the As_2O_3 arm, 196 (89%) received at least one dose of As_2O_3 during consolidation therapy; 175 of the 196 (89%) completed both courses of the As_2O_3 consolidation, and 166 of 196 (85%) completed all planned consolidation. There were no treatment-related deaths reported during consolidation therapy.

Results: EFS was significantly better for patients randomized to receive As_2O_3 consolidation therapy with 51 events compared with 97 events on the non- As_2O_3 arm (stratified log-rank test, P 0.0001); EFS at 3 years was 80% versus 63% (P <0 .0001). As_2O_3 consolidation provided significant benefit both to patients with low/intermediate risk (P <0 .0003) and to those with high risk APL (P<0 .015) (Figure 16).

Figure 16: A: Event free survival by treatment B: EFS by treatment and Risk group

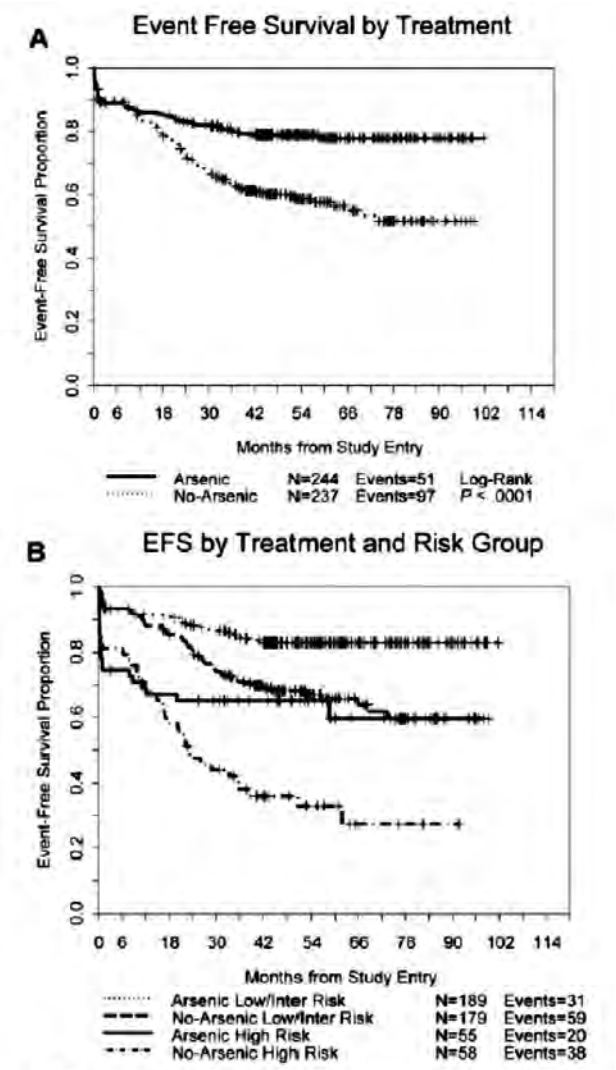


Figure 3. Event-free survival. (A) All 481 randomized patients by treatment arm. (B) By treatment arm and APL risk group.

The DFS was significantly better in patients on the As_2O_3 consolidation arm with 22 events compared with 72 events on the non- As_2O_3 arm (P 0 .0001); The DFS at 3 years was 90% versus 70% (P<0 .0001). There have been no relapses on the arsenic trioxide arm after 36

months; 1 patient died in remission at 40 months and another died in remission at 58 months both of unknown causes. Again, As_2O_3 consolidation provided significant benefit both to patients with low/intermediate risk (P< .0001) and to those with high risk APL (P< .0001) (Figure 17). Furthermore, As_2O_3 consolidation overcame the negative impact of high risk disease yielding DFS similar to that for patients in the low/intermediate risk group (P< 0 .24). Among the 219 patients randomized to the investigational arm who achieved a remission and were therefore eligible to receive consolidation therapy, 196 received at least 1 dose of As_2O_3 ; only 7 (4%) of these patients have relapsed.

Figure 17: Disease free survival by treatment (A) and treatment and risk group (B)

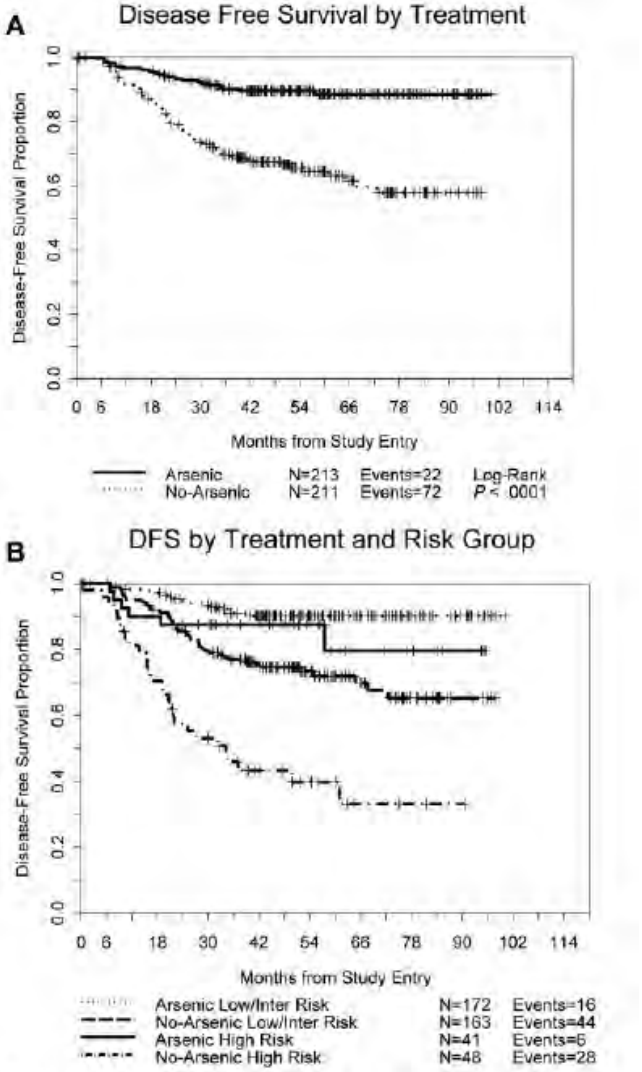
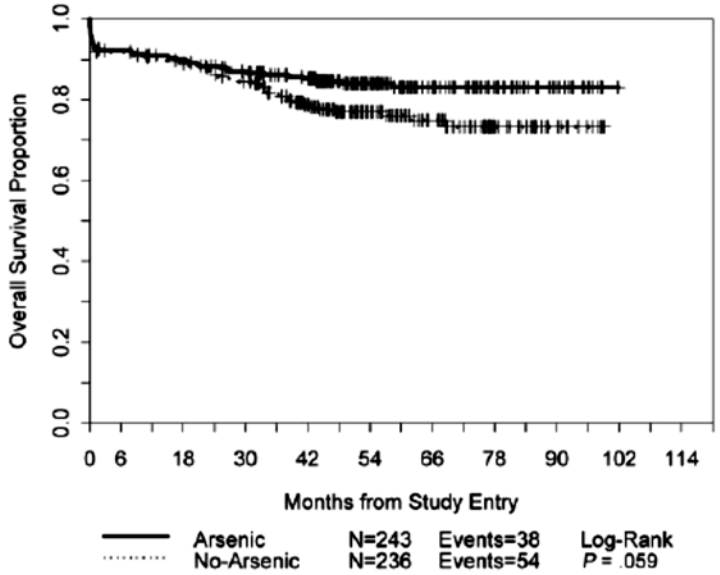


Figure 4. Disease-free survival. (A) All 424 patients who achieved a remission by treatment arm. (B) By treatment arm and APL risk group.

There were 38 deaths among patients assigned to receive As_2O_3 consolidation compared with 54 on the non- As_2O_3 arm (P<0.059). The survival at 3 years was 86% on the As_2O_3 arm compared with 81% in the standard arm (P0.07) (Figure 18).

Figure 18: Overall survival for all 481 randomised patients by treatment arm.



In general, the low and intermediate risk groups[16] had similar outcomes while the high risk group had worse outcomes. Complete remissions were achieved in 94% of patients in the low, 93% in the intermediate, and 71% in the high risk groups (P<.0001). Death during induction occurred in 4%, 4%, and 20% in the low, intermediate, and high risk groups, respectively (P<.0001). For the entire study group, EFS (P<0.24), DFS (P<0.38), and survival (P<0.72) were each similar between the low and intermediate risk groups, but EFS (P<0.0001), DFS (P<0.0001), and survival (P<0.0001) were all markedly inferior for patients in the high risk group compared with the low/intermediate risk group. However, although DFS was inferior for the high risk group on the standard arm (P<0.0001), DFS was similar between the low/intermediate risk group and the patients in the high risk group treated with As_2O_3 consolidation (P<0.24).

Patients in all risk groups benefited from the addition of to the As_2O_3 consolidation therapy. The following factors had no significant relationship with death during induction: age, performance status (PS), sex, serum creatinine, haemoglobin level, and percent CD56 expression. The following factors had no significant relationship with CR, EFS, DFS, or overall survival: age, sex, serum creatinine, haemoglobin level, and percent CD56 expression. However, there exists a significant relationship between PS and multiple outcomes: CR in both the non- As_2O_3 arm (P <0.0088) and the As_2O_3 arm (P<0 .018); EFS in both arms (P<0 .0001 for non- As_2O_3 arm, P <0.0098 for As_2O_3 arm); overall survival in both arms (P <0 .0001 for non-As_2O_3 arm, P<0 .0012 for As_2O_3 arm), and DFS in the non-As_2O_3 arm (P<0 .0023), but not in the As_2O_3 arm (P<0.47). Too few events have occurred to provide the desired power to detect differences related to maintenance therapy. Current results favour, but are not statistically significant for, ATRA plus chemotherapy compared with ATRA alone for DFS (P≤0.054) and overall survival (P ≤0.11), by the stratified log-rank test. The effect due to the interaction of induction and consolidation by maintenance was not significant for DFS (P ≤0.67) or survival (P≤0.97).

Evaluator's Comments: Overall, 481 patients (age > 15 years) with untreated APL were assigned to either a standard induction regimen of ATRA, cytarabine, and daunorubicin, followed by 2 courses of consolidation therapy with tretinoin plus daunorubicin, or to the same induction and consolidation regimen plus two 25-day courses of As_2O_3 consolidation

[16] risk group using the groups previously established to define risk of relapse: low (WBCs≤$10x10^9$/L and platelets ≥$40x10^9$/L); intermediate (WBCs≤$10x10^9$/L and platelets ≤$40x10^9$/L); high (WBCs>$10x10^9$/L).

immediately after induction. This large prospective randomized trial was analysed by intention-to-treat with no exclusions for performance status or protocol compliance. Other trials have excluded up to 9% of patients for poor clinical condition (4%-6%) or protocol violations (2%-6%).

Ninety percent of patients on each arm achieved remission and were eligible to receive their assigned consolidation therapy. Event-free survival, the primary end point, was significantly better for patients assigned to receive As_2O_3 consolidation, 80% compared with 63% at 3 years (stratified log rank test, P < .0001). Patients treated with As_2O_3 consolidation also showed better results for the secondary endpoints of Survival (86% compared with 81% at 3 years, p =0 .059) and disease-free survival (90% compared with 70% at 3 years, P < .0001). Patients in all risk groups benefited from the addition of to the As_2O_3 consolidation therapy.

Results from this study demonstrated that As_2O_3 given as initial consolidation therapy is safe and improves event-free, disease-free, and overall survival for newly diagnosed patients with APL. However, it is important that As_2O_3 was not used for remission induction in this study. The sponsors have proposed that ATO be used in induction and consolidation treatment phases in newly diagnosed APL, but this study only provides evidence to support use as consolidation therapy.

7.1.2.2. Uncontrolled studies of ATO in combination treatment

7.1.2.2.1. Ravandi et al, 2009

This was an open, single centre trial, uncontrolled, non-randomised (but stratified by risk) study to examine the potential for eliminating traditional chemotherapy, using a combination of ATRA plus ATO, with the addition of gemtuzumab ozogamycin (GO) as the only cytotoxic agent administered, for patients with high-risk or molecularly persistent disease. Patients newly diagnosed/untreated, with a morphological diagnosis of APL confirmed by standard cytogenetic analysis or by the presence of the PML-RARα fusion gene by reverse transcriptase PCR (RT-PCR) were enrolled. The only exclusion criteria were pregnancy and the presence of a pre-treatment QTc interval (> 480 ms on a 12 lead ECG) that could not be corrected by electrolyte replacement. Patients were identified by risk with high-risk presenting with a WBC count > 10 x 10^9/L and low-risk presenting with WBC count < 10 x 10^9/L.

Induction therapy: The first 68 patients (Feb 2002 to Jun 2007) received ATRA 45 mg/m^2 in 2 divided doses daily, and beginning 10 days later, ATO 0.15 mg/m^2 IV (Regimen A). High risk patients also received GO 9 mg/m^2 on Day 1. After Jun 2007 further patients (17) were treated with a modified regimen in which both ATRA and ATO were given starting from Day 1 (Regimen B). High-risk patients also received GO on day 1. Induction treatment continued until patients achieved CR, or to Day 85. A bone marrow examination was performed between Days 25 and 28 of therapy and repeated weekly if necessary. As soon as bone marrow reflected CR, ATRA and ATO were discontinued and the patient monitored until CR was achieved.

Maintenance therapy: Once in CR, subjects received ATO 0.15 mg/m^2 on weekdays, for 4 weeks every 8 weeks for a total of 4 cycles (4 weeks on and 4 weeks off) with ATRA 45 mg/m^2 in 2 divided doses daily for 2 weeks every 4 weeks for a total of 7 cycles (2 weeks on and 2 weeks off). If either ATRA or ATO were discontinued due to toxicity, GO 9 mg/m^2 was administered every 4 to 5 weeks (depending on the recovery of counts). Total post-remission therapy was continued until 28 weeks had elapsed from the CR date. Standard supportive care included prophylactic and therapeutic antibiotics and transfusion of blood products to maintain platelet counts at > 30 x 10^9/L, serum fibrinogen at > 1.5 g/L and the INR for PT at < 1.5. Heparin and

traxenamic acid were used only if indicated. Before June 2007 oral solumedrol 20 mg daily was administered (regimen A) and after June 2007 oral methylprednisolone 50 mg daily for 5 days (regimen B), to decrease the risk of APLDS.

Monitoring for PML-RARα was done at CR and every 3 months thereafter for 2 years. If the PCR test was still positive 3 months after the CR or at any later point, a repeat test was done 2 - 4 weeks later and If that was also positive a diagnosis of molecular relapse (or molecular failure if the test never became negative) was made, and patients received GO 9 mg/m^2 every 4 - 5 weeks (depending on recovery of blood counts) for 3 months while continuing or resuming ATRA and ATO. The same approach was used in the event of simultaneous molecular and clinical (haematologic or extramedullary) relapse. If the subsequent PCR test became negative, 3 more months of GO with ATRA and ATO were prescribed.

Criteria for evaluation included the number of patients achieving CR, haematological and molecular relapses. Survival and EFS were also reported.

Over the enrolment period 85 patients were enrolled but results were reported in only 82 patients[17]. Baseline demographics were summarised in Table 10.

Table 10: Ravandi et al, 2009. Demographic data and patient characteristics

Characteristic	All Patients	Regimen A	Regimen B
No. of patients	82	65	17
Age, years median (range)	47 (14-81)	47 (14-81)	49 (22-74)
Age ≥ 60 years, No. (%)	23 (28%)	20 (30%)	3 (18%)
Sex, male female	 44 38	 37 28	 7 10
WBC, x 10^9/L median (range)	2.5 (0.4 – 195.0)	2.6 (0.5 – 195.0)	1.8 (0.4 – 88.7)
Platelet count, x 10^9/L median (range)	32 (7-261)	30 (7-261)	37 (8-109)
Risk category, Low High	 56 26	 44 21	 12 5
Cytogenetics t(15; 17) t(15; 17) Other, PCR positive Not done, PCR positive Insufficient, PCR positive	 14 58 3 5 2	 10 48 2 5 0	 4 10 1 0 2
FAB morphology M3 M3v	 70 12	 54 11	 16 1
PML-RARα isoforms Short Long Positive – undefined Not done / suboptimal	 30 33 8 11	 26 33 2 4	 4 0 6 7

Overall, 74 patients achieved CR and 1 achieved CR without full platelet recovery, after the induction course – an overall response rate of 92%. Seven patients died after a median of 4 days (1 - 24) after inclusion in the study, from disease related complications. Of the patients with high risk disease, 25 of 26 received GO with induction. The CR rates for low-risk and high-risk patients were 95% and 81% respectively; 19 (83%) of the 23 patients aged over 60 years and

[17] 3 patients who received anthracyclines in induction or consolidation (treating physician's preference) were excluded from the analysis. Therefore a total of 82 patients were reported.

56 (95%) of the 59 patients < 60 years achieved CR; the difference was not statistically significant (P = 0.17). Among 75 patients who achieved a response, 3 with high risk disease experienced a relapse (at 39, 52 and 53 weeks). The overall incidence of relapse was 4%.

Haematologic and molecular responses after induction and consolidation: The median time to achieve CR was similar in both regimens (29 and 30 days respectively). Overall 60 patients had a confirmed molecular remission (CRm) after the completion of consolidation therapy; no patients required GO for molecularly persistent disease. Among the other 15 patients achieving CR, 3 patients did not have molecular testing, for the other 12 patients (all regimen B) it was too early for assessment. The median time to CR was 28 days (range 19-70) and the median time to molecular CR was 116 days (range 20 - 323). The mean time to molecular remission was 118 days (95% CI, ± 13 days) for regimen A versus 107 days (95% CI, ± 185 days) for regimen B. However fewer patients on regimen B were available for this assessment and the difference did not reach statistical significance. With continued follow-up all of the patients (excluding the 3 relapses) have remained in molecular remission. In addition to the positive PCR tests of the 3 relapsing patients, 4 other patients returned a weakly positive PCR, which after confirmatory PCR were found to be negative. All follow-up PCR tests have remained negative without evidence of relapse.

Outcome and Survival: The median follow-up is 99 weeks (range 2 - 282+). Three responding patients have relapsed and 4 (all regimen A) have died in CR. The median survival has not been reached (89+ weeks, range 0 - 282+); 13 patients have died (7 during induction, 3 from unrelated causes, 1 from an unknown cause and 2 after relapse). One patient who experienced a relapse remains alive in continuous second CR (for 74+ weeks). Overall 2, 9 and 11 patients have remained in CR for more than 5, 4 and 3 years respectively, indicating that the responses are durable (Figure 18). Among the patients older than 60 years, 74% remain alive and disease free at median follow-up of 108+ weeks (range 2 - 282+) (Fig. 7.6.4). The estimated 3- year survival rate is 85%.

Figure 18: Kaplan-Meier curve of event-free survival and survival for the entire group.

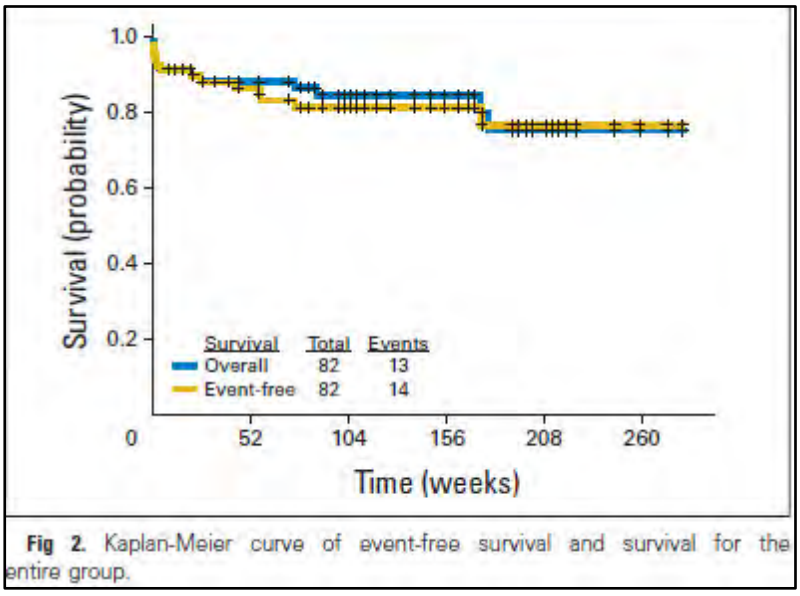


Fig 2. Kaplan-Meier curve of event-free survival and survival for the entire group.

Evaluator's Comments: This study was unique in that it specifically explored option of reducing exposure to CT in newly diagnosed patients with high risk APL by adding gemtuzumab ozogomycin (GO) to the proposed ATRA+ATO regimen. The CR rates for low risk and high risk patients was 95% and 81%, respectively with low incidence of relapse (only 3 high risk cases experienced relapse at 39, 52 and 53 weeks). Results from this study showed that a regimen of ATRA and ATO, with or

without GO, is safe and effective in patients with newly diagnosed APL and may provide an alternative to chemotherapy-containing regimens especially for patients who are unlikely to tolerate cytotoxic CT (elderly with cardiac dysfunction or multiple comorbidities). Among the patients older than 60 years in this study, 74% remain alive and disease free at median follow-up of 108+ weeks (range 2 - 282+). However, interpretation was limited due to very few patients with high risk (n = 17) and open-label, single-centre, non-randomised study design. Hence, this treatment strategy of reducing exposure to CT in newly diagnosed patients with high risk APL by adding gemtuzumab ozogomycin (GO) to the proposed ATRA+ATO regimen requires further evaluation.

7.1.2.2.2. Lou et al, 2012

The objective of this retrospective, single-centre, uncontrolled study was to evaluate the efficacy of ATRA+ATO based induction and maintenance treatment in 137 newly diagnosed patients with APL. Patients were stratified as high risk with WBC count > 10 x 10^9/L (n=45) and intermediate/ low-risk presenting with WBC count < 10 x 10^9/L (n=92). The diagnostic criteria of APL were based on morphological type and routine immunophenotyping and were confirmed genetically in all cases by the presence of PML-RARα fusion gene and/or chromosomal translocation t(15;17).

Patients received ATRA and ATO during induction until CR. Those who achieved CR received consolidation therapy following central nervous system (CNS) prophylaxis which consisted of 3 cycles of intrathecal CT consisting of MTX 10 mg, Ara-C 50 mg and DEX 5 mg. Following completion of consolidation therapy all patients who tested negative for the PML-RARα hybrid gene received as maintenance therapy sequential courses of ATO and ATRA with an interval of 14 days for 24 months (Figure 19).

Figure 19: Lou et al, 2012. Treatment schedule

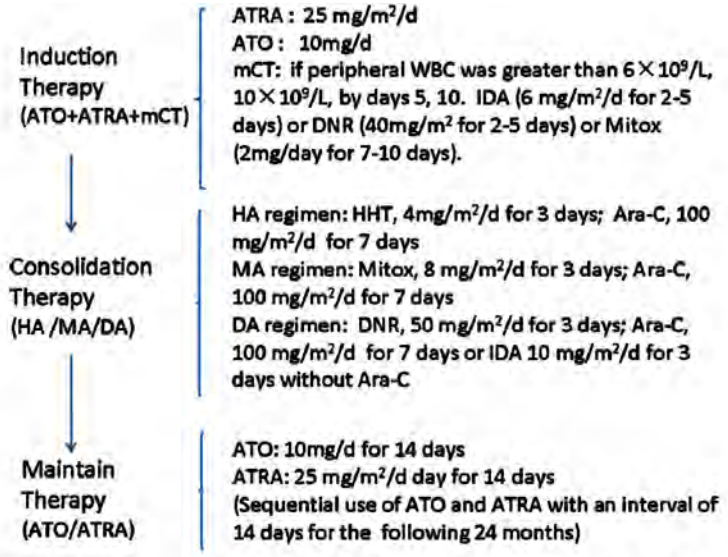


Fig. 1. Treatment schedule on the APL patients. ATO, arsenic trioxide; ATRA, all-trans retinoic acid; mCT, mini-dose chemotherapy; IDA, idarubicin; DNR, daunorubicin; Mitox, mitoxantrone; HHT, Homharringtonine; Ara-C, cytarabine.

Criteria for evaluation included number and proportion of patients achieving CR (either morphologic or molecular) with morphologic relapse and molecular relapse as defined according to international criteria. RFS and OS were determined, and rates of early death (during induction therapy). Student's t-test and Fisher's exact test were retrospectively used for comparisons of means and proportions. The probabilities of RFS and OS were estimated using Kaplan-Meier method. The relationships of clinical features (gender, pre-treatment WBC counts,

pre-treatment platelet counts, peak WBC counts during induction, and types of PML-RARα transcripts) to outcome were analysed using the Cox proportional hazard model. P values were calculated through the 2- tailed test. All P values of ≤ 0.05 indicated statistical significance.

Majority of patients were male (53.2%) and aged < 40 years (55.6% with only 2.9% >60years of age). Other baseline characteristics are summarised in Table 11.

Table 11: Baseline characteristics

Characteristics	All patients (*n* = 137)	High risk patients (*n* = 45)	Intermediate/low risk patients (*n* = 92)	*P* value
Age (years), median (range)	38.4 (13–77)	35.9 (14–75)	39.7 (13–77)	0.09
13–39, no. (%)	76 (55.5)	29 (64.5)	47 (51.1)	0.149
40–60, no. (%)	57 (41.6)	15 (33.3)	42 (45.7)	0.199
>60, no. (%)	4 (2.9)	1 (2.2)	3 (3.2)	1.00
Gender				
Male, no. (%)	73 (53.3)	26 (57.8)	47 (51.1)	0.473
Female, no. (%)	64 (46.7)	19 (42.2)	45 (48.9)	
White blood cell count ($\times 10^9$/L), median (range)	13.1 (0.4–109)	34.9 (10.1–109)	2.5 (0.4–10)	
<5, no. (%)	79 (57.7)	NA	79 (85.9)	
5–10, no. (%)	13 (9.5)	NA	13 (14.1)	
10–50, no. (%)	35 (25.5)	35 (77.8)	NA	
50 or higher, no. (%)	10 (7.3)	10 (22.2)	NA	
Platelet count ($\times 10^9$/L), median (range)	38.8 (3–225)	33.7 (4–225)	41 (3–135)	0.064
<40, no. (%)	90 (65.7)	33 (73.3)	57 (62.0)	0.25
40 or more, no. (%)	47 (34.3)	12 (26.7)	35 (38.0)	0.25
Hemoglobin (g/L), median (range)	90.8 (42–153)	90.2 (43–153)	91 (42–146)	0.847
PML–RARA isoform				
BCR1, no. (%)	79 (57.7)	19 (42.2)	60 (65.2)	0.016
BCR3/BCR2, no. (%)	55 (40.1)	25 (55.6)	30 (32.6)	0.015
Negative, no. (%)	3 (2.2)	1 (2.2)	2 (2.2)	1.00

Nine patients died during induction therapy. The early induction death rate was 6.6%. Four cases were attributable to intracranial haemorrhage, two were due to pulmonary haemorrhage, one to disseminated intravascular coagulation, one to infection, and one to APL differentiation syndrome. Eight of the nine early deaths occurred in the first week. Eight of the nine induction deaths occurred in the high-risk group. The median time from diagnosis to early death was 4 days. All remaining 128 patients (93.4%) achieved CR and of these 128 patients, 125 patients successfully completed consolidation therapy and molecular CR was achieved in all 125 patients with negative PML-RARα. There were significantly lower morphological CR rates and higher early death rates among high risk patients compared with low/intermediate-risk patients (P <0.001). Molecular CR was achieved in 34 of the 78 (43.6%) tested patients, occurring in 28 – 78 days (median 43.1 days) after commencing therapy; there were no significant differences in the 2 risk groups (high-risk and low to intermediate risk). The median follow-up was 35 months (range 6 - 101 months). Only 5 patients (4%) relapsed, with the first sites of relapse being: CNS (3 patients), BM (1 patient) and CNS/BM (1 patient). All 5 patients who relapsed achieved a second CR. There was a higher rate of relapse in the high-risk group compared with the low/intermediate group with a statistically significant difference (P = 0.0016). The characteristics of the relapsed patients is summarised in Table 12. The OS in both the high-risk and the low/intermediate risk patients was nearly equal (P = 0.53) (Figure 20) and was noted to be due to the efficient salvage treatment for relapse.

Table 12: Characteristics of relapse patients

Age/sex	First site of relapse	PML–RARA isoform	WBC count ($\times 10^9$/L)	Platelet count ($\times 10^9$/L)	Peak WBC count ($\times 10^9$/L)	Duration of CR1 (months)	Follow up outcome (months)
38/M	CNS	BCR3	59.5	12	130	16	24+ (CR2)
53/M	CNS	BCR3	13.1	20	59.3	20	28+ (CR2)
38/F	BM	BCR1	2.5	14	172	11	17+ (CR2)
43/F	BM and CNS	BCR3	50.5	47	160	13	24+ (CR3)
16/M	CNS	BCR3	23.9	9	112	4	11+ (CR2)

Figure 20: Overall survival by risk groups

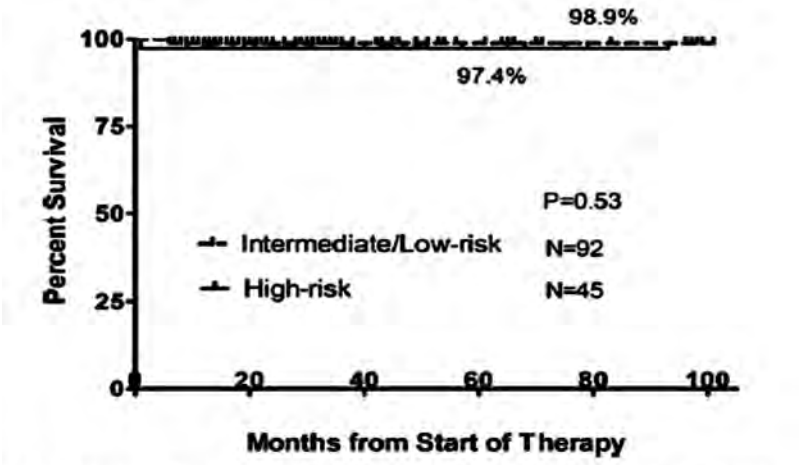


Fig. 3. Kaplan–Meier analysis of overall survival (OS) curve according to risk groups.

Significant factors affecting relapse included peak WBC counts of more than 50×109/L (P = 0.002) and initial WBC counts of more than 10×109/L (P = 0.03). Other analysed parameters (sex, age, pre-treatment platelet counts and types of PML–RARA isoforms) were found to have no significant impact on relapse rates.

Evaluator's Comments: Overall, results of this retrospective, uncontrolled study provided some evidence that ATRA+ATO based first-line therapy was effective for treatment of newly diagnosed APL.

Limitations of the study:

- Interpretation of results limited due to retrospective nature of study as well as only single-centre experience.
- The paper does not describe the method by which the data was retrospectively analysed although it does describe the method by which the initial data was obtained and patients treated.
- There were significantly lower morphological CR rates and higher early death rates among high risk patients compared with low/intermediate-risk patients.
- Majority of patients in the study were <60years old with only 4 patients (2.9%) aged > 60years.

7.1.2.2.3. Pei et al, 2012

A Phase III, open, uncontrolled single centre study in which a combination regimen of ATRA and ATO was used for induction and a sequential regimen of ATRA, ATO and CT was used for consolidation and maintenance in patients who achieved CR.

Patients were newly diagnosed with APL, without prior exposure to any anti-leukemic therapy.

The diagnosis of APL was established based on clinical presentation, morphological criteria (FAB classification) and confirmed by cytogenetic assay for t(15;17)(q22;q21) and RT-PCR analysis for PML-RARα transcripts.

As soon as patients were diagnosed patients were given ATRA at 25 mg/m^2/day (orally), and ATO at 0.16 mg/kg/day (IV) until CR was achieved. At the initiation of induction therapy, when patients' WBC counts were over 5 x 10^9/L, CT in the form of H 1 – 3 mg/day, for 3 – 10 days, was administered. Symptomatic therapy was provided for mild to moderate general side effects of ATRA and/or ATO. APLDS was treated with DEX 20 mg/day for 3 days and withdrawal of ATRA.

The dose of ATO was decreased to 0.08 mg/ kg per day, and symptomatic therapy added for those with Grade 1–2 liver dysfunction and was withdrawn immediately in the case of Grade 3-4. BM aspiration was performed when clinical presentations and the CBC achieved CR criteria. Antibiotics and antifungal drugs were administered for infection as required.

Patients who achieved CR received sequential therapy with CT, ATRA and ATO for consolidation and maintenance. CT regimens consisted of: - IDA 8 – 12 mg/m^2/day for 3 days; DAU 40 – 60 mg/m^2/day for 3 days; MIT 8 – 12 mg/m^2/day for 3 days; H 2 – 3 mg/m^2/day for 5 – 7 days or aclarubicin 40 – 60 mg/m^2/day for 3 days.

High-risk patients with WBC count > 10 x 10^9/L received CT plus cytarabine (Ara-C) in the first month post-remission. ATRA was administered at 25 mg/m^2/day for 15 days for the next month, and then ATO was given at 10 mg/d for 14 – 21 days in the third month. The interval between 2 courses was 1 month in the first year, 2 months in the second year and 3 months in the third year. Overall, the sequential therapy was administered for 6 – 8 courses over approximately 3 years. Prophylactic intrathecal injections of Ara-C 30 mg/m^2, MTX 10 – 15 mg and DEX 5 mg were given 6 times after remission. CR[18] rates, OS[19], DFS[20] and drug toxicity were observed and evaluated. Tumour burden was examined with PCR of the PML-RAR fusion transcripts.

Majority of patients were male (42/73) with median age of 37 years. Other baseline characteristics were as expected for this population (Table 13). Sixty-nine (94.5%) of the 73 patients achieved hematologic CR. The median time to achieve CR was 27 days (range 21 - 43 days). Four patients died during induction therapy: 3 patients died of cerebral haemorrhage and DIC within 72 hours, 1 older patient died of severe pulmonary infection on Day 12 of induction therapy. The WBCs of patients who died of cerebral haemorrhage were over 30 x 10^9/L. All 69 patients who achieved CR remained in good clinical CR with a median follow-up of 52 months (range 35 – 74 months). The 5-year OS rates for all patients (n = 73) and for those who achieved CR (n = 69) were 94.5% ± 2.7% and 100%, respectively. The 5-year DFS rate for those who achieved CR was 100%. RT-PCR results showed that 69.6% of patients (48/69) were negative for PML-RARα fusion gene at the time of CR, 21.8% (15/69) were negative at the end of the first course and 8.7% (6/69) were negative at the end of the second course of consolidation. The PML-RARα fusion gene of all patients stayed negative during treatment and at follow-up.

Evaluator's Comments: This study showed that the ATRA/ATO based treatment regimen for newly diagnosed APL resulted in an encouraging long-term survival rate greater than 90%. In this study, 16 patients with baseline WBC>10x109/L received CT plus cytrabine in the first post-remission month. Main limitations were:

- open-label, single centre study design.
- the dose of ATRA (25mg/m^2/day) and ATO (0.16mg/kg/day) used in this study are not the doses proposed for approval in this submission.
- efficacy results in 16 patients with WBC>10x109/L who received CT plus cytrabine were not provided.
- optimal duration of maintenance therapy with ATO needs further evaluation.

[18] CR was defined as: clinical evidence of APL was absent, neutrophil count > 1.5 x 10^9/L, Hb > 100 g/L and platelet count > 100 x 10^9/L (when no blood transfusion was given), normocellularity to moderate hypocellularity with < 5% blasts plus promyelocytes and absence of Auer rod-containing leukemic cells in BM aspirate

[19] OS was defined as time from initiation of induction therapy to last follow-up or death

[20] DFS was calculated from time of achieving CR to last follow-up or relapse, death from any causes or censoring of data of the patients.

Table 13: Pei et al, 2012 Patient demography and clinical characteristics

Gender Male/Female	42/31
Median age, years (range)	37 (14-72)
Median WBC, 10^9/L (range) Cases of WBC < 10 x10^9/L Cases of WBC ≥ 10 x10^9/L	2.3 (0.6-62.6) 57 16
Median platelets, 10^9/L (range) Cases of platelets < 40 x10^9/L Cases of platelets ≥ 40 x10^9/L	23 (5-138) 56 17
Median haemoglobin, g/L (range)	73 (52-132)
Median of blasts and promyelocytes in BM (range)	76 (64-95)
Cases of chromosomal translocation t(15, 17) positive	51
Cases of PML-RARα transcripts positive	73
L/S	46/27

7.1.2.2.4. Gore et al, 2010.

The main objectives of this open, uncontrolled, multicentre trial were to examine the efficacy of a single cycle of ATO-based consolidation therapy in a treatment regimen designed to decrease exposure to other cytotoxic agents and to determine whether the addition of ATO to first line CT could reduce the total amount of CT administered to patients with APL without affecting EFS.

Treatment scheme is summarised in Figure 21 below.

Figure 21: Treatment scheme

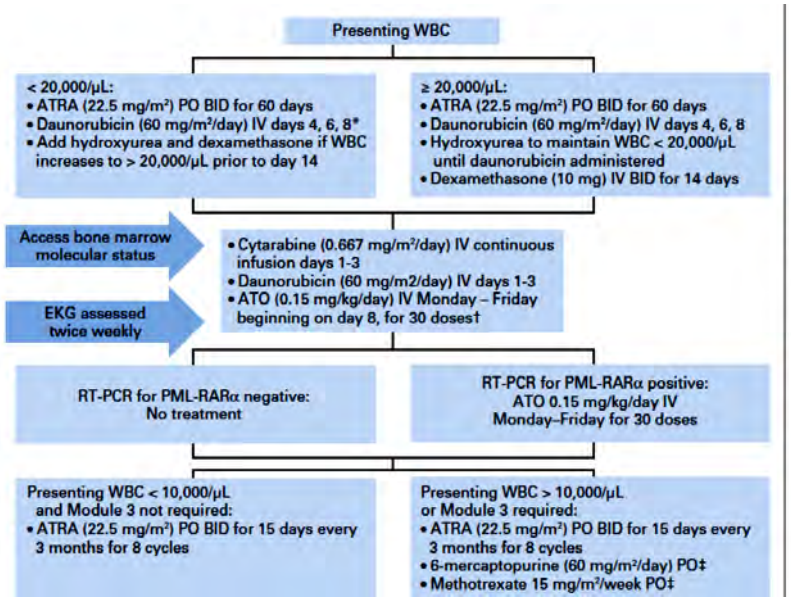


Fig 2. Treatment schema. *Daunorubicin initiated earlier in case of acute promyelocytic leukemia differentiation syndrome or leukostatis. †Arsenic trioxide (ATO) was administered on an outpatient basis and was withheld only for symptomatic QT prolongation. ‡6-Mercaptopurine and methotrexate adjusted for hepatic transaminases > 300, absolute neutrophil count < 1,500/µL, or platelets < 75,000/µL. ATRA, all-trans-retinoic acid; PO, orally; IV, intravenously; EKG, electrocardiogram; RT-PCR, reverse-transcriptase polymerase chain reaction.

Efficacy outcomes were CR, molecular remission (MR; confirmed by negative qualitative RT-PCR), OS, DFS and EFS. Survival analysis was performed according to the Kaplan-Meier method.

Overall, 51 subjects were enrolled with median age of 50 years (range 19 to 70) and according to the Sanz prognostic score risk was low in 36%, intermediate in 29%, and high in 32% of subjects. Five subjects lacked the PML-RARα gene and 1 withdrew consent so that 45 subjects with confirmed APL received induction therapy; of these 37 received consolidation therapy (including ATO).

Forty-one of 45 patients receiving induction therapy achieved remission; four patients died (one before treatment was initiated). Thirty-seven patients received consolidation and maintenance; of these one patient relapsed (CNS) and one died in remission during maintenance therapy (hepatic sickle cell crisis). One patient completing consolidation declined

further study participation due to prolonged QT interval. All 41 patients achieved CR during induction. In addition, 34 patients achieved MR (40 tested by QL-PCR). Of the 37 patients who completed consolidation 36 achieved MR and received maintenance therapy. One patient with a sickle cell variant, developed hepatic failure and died in remission. With a median follow-up of 2.7 years, estimated disease-free survival was 90%; overall survival for all patients was 88%. The systemic monitoring of ejection fraction before and after induction therapy in this study showed that this parameter decreased by 20% or more in 21% of patients after only 180 mg/m^2 of anthracycline which suggest the possibility that . ATRA may sensitize the myocardium to anthracycline

Evaluator's Comments: The open-label study design and use of ATO only in a single consolidation cycle (Figure 21) precluded interpretation of results of the proposed indication.

7.1.2.3. Uncontrolled studies of ATO as single agent treatment

7.1.2.3.1. ATO monotherapy studies in Adults:

7.1.2.3.1.1. Ghavamzadeh et al, 2006

It was an open, uncontrolled, single centre trial to define the efficacy and the safety of ATO in the treatment of 111 cases of APL (94 newly diagnosed and 17 relapses). Treatment immediately commenced when a diagnosis of APL was suspected, and treatment was continued until the confirmation or the exclusion of APL diagnosis by molecular methods (cytogenetics or FISH study for detection of t(15;17) and/or RT-PCR for PML/RARα transcript). Although both new and relapsed cases were included in the paper, only newly diagnosed APL cases were included in this summary.

Treatment regimen included the Induction Phase: ATO 0.15 mg/kg/day until achievement of CR or for up to 60 day; and the Consolidation phase which commenced 28 days after last dose of ATO in induction for those patients who achieved CR (ATO 0.15 mg/kg/day for 6 days a week, for a total of 28 infusions). Patients were hospitalised during remission induction. For consolidation phases, ATO was given in an outpatient chemotherapy facility. No maintenance therapy was administered.

Regular monitoring of haematology, liver and renal function was done and supportive treatment for prolonged QTc, abnormal LFTs and APLDS was provided.[21]

The median time of follow-up was 16.5 months (Table 14). Of the 94 newly diagnosed cases CR was observed in 82 patients (86.3%). The median time for complete remission was 30 days (range: 20 - 43). Median length of hospitalization was 32 days for the remission induction phase. Remission was observed in 82 new cases (86.3%) and 13 (76.5%) relapsed cases. This difference was not statistically significant. Sixteen patients died in the induction phase owing to complications of disease or treatment. Causes of death were cardiac arrest in two patients, APL differentiation syndrome in eight patients (with pulmonary haemorrhage and/or acute respiratory distress syndrome), cerebral haemorrhage in three patients and disseminated aspergilosis in one patient. Two patients did not respond and died due to disease progression

[21] In cases of prolonged QTc, magnesium and potassium were infused for correction of QTc. In cases of weight gain or severe oedema, diuretics were prescribed. LFTs were monitored and if they increased to >10 times the upper limit of normal, or bilirubin to >5 mg/dL or creatinine to >2 mg/dL, ATO was discontinued for several days. After correction of abnormalities, ATO administration was restarted at half of original dose and rapidly increased to full dose. In cases with hepatic or renal complications were observed during induction phase, a full dose of ATO was used as the consolidation phase, without any significant complications. APLDS (defined as weight gain, fever, polyserositis and dyspnoea with or without radiographic markers of pulmonary infiltration) was treated by DEX 10 mg twice daily, until patients' symptoms improved. For patients where APL differentiation progressed to adult respiratory distress syndrome or pulmonary haemorrhage, ventilation was commenced immediately with oxygen supplement and activated factor VII required.

after chemotherapy. The median time of death was day 20 (range 2 – 55) during the induction phase.

Table 14: Ghavamzadeh et al, 2006, 2011 Patient characteristics

Sex	
Female	60
Male	51
Type of disease	
Relapsed	17
New cases	94
Median age, years (range)	27 (6–79)
Median WBC count at presentation	2050
Median hospitalization time, days	32
Median highest WBC count for patients with hyperleukocytosis, /mm^3 (range)	49 500 (10 200–167 700)

WBC, white blood cell.

Twenty-four patients who relapsed (median time to relapse was 17 months) were retreated with the same treatment (arsenic trioxide) as before and 19 complete remissions (79.2%) were observed; five patients died during second remission induction by arsenic trioxide.

OS and DFS were the same for both newly diagnosed patients and previously treated patients During the first year after CR, 48 patients were followed up by semi-sensitive RT-PCR for detection of PM/RARα fusion gene mRNA. All patients were in CR (haematological) at the time of MRD assessment. RT-PCR was positive in 4 patients (8.3%), 3 of whom relapsed clinically.

7.1.2.3.1.2. Ghavamzadeh et al, 2011

This publication provided long-term results and a larger patient population than the earlier publication of the same trial (Ghavamzadeh et al, 2006) with similar study design and methodology. Some changes were made to the treatment regimen for consolidation and 'maintenance' (additional courses of consolidation).[22]

Therefore, patients who were administered treatment prior to 2006 received up to 90 days of treatment, whereas after 2006 patients received up to 172 days of treatment.

A total of 197 newly diagnosed APL patients were included in the study analyses and majority (58%) were females. The median age of patients was 29 years, with a range from 11 to 71 years. The median leukocyte count was 2.2 x 10^9/L (range, 0.3 to 154.1 x 10^9/L) and 19% of patients had leukocyte counts more than 10 x 10^9/L. The median platelet count was 32 x 10^9/L (range, 2 to 363 x 10^9/L), and 51.3% of patients had platelet counts less than 40 x 10^9/L at admission.

Overall, 169 (85.8%) achieved CR. The median time to achieve CR was 30 days. The median follow-up time of patients achieving a CR was 38 months from diagnosis (range 1 – 122 months).

The most common cause of remission failure was mortality during induction. Early death and remission failure were more common among patients with WBC counts greater than 10 x 10^9/L, as compared with those with lower counts (42% versus 6%; P = 0.001), while mortality during induction was higher in patients with platelet counts < 40 x 10^9/L as compared with platelet

[22] Induction (no change): ATO until achievement of complete remission (CR) or for up to 60 days.
Consolidation: ATO for 6 days per week for 28 days. From 2006 patients received 4 (28-day) courses of consolidation treatment. Patients received 2 courses of 28-day consolidation with 1-month intervals between induction and the first and second courses of consolidation therapy.
Maintenance: Although no maintenance therapy was administered, patients were given 2 additional 28-day courses of consolidation at 1 and 2 years after remission induction.

counts > 40 x 10^9/L (20% versus 8%; P = 0.11). In multivariate analysis, only blood cell counts > 10 x 10^9/L remained as an independent adverse prognostic factor for early mortality.

The median follow-up time of patients achieving CR was 38 months from diagnosis (range, 1 to 122 months); 25% of patients have been observed for more than 5 years. DFS rate was 66.7% ±4% at 5 years. Relapse of patients who remained in CR after 5 years was uncommon (1 relapse in 36 cases). Overall survival after diagnosis on an intention-to-treat analysis was 64.4% ± 4% at 5 years (Figure 22). Despite the adverse effects of high WBC counts at diagnosis and an increase in early mortality, long-term survival and DFS for patients who achieve CR were similar (P = .28 and .5 for DFS and OS difference between patients with lower or higher than 10 x 10^9/L WBC count). Patients who were treated prior to 2006 (1 course ATO in consolidation) and those treated after 2006 (4 courses of ATO in consolidation) were compared. The increased number of courses of ATO increased DFS, but had no significant effect on OS (Figure 23).

Figure 22: Disease free survival and overall survival for 197 new cases of APL

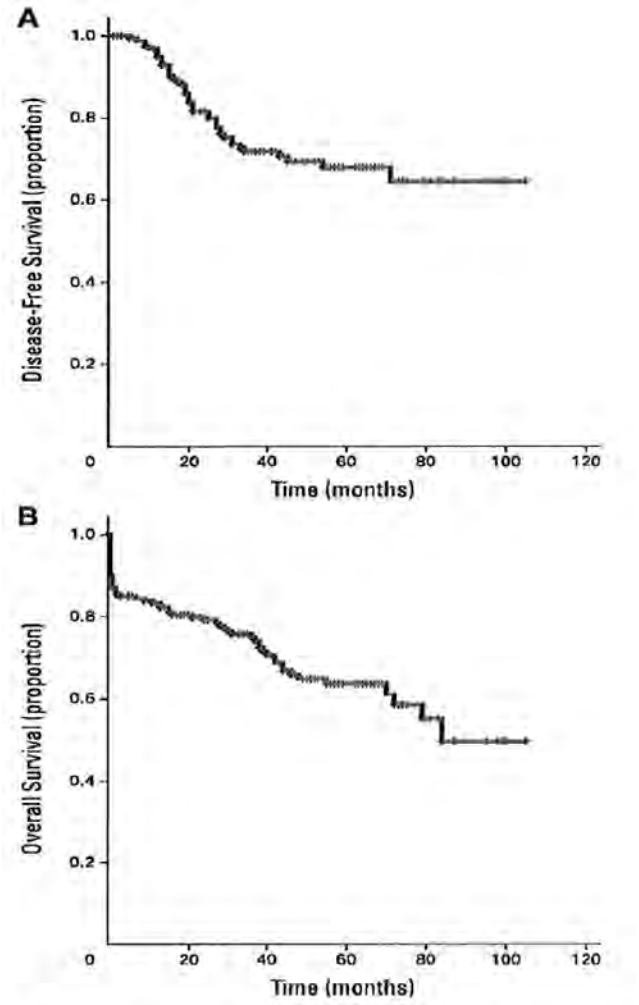


Fig 2. Disease-free survival and overall survival for 197 new cases of acute promyelocytic leukemia

Figure 23: Disease free survival with one consolidated course versus four consolidated courses.

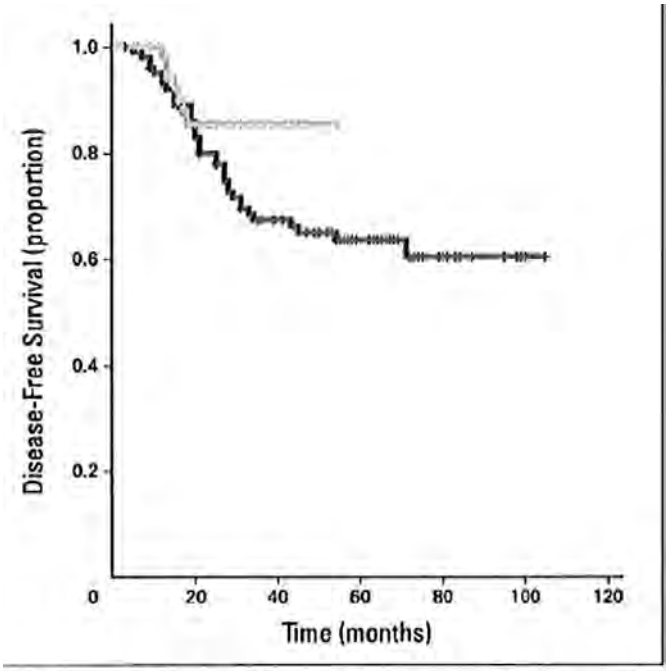


Fig 3. Disease-free survival with one consolidation course (blue line) versus four consolidation courses (gold line).

Evaluator's Comments: Results of the interim study showed that single agent ATO treatment (during induction and consolidation) was effective as first-line treatment for newly diagnosed APL with 86% of patients achieving CR. Furthermore, 19 of the 24 patients who relapsed and were retreated with the same treatment (ATO) showed CR. Results of the long term study showed that an increase in courses of ATO treatment during consolidation improves DFS with no effect on OS. Early deaths and remission failures were significantly higher in patients with WBC counts greater than 10 x 10^9/L.

Overall results of above 2 studies suggest that ATO may provide a better risk benefit profile for newly-diagnosed patients with APL compared to ATRA based and other chemotherapy regimens especially in patients who may not be able to tolerate complex treatment plans, toxicities including myelosuppression-associated complications and cardiotoxicity. However, the proposed use of single agent ATO is for newly diagnosed APL patients in whom ATRA and/or CT is contraindicated and these patients were not specifically evaluated in these studies.

7.1.2.3.1.3. Matthews et al 2006, 2010

This was an open, uncontrolled, single centre study conducted to collect data from the management of 72 newly diagnosed PML-RARα-positive APL[23] patients on a regimen of single agent ATO for remission induction, consolidation, and maintenance.

Induction: ATO 10 mg/day IV until CR (haematological) or for a maximum of 75 days (from January 2001 a maximum of 60 days). *Consolidation*: commenced 4 weeks after last dose of ATO for those patients who achieved CR, consisting of ATO 10 mg/day for 4 weeks. *Maintenance*:

[23] diagnosed morphologically to have APL on FAB criteria. This level of diagnosis was sufficient to commence ATO therapy. The diagnosis was subsequently confirmed by FISH or by RT-PCR assay for PM-RAR transcripts

(after another 4 weeks break) ATO for 10 days a month for 6 months (6 cycles) for patients continuing to remain in CR. When 2 sequential BCCs showed CR, BM analysis was performed. If the BM analysis showed evidence of persistent disease, ATO was continued until molecular CR or the maximum duration of the induction period. Supportive treatment[24] was provided for reduced platelet counts, high WBC counts and APDLS as required. After completion of scheduled therapy, patients were followed up once in 3 months for the first 2 years and once in 6 months for the next 3 years. Median follow-up 25 months (range 8 – 92 months). Majority of the 72 enrolled patients were male (52.8%) and aged between 21 and 55 years (61.1%).

Of the 72 eligible patients, 62 (86.11%) achieved hematologic complete remission (CR). Of the remaining 10, there were 7 early deaths (mean: 4.3 days, range: 2 - 7 days) secondary to intracranial (IC) bleeds. Three additional patients died prior to achieving a CR, on days 20, 23, and 49, secondary to uncontrolled sepsis, IC bleed, and a differentiation syndrome, respectively. Eight (11.1%) patients received an anthracycline in induction (7, mitoxantrone; 1, daunorubicin). Indications included a differentiation syndrome in 2 and high leukocyte count at presentation or a rapid leukocytic response in 6 cases. Hydroxyurea was administered to 53 (73.6%) patients for high leukocyte count at presentation or a leukocytic response following administration of As_2O_3. Hydroxyurea was administered for a median period of 11 days (range: 2 - 32 days) and a median cumulative dose of 12 g (range: 1 - 40.5 g). The median time to achieve CR was 42 days (range: 24 - 70 days). Results for molecular monitoring of PML/RARα by RT-PCR were available in 54 patients at the end of induction, of which 43 (79.6%) were positive and 11 (20.3%) were negative. RT-PCR performed again, prior to onset of consolidation, after a drug-free interval of 4 weeks showed that all 11 who had earlier attained molecular remission (MR) remained negative, while 30 of the 43 who were positive had become negative and 12 continued to remain positive, and RT-PCR was not done in 1 of these patients, at this time point. The median hospital stay in induction was 22 days (range: 0 - 65 days). During this period, the median time on antibiotics was 11.2 days (range: 0 - 56 days). Median red cell, platelet, and FFP support in induction were 2.5 units (range: 0 - 16 units), 15.5 units (range: 0 - 66 units), and 2 units (range: 0 - 16 units), respectively.

Consolidation and maintenance courses were administered on an outpatient basis without cardiac monitoring in patients who continued to remain in CR. Of the 62 patients who achieved CR, in 2 patients therapy was discontinued, 1 due to persistent neutropenia and the other due to recurrent Grade 3 transaminitis. Both patients were subsequently treated with a combination of ATRA and chemotherapy.[25] One patient had an isolated CNS relapse detected during the second maintenance course. Of the remaining 59 patients who completed the consolidation and maintenance course as scheduled, only 4 patients required hospital admission26 during this period. Four of the 60 patients who received the consolidation course developed transient Grade 3/4 neutropenia; only 1 of these patients required admission. None of the remaining patients had Grade 3/4 cytopenia or mucositis during either consolidation or maintenance. All patients who had achieved molecular remission prior to onset of consolidation remained in MR

[24] Platelet concentrates were transfused to maintain a platelet count higher than 20 x 10^9/L. Packed red cell transfusions were infused to maintain a haemoglobin level higher than 8 g/L. Antibiotics and antifungal drugs were administered for fever as required. Supplemental electrolytes were administered intravenously, if required, to maintain electrolyte levels within the normal range. For patients who presented with high WBC counts at diagnosis or had leukocytosis following initiation of therapy, hydroxyurea was administered. One or 2 doses of an anthracycline were administered at the clinician's discretion if patients developed a differentiation syndrome not resolving or continuing to worsen after administration of DEX, or if there was leukocyte count higher than 50 x 10^9/L at presentation or rapidly progressive leukocytosis defined as a rise higher than 30 x 10^9/L in the first week or higher than 10 x 109/L in the second week in spite of administering hydroxyurea.

[25] The patient with persistent neutropenia relapsed on day 572. The patient with transaminitis also had persistent high-grade fever and was found on liver biopsy to have a noncaseating granulomatous hepatitis that resolved on antituberculous therapy; this patient continues to be in remission at 1 year.

[26] The admissions were for febrile neutropenia, acute onset diarrhoea, nonneutropenic fever, and hepatitis, and the duration of admission was 8, 3, 5, and 4 days, respectively.

at the end of consolidation, while of the 12 who were positive 11 achieved MR at the end of consolidation and 1 patient achieved MR at the end of the first course of maintenance.

A univariate analysis of factors at diagnosis that had an adverse impact on EFS concluded that a statistically significant adverse effect was seen in patients with: WBC count higher than 5 x 10^9/L (P = 0.032), a platelet count lower than 20 x 10^9/L (P = 0.020) and a prolonged PT (P = 0.023). In a multivariate analysis, only a low platelet count (< 20 x 10^9/L) retained a statistically significant adverse effect (R 5.23, P = 0.034), while WBC count higher than 5 x 10^9/L and prolonged PT showed an increase in relative risk (RR 1.4 and 2.8, respectively) with a trend to statistical significance.

Using the WBC and platelet count at diagnosis, 2 risk groups were identified: patients with good risk (WBC count < 5 x 10^9/L and platelet count > 20 x 10^9/L; n = 22) and the remaining patients (at high risk; n = 50). In the good risk group (30.6%) EFS, OS, and DFS were 100% while in the remaining patients at high risk, EFS was 62.78% (+ 6.1), OS was 80.00% (+ 5.6) and DFS was 79.24% (+7.69). Statistical analysis of these 2 groups by log-rank test for EFS, OS and DFS, was significant (P = 0.002, 0.021, and 0.045 respectively).

The Matthews et al, 2010 publication provides the long-term follow-up data that was collected in July 2009 from the same 72 patients reported in Mathews et al 2006 (conducted from January 1998 to December 2004). The median follow-up at the time of this report was 60 months. Of the 62 patients who completed induction, 6 patients who had relapsed were reported in Mathews et al 2006. Follow-up data (Mathews et al 2010) showed an additional 7 patients to have relapsed. Over the combined treatment period and long-term follow-up the total number of relapsed patients was 13 with only 2 in the Good risk group and 11 in the High Risk group. The 5-year cumulative incidence of relapse was 17% and the median time to relapse was 1.5 years. Five relapses (38.5%) occurred beyond 2 years, and 2 relapses occurred beyond 4 years (both patients from the 'good risk' group). Causes of relapse were medullary (10), medullary and CNS (2) and isolated CNS (1). Comparison of relapse of patients with and without hepatotoxicity showed that presence of hepatotoxicity was associated with lower relapse rates (Table 15).

Table 15: Relapse cases and hepatotoxicity

	Number of Patients	Number of Relapses
Patients with CR with hepatotoxicity	23	2 (8.2%)
Patients with CR without hepatotoxicity	39	11 (28%)

The 60 month (5-year) survival the 5-year Kaplan-Meier OS, EFS, and DFS of the entire cohort was 74.2% (± 5.2), 69% (± 5.5) and 80% (± 5.2), respectively. The 5-year OS and EFS of the good-risk and high-risk group was 100% (± 0.0) versus 63% (± 7.0), and 90% (± 6.7) versus 60% (± 7.0), respectively. Beyond induction, all deaths followed relapse of disease except 1 (i.e., viral encephalitis). At last follow-up 55 patients were alive, 49 in first CR.

Evaluator's Comments: Overall, results of the long-term follow-up for up to 60 months suggest that single agent ATO in management of newly diagnosed APL was associated with stable remission with no major safety concerns. However, interpretation was limited by fact that the methodology for collection of follow-up data was not provided. Furthermore, compared to patietns with good-risk, those with high risk showed lower 5-year OS (100% versus 63%) and EFS (90% versus 60%).

7.1.2.3.1.4. Alimoghaddam et al, 2006

This was an open, uncontrolled study to evaluate the clinical efficacy and anti-angiogenesis effect of ATO in 17 newly diagnosed APL patients. Patients were included following a diagnoses of APL based on clinical presentation, morphological criteria, FAB classification and cytogenetic evaluations for the presence of t(15,17). All patients were reviewed for molecular diagnosis and remission by detecting PML RARα transcript using RT-PCR.

The treatment regimen included 2 phases of treatment for induction of remission and consolidation. Induction included ATO 0.15 mg/kg/day until achievement of CR. After a 28 day break, consolidation commenced for those patients who achieved CR: ATO 0.15 mg/kg/day for 28 days. All relapsed cases were treated with the same induction and consolidation protocol with ATO as used for the primary treatment. Duration of treatment during the study was 56 days: treatment in 2 cycles of 28 days with a break of 28 days between cycles. For patients who developed APLDS, DEX 16 mg per day was commenced without discontinuation of ATO. For severe cases ATO was temporarily discontinued and DAU (60 mg/m^2) commenced for 3 days. If APLDS was improved, ATO was resumed or dosage was reduced based on clinical judgement.

All 17 patients (100%) achieved CR. The mean time to CR was 30 days (range 21 – 35). All patients had negative RT-PCR for PM-RARα after treatment with ATO. OS was 75% at the median 860 days of follow-up.

A total of 8 patients (58.8%) experienced 1 or more relapses in the course of follow-up. Six of the relapsed cases died and 2 survived re-induction and consolidation with ATO. Except for 3 patients who expressed the long form of the PML-RARα protein and relapsed during the course of follow-up, all cases who relapsed in the long-term follow-up expressed the short form of the PM-RARα protein. Pre- and post-treatment BM specimens were examined for microvascular density. A dramatic reduction in vascular density, particularly in micro-vessels, was evident post-treatment.

Evaluator's Comments: Interpretation of results from this study was limited by open-label, uncontrolled study design in only 17 patients with follow-up of only 860 days.

7.1.2.3.2. ATO monotherapy studies in Children:

7.1.2.3.2.1. George et al 2004

This was an open, uncontrolled, single centre study on use of ATO in 11 children (age 6 - 14 years) with newly diagnosed APL. Eight cycles of As_2O_3 (0.15 mg/kg/day) were administered (induction, consolidation and six cycles of maintenance) over a period of 12 months. A total of 10 patients (91%) achieved haematological remission at a mean duration of 48 days (range: 41 – 60) with all 10 patients achieving molecular remission at a median duration of 81 days (range: 64 – 109). A total of 9 patients (90%) were PT-PCR transcript negative for PML-RAR αat the end of consolidation therapy, while 1 patient (10%) became RT-PCR transcript negative during maintenance therapy Mean dose of ATO administered during induction was 359 mg (range 180 – 600) amounting to a mean dose of 9.1 mg/kg (range 7.1 - 12.2). The cumulative dose in patients who completed treatment was 962 mg (range 655 - 1480) amounting to a mean dose of 26 mg/kg (range 21 - 30). Toxicity was minimal with leucocytosis in six patients, ichthyosis and hyperpigmentation of skin in five and mild peripheral neuropathy in one patient. One patient who relapsed 6 months after completing therapy achieved a second haematological and molecular remission with As_2O_3. A total of 8 patients completed treatment, and 2 remained on treatment at the time of publication. One patient had a haematological relapse 6 months after completion of therapy with cytogenic abnormalities along with t(15;17) on routing karotyping at diagnosis.

With a median follow-up of 30 months (range: 4 – 62), the overall (OS) survival is 91% with a relapse-free survival (RFS) of 81%.

7.1.2.3.2.2. Zhou et al, 2010

Another open, uncontrolled, single centre study in 19 children (age 4 - 15 years) with newly diagnosed APL. Induction treatment included ATO 0.20 mg/kg for children 4 to 6 years of age and 0.16 mg/kg for those older than 6 years of age, with a maximum daily dose of 10 mg until achievement of CR, or a maximum 60 days. Post Remission/Maintenance treatment was ATO 0.15 mg/kg/day for 14 consecutive days per course, each course repeated at 4-week intervals

during the first year, then interval between courses increased to 2 months during the second year and 3 months during the third year. The duration of cycles was adjusted to 21 to 28 days, and the interval shortened for the following events:- Re-appearance of the PML/RARα fusion gene; -Blasts plus promyelocytes in bone marrow increased to 3.5 - 5%, or the WBC count did not decrease markedly after 14 days of ATO (compared to baseline). Prophylactic intrathecal injection of MTX 4 - 5 mg, Ara-C 10 – 15 mg, and DEX 2 – 3 mg was given once or twice a week up to 6 times after remission. Supportive treatment included platelet transfusions (to maintain platelet counts > 20x109/L), hydroxyurea (1 to 2g) WBC was > $20x10^9$/L, DEX 5mg twice daily if patients developed ALDS and antibiotics as required to control infections and fevers.

A total of 17 (89.5%) patients achieved CR. One of these was lost to follow-up. The median time to CR was 38 days (range 26 - 55). The failure to achieve CR in 2 patients was due to early death. Both patients presented with the highest leukocyte counts at diagnosis and both had severe leucocytosis as WBC counts increased dramatically with ATO treatment.

According to RT-PCR measurements, 9 patients achieved molecular CR. One patient achieved molecular CR immediately after CR and the remaining 8 achieved molecular CR between 3 – 9 months after CR (median: 3 months). No isolated molecular relapse (not leading to hematologic relapses) occurred during the follow-up period. The 5 year OS was 83.9% (95% CI, 67.2 to 100) and EFS – 72.7% (95% CI, 52.3 to 93.2).

Evaluator's Comments: Results from this study along with those of the earlier study by George et al show that monotherapy with As_2O_3 achieves haematological and molecular remission in majority of for newly diagnosed paediatric patients with APL aged < 15 years (n=30). Furthermore, results appeared to be comparative to those observed with ATRA+ daunorubicin-cytarabine or ATRA + idarubicin (Table 16). However, long-term follow-up is required to evaluate late effects of As_2O_3 and study the minimum dose and duration required for a sustained remission.

Table 16: Paediatric studies. Primary published clinical studies of childhood APL treated with ATO or ATRA plus CT

Study, year	No. of patients	Age, y	Induction	HCR (%)	Postremission therapy	Duration of postremission therapy	Estimated 5-year OS, %	Estimated 5-year EFS, %
George et al,[22] 2004	11	≤ 15	ATO	91	ATO	8 mo	91	81
Present study, 2009	19	≤ 15	ATO	89	ATO	3 y	84	73
de Botton et al,[3] 2004	31	≤ 18	ATRA + daunorubicin-cytarabine	97	CT and/or ATRA, BMT (n = 2)*	2 y, 2 mo	90	71
Testi et al,[4] 2005	107	≤ 18	ATRA + idarubicin	96	CT and/or ATRA, BMT (n = 3)*	2 y, 3 mo	89	81
Ortega et al,[2] 2005	66	≤ 18	ATRA + idarubicin	92	CT + ATRA	2 y, 3 mo	87	77

ATO indicates arsenic trioxide; ATRA, all-*trans* retinoic acid; CT, chemotherapy; BMT, bone marrow transplantation; EFS, event-free survival; HCR, complete hematologic remission; and OS, overall survival.
*Denotes the number of patients who had a BMT in first remission.

7.1.2.4. Study APML3

No ATO was administered in this study and it is discussed here as it was used as historical control for the pivotal APML4 study.

APML3 was an open-label, multicentre study to determine the following in newly diagnosed patients with APL:- the prognostic significance between pre-treatment variables; the anti-leukemic activity of only 2 cycles of IDA in combination with ATRA and the impact of maintenance therapy on remission duration. Inclusion criteria were morphological diagnosis according to FAB criteria; demonstration of PML-RARα fusion transcripts by RT-RCR or cytogenic demonstration of a T(15;17) translocation; age >18 years; LVEF > 50%; negative pregnancy test; absence of serious cardiac, pulmonary, hepatic or renal disease. Patients with genetic variants of APL (X-RAR where X was not PML) were ineligible for the study.

Induction: All patients received ATRA 45 mg/m^2/day in divided doses (capped at 80 mg/day) from Day 1 until CR.

Consolidation: All patients aged < 60 years received IDA 12 mg/m^2 IV on Days 2, 4, 6 and 8 (9 mg/m^2 for patients 61 – 70 years and 6 mg/m^2 for patients > 71 years). Following 2 cycles of chemotherapy, all patients received intermittent ATRA: 45 mg/m^2/day given for the first 2 weeks in each 4-week cycle. The study protocol was amended in June 2000 to include 2 years of maintenance given as 3 month cycles of: 2 weeks of ATRA 45 mg/m^2/day (maximum 80 mg/day) every 3 months, followed by oral MTX 15 mg/m^2 once weekly, and oral 6MP 90 mg/m^2/day.

A total of 107 patients were enrolled into the study with 101 patients suitable for analysis of efficacy and toxicity. Six patients excluded due to failure to demonstrate either t(15;17) or PML-RARα transcripts at diagnosis. The median age was 40 years (19-73 years) and 53 patients (52%) were male.

7.1.2.4.1. Efficacy endpoints, statistical analysis:

Outcomes included: hematologic and molecular CR, remission duration (RD), relapse, DFS, OS and failure free survival (FFS). Categorical factors at baseline which were investigated for their prognostic value included WCC, platelet count, Sanz risk stratification, PML breakpoint, and FLT3 status. Continuous-scale factors included age and log-transformed normalized PML-RARA transcripts.

A maintenance-cohort factor which indexed patients according to whether they were registered before or after activation of the maintenance amendment enabled an intention-to-treat (ITT) analysis of post remission maintenance as a prognostic factor.[27]

The association of baseline prognostic variables with both the incidence of early death and the achievement of CR were investigated using binary logistic regression. For time-to-event endpoints of survival and durations, uni-factor associations of categorical prognostic factors were investigated with the log-rank test while uni-factor associations of continuous-scale covariates and all multifactor analyses were investigated via Cox proportional hazards regression and the score test. Competing events, such as relapse and death in complete remission, were analysed by estimating cumulative incidences using a competing risks analysis. Unless otherwise stated, all statistical tests were 2-tailed tests without adjustment for multiple comparisons.

7.1.2.4.1.1. Results:

Of 93 patients who survived more than 30 days, 2 were taken off study because of failure to reach hematologic CR. One patient was withdrawn prematurely at Day 18 because of persistent DIC. Therefore 91 of the 101 patients enrolled (90%) achieved CR (73 following cycle 1 of IDA and 18 following cycle 2 of IDA) including 4 patients who received Ara-C/etoposide in the second cycle.

WCC at diagnosis was associated with the achievement of CR: 100% of the 55 patients with WBC <2.5 x 10^9/L achieved CR while 78% of the 46 patients with WBC >2.5 x 10^9/L achieved CR.

A total of 85 patients completed 3 cycles of intermittent ATRA within 145 to 230 days. A total of 81 patients tested were RT-PCR negative (molecular CR 100%). The 4 patients not tested were already in molecular remission before commencing intermittent ATRA. Of the 91 patients who

[27] Given that some patients who were registered prior to the amendment did receive maintenance, and some patients registered after the amendment did not, analysis of the association of actual post-remission maintenance with survival was also conducted; in this analysis separate indicator variables for ATRA, 6MP and MTX maintenance administration in each 3-month period after consolidation were included as time-dependant covariates.

achieved CR, 25 (27%) relapsed and 2 patients died in CR as a result of complications of the second cycle of IDA.

The estimated 4 year DFS was 69.7% (95% CI: 58.9 to 78.1). The 4 year actuarial OS was 83.7% (95% CI: 74.8 to 89.7). Increasing WBC were associated with decrease OS. A total of 40 treatment failures occurred from the 101 eligible patients. The 4-year FFS was 59.7% (95% CI: 49.3 to 68.7).

Evaluator's Comments: The APML3 protocol shows that an induction and consolidation strategy that combines ATRA with relatively low anthracycline exposure (delivered in only two chemotherapy cycles), followed by 2 years of triple maintenance, is capable of achieving prolonged disease-free survival in the majority of patients. However, high risk subgroups (for example, patients with FLT3 mutations and/or high WCC) require either more intensive therapy or therapy with alternative anti-leukemic agents such as arsenic trioxide. The ALLG APML4 study (discussed in section 7.1.1) combined arsenic trioxide with ATRA and idarubicin for induction, and uses only ATRA and arsenic trioxide without further anthracycline for consolidation (total idarubicin exposure only 48 mg/m^2). Results of this study have indicated that this strategy has been highly successful in reducing relapses and improving long-term disease free survival. In the analysis of the pivotal APML4 study, the maintenance cohort (n=70) was used as the control group.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

7.1.3.1. Pooled or Meta-analysis:

Nine of the studies summarised individually in section 7.1.1 above included ATO as part of a combination treatment regimen with ATRA. Not all treatment regimens were the same and only 3 studies compared the combination of ATO + ATRA to ATRA alone during induction (Lo-Coco et al., 2013, Shen et al, 2004 and Dai et al, 2009).

An exploratory comparison between the APML4 study to an historical control, that is, the APML3 study (Iland et al, 2012) also provided some data comparing combination of ATO + ATRA to ATRA alone on as the main difference between the trials was the addition of ATO in APML4. There were some difference in the duration and dosage of 6MP and MTX that were administered during maintenance therapy in the APML3 and APML4 trials.

Two studies included ATO only after remission was achieved, in the consolidation phase (Powell et al, 2010 and Gore et al, 2010); while the studies reported by Dai et al (2009), Lou et al (2012) and Pei et al (2012) included substantial CT during the consolidation phase.

Due to the differences in the studies (as described above), no pooled or meta-analysis of these 9 studies was provided in the submission and only results of the individual studies were discussed.

There was one formal published metanalysis (Wang et al, 2011) which included 5 studies in which patients with newly diagnosed APL were treated with ATRA and/or ATO during induction. As neither ATRA nor ATO is approved for treatment of newly diagnosed APL patients in Australia, comparison of these treatments in this metanalysis was not valid. Furthermore, only 2 of these were randomised: Shen et al, 2004 and SU et al, 2006. The other 3 studies were non-randomised, single-centre (Chinese) studies (Li et al, 2008; Bai et al, 2007; Wang et al, 2004) and these data were not included in the analysis. Overall, only results from the Shen et al study were discussed in this meta-analysis. This study has already been discussed in detail in section 7 above.

7.1.3.2. Efficacy in subgroups

The only sub-population that can be said to have been studied (published) is that of children. The studies described by George et al (2004) and Zhou et al (2010) follow very similar treatment regimens. The only difference in the regimens is in maintenance phase in the number of days of treatment per month, and the duration of treatment (George et al, reporting a less intense and shorter duration of maintenance). The dose and regimen are also very similar to the dose for adults (0.15 mg/kg/day) used by Alimoghaddam et al (2006) and Mathews et al (2006, and 2010) for single agent treatment in adults In both studies a high proportion of children achieved CR (over 89.5%) and OS was high: 83.9% (estimated, at the median 30 month follow-up) in Zhou et al (2010) and 91.0% in George et al (2004). These survival data were higher than some of the rates calculated for adults.

7.1.4. Evaluator's conclusions on clinical efficacy

for the 'indication of remission and consolidation in patients with previously untreated Acute promyelocytic leukaemia (APL) in combination with all-trans retinoic acid (ATRA) and chemotherapy unless ATRA and/or chemotherapy is contraindicated'.

A total of 1214 patients in the individual studies (including APML4 and the published studies) were exposed to ATO (with or without ATRA) as part of their study regimen, while 458 patients received ATRA alone (controlled trials). All the studies were conducted in newly diagnosed, previously untreated APL patients with genetic diagnosis of APL established by detection of the PML-RARα fusion gene (by RT-PCR assay), demonstration of the t(15;17) translocation [by means of conventional karyotyping or fluorescence in situ hybridization (FISH)]. The published studies (pivotal and supportive studies) have mainly been conducted in China or India. The pivotal clinical study, APML4, was conducted in Australia and New Zealand.

7.1.4.1. ATO as combination treatment in newly diagnosed, previously untreated APL

Nine of the studies summarised individually in section 7.1.1 included ATO as part of a combination treatment regimen with ATRA. Not all treatment regimens were the same and only 3 studies compared the combination of ATO + ATRA to ATRA alone during induction (Lo-Coco et al., 2013, Shen et al, 2004 and Dai et al, 2009). The APML4 study was compared to the APML3 study (Iland et al, 2012) as the main difference between the trials was the addition of ATO in APML4 although interpretation was limited due to exploratory nature of analysis and some difference in the duration and dosage of 6MP and MTX that were administered during maintenance therapy in the APML3 and APML4 trials. Two studies included ATO only after remission was achieved, in the consolidation phase (Powell et al, 2010 and Gore et al, 2010); while the studies reported by Dai et al (2009), Lou et al (2012) and Pei et al (2012) included substantial CT during the consolidation phase. Overall, 913 patients were treated with ATRA+ATO, 458 patients treated with ATRA alone and 20 patients with ATO alone in the combination treatment studies; this sample was adequate to assess efficacy and safety of ATO used in combination with ATRA for the proposed new indication in newly diagnosed, previously untreated APL.

In APML4 study as well as all other published literature, patients irrespective of risk (Sanz risk classification)[28] were included. The only exceptions were Lo-Coco et al 2013 and Alimoghaddam et al 2006 which included only low-intermediate risk patients. Furthermore, patients who had significant arrhythmias, ECG abnormalities or neuropathy; other cardiac contraindications for intensive chemotherapy (LVEF <50%) were excluded from the Coco et al 2013 study. Dai et al, 2009 excluded patients with dysfunction of liver or kidney; any heart diseases or cardiac functional insufficiency. Ravandi et al, 2009 excluded patients who had pretreatment QTc

[28] Patients with APL may be stratified into three risk categories on the basis of white blood cell (WBC) count and platelet count. Low risk is a WBC count < $10x10^9$/L and a platelet count > $40x10^9$/L; intermediate risk is a WBC count < $10x10^9$/L and a platelet count < $40x10^9$/L; high risk is a WBC count > $10x10^9$/L.

interval of > 480 ms. Ghavamzadeh et al 2006 and Ghavamzadeh et al 2011 excluded patients with severe renal, hepatic or cardiac dysfunction (creatinine > 2 mg/dl, bilirubin> 5 mg/dl, and ejection fraction <50%). It is important to note that majority the patients in the APML4 pivotal combination study had ECOG PS of 0 or 1 (87%) while ECOG PS status was not provided for the other 2 pivotal studies (Lo Coco et al, 2013 and Dai et al, 2009).

In the analysis of the APML4 study informal comparisons with the historical APML3 maintenance cohort indicated considerable improvements in TTR, DFS, OS and EFS with the addition of ATO to the standard ATRA plus CT regimen. However, these results should be interpreted with caution due to the post hoc, exploratory nature of the analysis and certain differences in treatment regimens in the APML4 and APML3 studies. However, results from this Phase II open-label study did demonstrate that induction and consolidation treatment with ATO with ATRA/CT results in CR of 95% at end of induction with median time to relapse of only 53 days and observed annual relapse-free rates of 97.3% at 1 and 2 years and 95.4% at 3, 4 and 5 years. Furthermore, use of ATO in the consolidation cycle enabled reduced exposure to CT as it substituted IDA (which was used in Study APML3).

The study by Lo-Coco et al, (2013) showed that a combination of ATRA and ATO given for induction and consolidation therapy is at least not inferior and is possibly superior to standard ATRA and anthracycline based CT for adults with newly diagnosed, low-to-intermediate-risk APL. The observed advantage in the 2-year event-free survival (which was primary efficacy endpoint) with ATRA + ATO compared to ATRA +CT (97% versus 86%) appears to be due mainly to lower mortality from causes other than relapse, probably as a consequence of reduced severe hematologic toxicity together with similar antileukemic efficacy. The study reported CR in all (100%) ATRA+ATO patients after a median 32 days of induction.

Dai et al (2009) reported high rates of RFS, with combination treatment, while patients receiving ATRA alone had significantly higher relapse rates and lower RFS. The estimated OS of 85% reported by Ravandi et al (2009; with a median 99 weeks follow up) was in line with the results from other studies.

In Shen et al, (2004) and Dai et al, (2009) the combination of ATRA + ATO during induction allowed CR to be achieved more quickly (statistically significantly in Dai et al), although there was not a significant difference in the proportion of patients achieving CR. This comparative reduction in median time to achieve CR was also confirmed by the results of APML3 and APML4 (refer Table 17 below).

Table 17: Number and proportion of subjects achieving CR, median time to CR

	Lo-Coco et al (n=79)	Shen et al Group 1 (n=20)	Dai et al Group A (n=72)	APML3 (n=101)	Lo-Coco et al (n=77)	Shen et al Group 3 (n=21)	Dai et al Group B (n=90)	APML4 (n=124)
Induction Treatment	**ATRA**				**ATRA + ATO**			
Number Achieving CR (%)	75 (95.0)	19 (95.0)	65 (90.3)	91 (90.1)	77 (100.0)	20 (95.2)	84 (93.3)	118 (95.2)
Median Days to CR (range)	35 (26-63)	40.5 (25-65)	39 (25-62)	-	32 (22-68)	25.5 (18-35)	31 (18-59)	53 (34-83)

* APML3 is considered to be the control group (ATRA) for APML4 – together they are presented as a 'controlled trial'

The uncontrolled trial Ravandi et al (2009) reported CR achieved in a median of 28 days, confirming that achievement of CR after combination treatment with ATRA + ATO is rapid.

DFS, RFS or EFS and OS and relapse rates were reported for most studies and are summarised in Table 18 below:

Table 18: Comparison of primary efficacy outcomes in studies with ATRA+ATO

Study Identifier (Author)	Group	Relapses n (%)	DFS %	RFS %	EFS %	OS %
Lo-Coco et al[3] 2013, module 5.3.5.1.1	ATRA	5 (6% 2y)	90.0 (2y)	-	85.0 (2y)	91.0 (2y)
	ATRA + ATO	2 (1% 2y)	97.0 (2y)	-	97.0 (2y)	99.0 (2y)
Shen et al[6], 2004 , module 5.3.5.1.2	ATRA	5 (26.3)	13 mth	-	-	-
	ATRA + ATO	0	20 mth	-	-	-
Powell et al[5], 2010, module 5.3.5.1.3	ATRA	-	70.0	-	63.0	81.0 (3y)
	ATRA+ ATO	-	90.0	-	80.0	86.0 (3y)
Dai et al[4], 2009 module 5.3.5.1.4	ATRA+ ATO	1 (5.0)	-	93.8	-	-
	ATRA	10 (22.2)	-	72.4	-	-
	ATRA+ ATO	4 (4.8)	-	92.6	-	-
ALLG APML4[1] module 5.3.5.2.1	All patients ATRA+ ATO	5	97.0 (2y) 95.0 (5y)	-	§92.0 (2y) 90.0 (5y)	94.0 (2y) 94.0 (5y)
Ravandi et al[7] 2009 module 5.3.5.2.2	All patients ATRA+ ATO	3 (4)	-	-	-	85.0 (99 wk*)
Lou et al[8] 2012 module 5.3.5.2.3	Low risk	5 (4)	-	87.9	-	97.4 (5y)
	High risk	-	-	98.7	-	98.9 (5y)
Pei et al[9] 2012 module 5.3.5.2.4	ATRA + ATO	-	100.0 (5y)	-	-	100.0 (5y)
Gore et al[10] 2010 module 5.3.5.2.5	All patients	-	88.7	-	76.0	88.0 (3y)

* Median follow-up was 99 weeks at publication. § EFS alternative definition

NB: Lou et al 2012 was published in 2013 as Lou Y, *et al.* High efficacy of arsenic trioxide plus all-trans retinoic acid based induction and maintenance therapy in newly diagnosed acute promyelocytic leukemia. Leuk Res. 2013 Jan;37(1):37-42.

Evaluator's Comments: The above table from the clinical summary in had errors in reporting results of the Lou et al, 2012 study. A question regarding this has been included in section 11 of this report.

The study reported by Powell et al (2010) involving 481 patients with newly diagnosed APL shows that addition of As_2O_3 to consolidation therapy to regimens using ATRA and anthracycline based CT improves EFS. Gore et al (2010) has shown similar results as those reported by Powell, substituting a consolidation cycle of CT for ATO. However, both these studies did not use ATO for remission induction although the proposed indication suggests use of ATO for induction and consolidation in newly-diagnosed APL.

Overall, there was adequate evidence to support use of ATO in combination with ATRA and/or CT in newly diagnosed, previously untreated patients with APL.

However, there are several unanswered questions such as:

- the optimal timing for the As_2O_3 therapy in the overall treatment regimen:

  The proposed dosing regimen for ATO as combination therapy for newly diagnosed APL was used in the 3 pivotal studies discussed in section 7.1.1 (APML4 study. Lo Coco, 2013 and Dai, 2009). Results from the large study involving 481 newly diagnosed patients with APL (Powell, 2010) demonstrated that As_2O_3 given as initial consolidation therapy is safe and improves event-free, disease-free, and overall survival for newly diagnosed patients with APL. Similar results were observed in Gore et al 2010. However, both studies did not use As_2O_3 for remission induction.

- the best approach to decrease early deaths especially in patients with high risk disease (WBCs>$10x10^9$/L) and the role of cytarabine in APL:

  The APML4 study included 19% of patients with high risk and the Powell study included 23% of patients with high risk. Lo Coco, 2013 excluded patients with high risk and

baseline risk was not provided in Dai, 2010, Shen, 2004 studies. In one published study (Pei, et al, 2012), 16 of the 73 patients with newly diagnosed APL had WBC> 10x10^9/L and received CT plus cytarabine, plus results in these patients was not provided. The APML4 study also used mandatory steroids (10 mg prednisone) during first 10 days of induction therapy and aggressive platelet support to meet haemostatic targets which helped to reduce early deaths due to APDLS. Similar supportive treatment has been proposed for the proposed new indication.

- choice of anthracycline to be used in combination with ATO is not specified. IDA was used in studies APML4 and Lo Coco, 2013, but DA was used in studies published by Dai (2009), Shen (2004) and Powell (2010).

7.1.4.2. ATO as single agent treatment in newly diagnosed, previously untreated APL:

The 6 studies with ATO single agent treatment identified in the literature search provided data on 281 patients with newly diagnosed APL (including 30 children aged < 15 years) exposed to single agent treatment with ATO. The proportion of patients achieving CR was approximately 86% in both the interim report (82/94 , Ghavamzadeh, 2006) and the long-term follow-up (169/197; Ghavmazadeh, 2011) with median time to CR of 30 days in both studies. The main reason for failure of ATO therapy was early mortality during remission induction phase mainly due to APL differentiation syndrome, cerebral haemorrhage and cardiac arrest (Ghavamzadeh, 2006). In the long-term report (Ghavmazadeh, 2011), early death and remission failure were more common among patients with WBC counts greater than 10 x 10^9/L compared with those with lower counts (42% versu 6%; P = 0.001), while mortality during induction was higher in patients with platelet counts < 40 x 10^9/L as compared with platelet counts > 40 x 10^9/L (20% v 8%; P = 0.11). The increased number of courses of ATO increased DFS, but had no significant effect on OS. The 2 reports by Matthews (2006 and 2010) following ATP monotherapy induction and consolidation treatment showed similar results with CR of about 86% and better response in patients with low/ intermediate risk compared to those with high risk at baseline. Two studies (George, 2004 and Zhou 2010) in 30 paediatric patients (aged < 15years) provided some preliminary evidence for efficacy of ATO monotherapy in newly diagnosed APL, but this needs to evaluated further due to risks of early mortality during remission induction phase as well as unknown long-term risks associated with arsenic trioxide (hepatotoxicity, secondary cancers).

Overall results of above studies suggest that ATO may provide a better risk benefit profile for certain newly-diagnosed adult patients with APL. There were no direct comparisons of ATO monotherapy against ATRA based and other chemotherapy regimens in newly diagnosed patients, but this is not a limitation of the submission since sponsors proposed use of ATO monotherapy only in newly diagnosed APL when ATRA and/ or chemotherapy is contraindicated. However, due to risk of early mortality during remission induction phase with ATO treatment, it is important to determine the subgroups of patients likely to benefit from ATO monotherapy. It appears that patients at low/intermediate risk showed better results compared to those with high risk and this was shown in both Ghavmazadeh 2011 and Matthews, 2006 reports. Good outcomes to treatment with ATRA and anthracycline based CT can be achieved, but for some patient groups CT may be considered too toxic [in some countries ATRA and CTs may not be widely available/affordable]. ATO monotherapy may also be beneficial in patients who may not be able to tolerate complex treatment plans, toxicities including myelosuppression-associated complications and cardiotoxicity. The sponsors proposed that ATO be used as single agent therapy in newly diagnosed APL in patients in whom ATRA and/or chemotherapy is contraindicated. However, the patients evaluated in the six monotherapy studies did not represent this target patient population (2 of 6 studies included only paediatric patients aged 4 - 15 years and median age of patients in other studies was only 28 - 30 years). Patients with contraindications to ATRA and/or chemotherapy are more likely to be elderly patients with comorbidities, but these patients were not evaluated in any of the submitted

single agent ATO studies. Overall, the evidence for efficacy and safety of use of ATO as single agent in newly diagnosed APL is inadequate.

The dose of ATO used in most of the published clinical studies was fairly consistent, either a dose of 0.15 or 0.16 mg/kg body weight (for a 70 kg patient 10.5 mg/day), or a 10 mg/day dose. The dose of ATO was reduced in cases of toxicity (arsenic-related QTc interval prolongation and possible arrhythmias, Grade 3-4 haematological and hepatic toxicity).

Persistence of efficacy and/or tolerance: The effectiveness of ATO throughout the induction, consolidation and maintenance cycles does not appear to change or diminish over time and with repeated exposure. The duration of follow-up in APML4 study was 3-5 years, while that in other combination studies ranged from 2 years to 5 years. The published ATO monotherapy studies by Mathews et al, 2010 and Ghavamzadeh et al 2011 provide longer term follow-up of patients, providing up to 5 year data. However, interpretation from these studies was limited as this longer term follow-up does not describe dosage beyond the maintenance treatment that was planned. In some studies (eg Ghavamzadeh et al 2006, Wang et al 2011), it was common to repeat an induction cycle and continue treatment in patients who relapsed.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies (APML4, Coco et al and Dail et al, 2009), the following safety data were collected:

All patients who received any dose of study drug (ATO or ATRA) were monitored throughout their participation in the study and included in the safety population analysis. Each study site's local laboratory performed haematology, biochemistry and coagulation assessments of samples taken throughout the study. All other study related procedures were performed at the study site, and the results were assessed by the appropriate study site personnel. These included: Oxygen saturation (arterial), Body weight, Height, chest X-Ray, ECG (QTc interval), LVEF. Vital signs (pulse, respiration, body temperature, blood pressure), pregnancy testing, BM aspirate for cytogenetics.

Evaluator's Comments: Although included in the protocol, pulse, respiration and blood pressure were not included in the CRF of the APML4 pivotal study.

All AEs that occurred while a patient was receiving treatment (study drugs) on the trial were recorded in the CRFs, including the nature of the event and a toxicity grading using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The causal relationship[29] to treatment (attribution of causality), as assessed by the Investigator was also recorded, with the temporal relation between the AE and the study drugs included in the documentation being considered as decisive in attribution. All serious AEs (SAEs) that occurred while receiving treatment and within 30 days of the last dose of a study drug as treatment, were

[29] The following definitions of the causality to treatment were used:
- Definite: The AE is clearly related to treatment/study drug
- Probable: The AE is likely related to treatment
- Possible: The AE may be related to treatment
- Unlikely: The AE is doubtfully related to treatment
- Unrelated: The AE is clearly NOT related to treatment

required to be reported.[30] Local IECs were also required to be notified of SAEs according to institutional guidelines.

8.1.2. Pivotal studies that assessed safety as a primary outcome

None.

8.1.3. Dose-response and non-pivotal efficacy studies

Brief description of safety/toxicity findings were provided in most of the published studies included in the submitted dossier.

Evaluator's Comments: As this submission is a hybrid literature based submission with the clinical data coming from published clinical studies using a number of different 'study products' (ATO), no formal safety evaluation plan or integrated narrative is available. However, a brief description of the safety data available from each of the individual studies is provided. Drug concentration data (whole blood arsenic levels) were not available for any of the studies with exception of 2 single agent studies (Matthews et al, 2010 and Zhou et al, 2010).

8.2. Pivotal studies that assessed safety as a primary outcome

None.

8.3. Patient exposure

A total of 1214 patients in the individual studies (including APML4 and the published studies) were exposed to ATO (with or without ATRA) as part of their study regimen, while 458 patients received ATRA alone (controlled trials).

In the combination treatment studies, 913 patients were treated with ATRA+ATO, 458 patients treated with ATRA alone and 20 patients with ATO alone (Table 19). Overall, 281 patients with newly diagnosed APL (including 30 children aged < 15 years) were exposed to single agent treatment with ATO (Table 20).

[30] All SAEs considered by the site investigator to be related to ATO or for which a causal relationship to ATO could not be ruled out, were also to be faxed immediately to Phebra. Once an SAE had resolved, a follow-up SAE report was required to be faxed to the Trial Centre (and Phebra if ATO was implicated).

Table 19: Patient exposure in combination treatment studies

Study Identifier (Author)	Patients Exposed			ATO dose and treatment regimen
	ATRA (or no ATO)	ATRA + ATO	ATO	
As combination treatment				
Lo-Coco et al[3] 2013, module 5.3.5.1.1	79	77	0	0.15 mg/kg/day iv, during induction and consolidation
Shen et al[6], 2004 , module 5.3.5.1.2	20	21	20	0.16 mg/kg/day iv, during induction and maintenance
Powell et al[5], 2010, module 5.3.5.1.3	237	244	0	0.15 mg/kg/day iv, for post-remission treatment (prior to consolidation)
Dai et al[4], 2009 § module 5.3.5.1.4	52	110	0	10 mg/day iv, during induction and consolidation/maintenance.
ALLG APML4[1] 4 module 5.3.5.2.1	0	124	0	0.15 mg/kg/day iv during induction, and intermittent cycles in consolidation
Iland et al[2] 2012, *ALLG APML3*	*70*	*0*	*0*	*No ATO regimen – the maintenance cohort (total study n=101)*
Ravandi et al[7] 2009 module 5.3.5.2.2	0	82	0	0.15 mg/kg/day iv, during both induction and maintenance
Lou et al[8] 2012 Module 5.3.5.2.3	0	137	0	10 mg day iv, during both induction and maintenance
Pei et al[9] 2012 module 5.3.5.2.4	0	73	0	0.16 mg/kg/day iv, during induction and 10 mg/day iv for 14-21 days in 3rd month during maintenance for 6–8 courses over approximately 3 years
Gore et al [10]2010 module 5.3.5.2.5	0	45	0	0.15 mg/kg/day iv, on weekdays (30 doses) from Day 8, during consolidation
Sub total	**458**	**913**	**20**	

§Dai: from 72 patients in Group A receiving only ATRA, 20 received ATO in Group A1 in addition to the 90 patients initially exposed in Group B

Table 20: Patient exposure in single-agent studies

Study Identifier (Author)	Patients Exposed			ATO dose and treatment regimen
	ATRA (or no ATO)	ATRA + ATO	ATO	
As single agent treatment				
Ghavamzadeh et al[11]2006 module 5.3.5.2.6	0	0	94	0.15 mg/kg/day iv, for induction (Bk), and 6 days/week for 28 days consolidation.
Ghavamzadeh et al[12]2011 module 5.3.5.2.7	0	0	+ 68 (in addition to 111† in 2006 paper)	0.15 mg/kg/day iv, for induction (Bk), and 6 days/week for 28 days consolidation. Additional consolidation courses at 1 and 2 years
Mathews et al[13] 2006 module 5.3.5.2.8	0	0	72	10 mg/day iv, during induction (Bk), 28 days daily for consolidation, then 6 cycles of maintenance 10 days every month.
Mathews et a[14] 2010 module 5.3.5.2.9	0	0	(no additional)	No treatment – long term follow-up of Mathews et al 2006
Alimoghaddam et al[15] 2006 module 5.3.5.2.10	0	0	17	0.15 mg/kg/day iv, during induction (Bk), 28 days daily for consolidation. No maintenance.
As single agent treatment in children				
George et al[16] 2004 module 5.3.5.2.11	0	0	11	0.15 mg/kg/day iv, during induction (Bk), 28 days daily for consolidation (Bk), then 6 cycles of maintenance 10 days every month.
Zhou et al[17] 2010 module 5.3.5.2.12	0	0	19	0.15 mg/kg/day iv, during induction (Bk), 28 days daily for consolidation (Bk), then maintenance 14 days every month in 1st year, every 2 months in 2nd year, every 3 months in 3rd year.
Single agent total	**0**	**0**	**281**	*†While 111 patients were reported in the paper published in 2006, only 94 were newly diagnosed. Bk indicates a break in treatment (between cycles)*
Total	**458**	**913**	**301**	

Evaluator's Comments: The exposure was adequate to evaluate the adverse event profile of Phenasen for the proposed indication for treatment of newly diagnosed APL patients as combination therapy (with ATRA/CT). However, the studies for ATO monotherapy were not conducted in newly diagnosed patients with contraindications to ATRA and/ or CT and the published studies only provided brief description of safety data.

In the pivotal Phase II open-label Study APML4, 124 patients commenced induction treatment and were evaluable for safety analysis. All 124 patients received both ATRA and ATO, the maximum exposure for patients to ATO would be 81 days over the courses IND, CON1 and CON2. Although 112 patients completed these 3 courses, patients did not all receive the full protocol prescribed dose (particularly during IND), although close to 50% received between 90 and 100% of the protocol prescribed dose (60/124, 48% in IND; 59/112, 53% in CON1 and CON2) (Table 21).

Table 21: APML4 study Potential exposure to ATRA, ATO and IDA

Period of Exposure	ATRA 45 mg/m^2/d	ATO 0.15 mg/kg/d	IDA 12 mg/m^2/d	No of Patients
Induction	36 d	28 d	4 d	124
Consolidation #1	28 d	28 d	-	112
Consolidation #2	21 d	25 d	-	112
Maintenance	112 d	-	-	98-112
Total days exposure	**197 d**	**81 d**	**4**	-
Total dose	**8,865 mg/m^2**	**12.15 mg/kg**	**48 mg/m^2**	-

Note: exposure during IND to 124 patients, during CON1 and CON2 112 patients and during MNT 112 patients began MNT, but only 98 patients completed 24 months (8 cycles).

Evaluator's Comments: The dose of ATO prescribed in this study is the same as that approved for use in patients with relapsed APL. Additionally, the total exposure is similar to that recommended in the product information for Phenasen (ATO) in relapsed APL (60 days for induction and 25 days for consolidation, total 85 days refer to Phenasen PI). Drug concentration data (whole blood arsenic levels) were not available.

8.4. Safety results in the combination treatment studies

8.4.1. Safety results from pivotal Phase III studies

8.4.1.1. APML4 study:

8.4.1.1.1. Adverse events:

All patients experienced AEs that included events likely to be related to the underlying disease, concomitant illness or related to one or more of the study products. Specific consideration was given to AEs occurring at Grade 3 and 4, and AEs of particular interest. AEs identified as being of particular interest (cardiac, hepatic/metabolic, neurology/pain, gastrointestinal, haematological, infection, dermatological, ocular) were assessed according to CTCAE v3.0 at the completion of each cycle of therapy. AEs were more frequent and more severe during IND.

AE assessments were completed for 121 of 124 patients who commenced IND, all 112 patients who commenced CON1 and 111 of 112 patients who commenced CON2. AE assessments were not completed for 3 patients who died during IND; and for 1 patient assessment was not completed after the medical record was lost.

During induction, Grade 3 - 4 APLDS was reported in 14%, which is similar to reports of APLDS occurring with ATRA + chemotherapy without ATO. Importantly, there were no deaths attributable to APLDS. QTc prolongation to > 500 ms occurred during ATO induction therapy in 14% of patients, but there were no instances of torsades de pointes or other severe arrhythmias. One patient developed marked T-wave inversion after the first dose of ATO. Despite cessation of ATO, T-wave inversion persisted and the patient was withdrawn[31] from the study. Biochemical hepatotoxicity was common, but responded to protocol-specified ATO dose reduction and resolved after ATO withdrawal. Other potential contributors to the observed hepatotoxicity include ATRA, idarubicin, allopurinol, and antifungal prophylaxis.

In general, consolidation was associated with considerably less toxicity than induction, and this was especially evident for hepatic, gastrointestinal, infective, and metabolic AEs. No APLDS was observed in consolidation. Compared with the first cycle of consolidation, biochemical hepatotoxicity and infections were also less frequent in the second cycle when ATO and ATRA

[31] Whether the preceding 4 doses of idarubicin (total dose, 35 mg/m^2) or the single dose of ATO (0.15 mg/kg) was responsible is unclear.

were given on an intermittent schedule (weekdays only for ATO and alternate weeks for ATRA) (Table 22).

Table 22: Adverse events reported by worst grade in IND and CON

		Induction		Consolidation 1		Consolidation 2	
Adverse Event	**Grade**	***N***	**% of 121**	***N***	**% of 112**	***N***	**% of 111**
Cardiac							
Conduction abnormality	1	2	2	2	2	1	1
Supraventricular arrhythmia	0	96	79	93	83	100	90
	1	18	15	15	13	9	8
	2	6	5	4	4	2	2
	3	1	1	0	0	0	0
Ventricular arrhythmia	1	3	2	0	0	0	0
	2	0	0	1	1	0	0
	4	0	0	1	1	0	0
Left ventricular systolic dysfunction	1	0	0	1	1	0	0
	2	1	1	1	1	1	1
Prolonged QTc	1	29	24	24	21	26	23
	2	33	27	35	31	26	23
	3	17	14	10	9	5	5
Hepatic/Metabolic							
Bilirubin	1	18	15	4	4	2	2
	2	7	6	1	1	0	0
	3	7	6	0	0	0	0
GGT	1	23	19	28	25	14	13
	2	35	29	10	9	5	5
	3	41	34	9	8	1	1
	4	3	2	0	0	0	0
ALT/AST	1	33	27	39	35	23	21
	2	33	27	10	9	3	3
	3	28	23	6	5	0	0
	4	2	2	0	0	0	0
Liver dysfunction	2	1	2	1	1	0	0
	3	1	2	0	0	0	0
	4	1	1	0	0	0	0
Hyperglycaemia	1	16	13	13	12	10	9
	2	18	15	5	5	2	2
	3	7	6	1	1	1	1
	4	2	2	0	0	0	0
Neurology/Pain							
Dizziness	1	13	11	8	7	4	4
	2	8	7	0	0	0	0
Mood alteration	1	13	11	5	4	4	4
	2	11	9	0	0	2	2%
	3	2	2	1	1	0	0
Pain, musculoskeletal	1	14	12	12	11	6	5
	2	9	7	5	5	2	2
	3	3	2	0	0	0	0

Table 22 continued: Adverse events reported by worst grade in IND and CON

		Induction		Consolidation 1		Consolidation 2	
Adverse Event	Grade	*N*	% of 121	*N*	% of 112	*N*	% of 111
Pain, head/headache	1	37	31	19	17	17	15
	2	28	23	16	14	7	6
	3	4	3	1	1	0	0
Seizures	2	0	0	0	0	0	0
	3	1	1	0	0	0	0
Gastrointestinal							
Nausea	1	33	27	25	22	28	25
	2	32	26	9	8	1	1
	3	9	7	1	1	0	0
Vomiting	1	23	19	13	12	8	7
	2	19	16	6	5	3	3
	3	4	3	0	0	0	0
Diarrhoea	1	41	34	13	12	8	7
	2	28	23	1	1	6	5
	3	12	10	2	2	1	1
Mucositis	1	8	7	5	4	3	3
	2	50	41	2	2	0	0
	3	16	13	0	0	0	0
	4	1	1	0	0	0	0
Haematological							
Thrombosis/thrombus/embolism	2	9	7	4	4	1	1
	3	7	6	7	6	2	2
	4	1	1	0	0	1	1
CNS haemorrhage	1	1	1	0	0	0	0
	2	2	2	0	0	0	0
Haemorrhage, GI	1	15	12	0	0	0	0
	2	3	2	0	0	1	1
	3	5	4	0	0	0	0
Haemorrhage, pulmonary	1	15	12	1	1	1	1
	2	5	4	0	0	0	0
	3	5	4	0	0	0	0
	4	2	2	0	0	0	0
Platelets	1	0	0	15	13	8	7
	2	0	0	1	1	0	0
	3	7	6	0	0	0	0
	4	114	94	0	0	0	0
Neutrophils	1	0	0	7	6	12	11
	2	0	0	15	13	22	20
	3	0	0	42	38	27	24
	4	121	100	27	24	3	3
Infection							
Febrile neutropenia	3	47	39	6	5	0	0
	4	3	2	0	0	0	0
Infection (documented clinically)	2	11	9	3	3	12	11
	3	55	45	10	9	3	3
	4	2	2	1	1	1	1
Dermatological							
Rash	1	31	26	10	9	10	9
	2	31	26	5	4	6	5
	3	4	3	0	0	0	0
	4	1	1	0	0	0	0
Pruritis	0	98	81	105	94	106	95
	1	14	12	6	5	4	4
	2	7	6	1	1	1	1
	3	2	2	0	0	0	0
Ocular							
Dry eye syndrome	1	6	5	6	5	4	4
	2	6	5	0	0	1	1
Syndromes							
Retinoic acid syndrome	1	1	1	1	1	0	0
	2	11	9	0	0	0	0
	3	9	7	0	0	0	0
	4	8	7	0	0	0	0

Adapted from Source Table 29 SR (grades with 0 patients, not included)

Myelotoxicity associated with ATO was also schedule dependent, because Grade 3 - 4 neutropenia occurred in 69 of 112 patients in CON1, compared with 30 of 112 patients in CON2. No Grade 3 - 4 thrombocytopenia was seen in either cycle of consolidation. QTc prolongation was less frequent during consolidation than during induction, but the differences were not statistically significant. One episode of ventricular tachycardia occurred in a single patient during the first cycle of consolidation, but this was transient and was not associated with serious outcomes.

Toxicities experienced by the 4 paediatric and adolescent patients (ages 3, 15, 16, and 17 years) were comparable with those seen in adult patients.

During MNT therapy AEs were more frequent and more severe during the earlier cycles of MNT. There were no cases of CNS haemorrhage, 2 cases of gastrointestinal haemorrhage and 3 cases of pulmonary haemorrhage.

8.4.1.1.2. Deaths and SAEs:

There were 7 deaths during the APML4 trial, prior to the closeout date. In addition to the 4 patients with early deaths during IND, 3 patients died in the period between CON and closeout. Two of the early deaths were caused by intracerebral haemorrhage, with other causes of death reported as: myocardial ischaemia, cerebral oedema, infection (2 deaths due to Klebsiella pneumonia) and progressive AML.

Overall, 91 of the 124 patients commencing induction treatment (73%) experienced SAEs. Of the 91 patients 63 (69%) experienced more than 1 SAE; 1 patient experienced 11 SAEs The most common SAEs were: reduced neutrophils/ granulocytes, febrile neutropenia, elevated liver function tests and infection (with Grade 3 or 4 neutrophils) occurring in more than 10% of patients. Elevated GGT, prolonged QTc interval and APLDS occurred in more than 5% of patients.

8.4.1.1.3. Other significant AEs:

8.4.1.1.3.1. APLDS:

APLDS was identified as an AE of particular interest. A comparison of CTCAE v3.0 with an alternative grading[32] approach for APLDS is presented in Table 23. The use of CTCAE criteria for APLDS appears to overestimate the incidence and severity of APLDS when compared with the commonly reported clinical criteria. According to CTCAE grading, 14% had Grade 3 - 4 APLDS, whereas only 8% had definite or severe APLDS using the clinical features that are generally regarded as indicative of APLDS. The incidence of documented APLDS in the APML3 report was 20% (all grades) which was similar to the 24% in APML4 (all grades). APLDS was a contributory factor in the early deaths of 2 patients in APML3, but not in APML4.

Evaluator's Comments: A direct comparison of APLDS between APML4 and APML3 is not possible, as APLDS was not graded in detail in APML3. Interpretation of any comparison was also limited by use of obligatory corticosteroids in APML4 study.

[32] The alternative grading approach considers the following APLDS features: weight gain, unexplained fever, respiratory distress, pulmonary infiltrates, pleural effusion, pericardial infusion, hypotension and renal failure. Patients reporting 0 features or 1 feature only are not considered to have APLDS. Possible APLDS is defined as 2 features, definite APLDS as 3 features and severe APLDS as life- threatening respiratory failure, ventilatory support, dialysis) or at least 4 features.

Table 23: Comparison of CTCAE v3.0 with alternative grading approach for APLDS

Differentiation syndrome	Induction		Consolidation 1		Consolidation 2	
	N	% of 121	*N*	% of 112	*N*	% of 111
CTCAE v3.0						
Grade 0	92	76	111	99	111	100
Grade 1	1	1	1	1	0	0
Grade 2	11	9	0	0	0	0
Grade 3	9	7	0	0	0	0
Grade 4	8	7	0	0	0	0
Alternative grading						
No DS	96	79	112	100	111	100
Possible DS	15	12	0	0	0	0
Definite DS	4	3	0	0	0	0
Severe DS	6	5	0	0	0	0
Grade 1						
Not DS	0	0	1	100	0	-
Possible DS	1	100	0	0	0	-
Definite DS	0	0	0	0	0	-
Severe DS	0	0	0	0	0	
Grade 2						-
Not DS	4	36	0	-	0	-
Possible DS	6	55	0	-	0	-
Definite DS	1	9	0	-	0	-
Severe DS	0	0	0	-	0	-
Grade 3						
Not DS	0	0	0	-	0	-
Possible DS	6	67	0	-	0	-
Definite DS	3	33	0	-	0	-
Severe DS	0	0	0	-	0	-
Grade 4						
Not DS	0	0	0	-	0	-
Possible DS	2	25	0	-	0	-
Definite DS	0	0	0	-	0	-
Severe DS	6	75	0	-	0	-
Individual DS symptoms						
Weight gain and/or fluid retention	15	52	1	100	0	-
Unexplained fever	7	24	0	0	0	-
Respiratory distress	22	76	0	0	0	-
Pulmonary infiltrates	12	41	0	0	0	-
Pleural effusion	3	10	0	0	0	-
Pericardial effusion	1	3	0	0	0	-
Hypotension	2	7	0	0	0	-
Renal failure	0	0	0	0	0	-

8.4.1.1.3.2. Neutropenia and thrombocytopenia's:

Almost all patients experienced Grade 3 - 4 neutropenia and thrombocytopenia in IND, as expected in a population of patients with APL treated with a protocol that included 4 doses of idarubicin; this was similar to observations in studyAPML3. In consolidation, no idarubicin was used, and since ATRA is not regarded as being myelosuppressive, any significant degree of neutropenia and/or thrombocytopenia was attributable to ATO. No Grade 3 - 4 thrombocytopenia was actually seen in either cycle of consolidation. In contrast, Grade 3 - 4 neutropenia was common but occurred with higher incidence in CON1 (69 of 112 patients) compared to CON2 (30 of 112 patients) (Table 24).

Table 24: Duration of neutropenia and thrombocytopenia in IND and CON

		Induction	Consolidation	Consolidation
Number of patients commencing cycle		124	112	112
Duration (in days) from day 1 until:				
Neutrophils ≥ 0.5 × 10^9/L	*N*	121	26[a]	3
	Median [Min, Max]	33 [13, 56]	30 [14, 44]	32 [4, 35]
Neutrophils ≥ 1.0 × 10^9/L	*N*	122[b]	69	30
	Median [Min, Max]	37 [16, 73]	38 [22, 56]	39 [14, 63]
Platelets ≥ 20 × 10^9/L	*N*	94	0	0
	Median [Min, Max]	19 [1, 31]		
Platelets ≥ 50 × 10^9/L	*N*	121	0	0
	Median [Min, Max]	24 [4, 40]		

[a] Neutrophils were reported as a grade 4 adverse event for WES002 in CON1 however minimum neutrophil count was 0.5 rather than <0.5 x 10^9/L. [b] NEP001 was not assessed for adverse events in IND due to death however neutrophil count fell below 1.0 x 10^9/L prior to death. *Source Table 38 SR*

8.4.1.1.3.3. Physical examination: ECOG performance status, body weight and BSA:

ECOG performance status was required to be ≤ 3 for eligibility, and this was confirmed prior to the IND treatment cycle; 52% of patients had an ECOG PS of 0, 35% were ECOG 1, 9% were ECOG 2 and only 5% of patients were ECOG 3. After successive treatment cycles mean ECOG reduced so that after IND (prior to CON1) all patients had an ECOG score ≤ 2, with only 5% of patients at ECOG 2; after CON1 only 1% of patients had an ECOG score of 2 (99% ≤ 1) and after CON2 all patients had an ECOG score of ≤ 1. This overall improvement in ECOG was recognised by the investigators in line with response to treatment.

Body weight appeared to be reduced after treatment with IND (from a mean of 83.1 kg prior to IND to a mean of 78.2 kg prior to CON1). However, the mean body weight was increased over the CON treatment cycles (back to 78.9 kg prior to MNT), while the median did not reflect the same degree of change. Mean BSA showed a small reduction with similar changes to those observed for change in mean bodyweight.

8.4.1.1.3.4. Chest and cardiac investigations:

The highest number of abnormal chest x-rays (20 patients, 17%) and ECGs (27 patients, 22%) were noted prior to the IND cycle, that is at baseline with fewer abnormal reports for patients after the IND and CON cycles. The abnormalities were not considered to be specifically treatment related. Cardiac investigations indicated toxicity due to chemotherapy and ATO. The LVEF and QTc data are summarised in Table 25. Inclusion criteria required that all patients had a QTC < 500 ms at baseline. For the majority of patients the duration of the QTc interval lengthened in successive study phases from a mean 416 ms prior to the IND cycle (baseline) to a mean of 425 ms prior to the first MNT cycle, and there was a corresponding upward shift in the range. However there was virtually no change in the median figure (419 - 421 ms). The range around the median QTc indicates that the QTc interval exceeded 500 ms at measurements taken before the CON1, CON2 and MNT1 cycles in some patients, but review of the CRFs identified only 1 patient with a QTc of 543 ms at the start of both CON1 and CON2, and only 1 patient with a QTc of 530 ms at the start of MNT. Taken together, these data suggest a possible cumulative effect of repeated ATO administration on QTc prolongation in some patients however, interpretation was confounded by electrolyte disturbances (hypomagnesaemia and hypokalaemia) and the use of other drugs capable of prolonging QTc.

Table 25: Cardiac investigations prior to each treatment cycle.

Investigation	Prior to IND (n=124)	Prior to CON1 (n=112)	Prior to CON2 (n=112)	Prior to MNTI (n=112)
QTc interval (msec)				
N	123	105	103	63
Mean (SD)	416 (31)	422 (32)	422 (30)	425 (26)
Median (range)	419 (320-487)	421 (360-543)	421 (326-543)	421 (380-530)
Not done	1	7	9	49
LVEF (%)				
N	121	95	12	0
Mean (SD)	64.2 (7.2)	59.5 (7.8)	55.7 (11.3)	
Median (range)	65 (42-85)	59 (37-78)	59 (37-71)	
Not done	3	17	100	

Adapted from source table 14.3.4.1

Similarly, LVEF decreased over the successive cycles. There was a 4.7% reduction in mean LVEF observed between results taken prior to the IND cycle (mean LVEF 64.2%) and prior to the commencement of CON1 cycle (mean LVEF 59.5%; during the period of treatment with the anthracycline IDA); followed by a further reduction in mean LEVF (3.8%) after the CON1 cycle.

Evaluator's Comments: However, interpretation was limited due to fact that the number of patients for whom LVEF was measured at the end of the CON 1 cycle (n = 12) was substantially lowered from the number of patients prior to the CON1 cycle (n = 95). No test of statistical significance has been performed, to be able to confirm that the difference in pre-IND and pre- CON1 is statistically significant although it is a recognised effect of anthracycline chemotherapy. Furthermore, the confounding effects of sepsis on LVEF have not been taken into account is this analysis.

8.4.1.2. Lo-Coco et al, 2013.

The ITT analysis included 156 patients who all received at least 1 dose of the assigned therapy after randomization (thus also the safety population). There were 4 patients in the ATRA + CT group who died during induction therapy: 2 from the APLDS, 1 from ischemic stroke, and 1 from bronchopneumonia. Induction therapy was terminated early in 2 patients. One in the ATRA + ATO group due to a severe prolongation of the QTc interval and electrolyte abnormalities on Day 3, the other was a major protocol violation.

APLDS, including moderate and severe forms, developed in 15 patients in the ATRA + ATO group (19%) and in 13 patients in the ATRA + CT group (16%) (P = 0.62). Severe APLDS occurred in 10 patients (5 [6%] in each group, P = 0.99) and was fatal in 2 patients assigned to ATRA + CT. Leukocytosis (WBC >10×109/L) developed during induction therapy in 35 of 74 patients in the ATRA + ATO group (47%) and in 19 of 79 patients in the ATRA + CT group (24%) (P = 0.007). All cases were successfully managed with hydroxyurea therapy (according to the recommended protocol).

A total of 146 patients in hematologic CR proceeded to consolidation therapy. Two patients in the ATRA + CT group did not receive consolidation therapy because of a cardiotoxic effect, and were lost to follow-up and 1 in the ATRA + ATO group was taken off protocol after induction therapy owing to repetitive tachycardia. Four patients died during consolidation therapy (3 in the ATRA + CT group and 1 in the ATRA + ATO group). The 3 patients in the ATRA + CT group died from haemorrhagic shock, pulmonary embolism, and bronchopneumonia. The patient in the ATRA + ATO group died from bronchopneumonia associated with H1N1 virus infection.

8.4.1.2.1. Hematologic toxicity:

Grade 3 or 4 neutropenia lasting more than 15 days and Grade 3 or 4 thrombocytopenia lasting more than 15 days were significantly more frequent both during induction therapy and after each consolidation course in the ATRA + CT group than in the ATRA + ATO group. Counting together fever of unknown origin and documented infectious episodes occurring during induction or consolidation therapy, 26 episodes were recorded in the ATRA + ATO group and 59 episodes in the ATRA + CT group ($P < 0.001$).

8.4.1.2.2. Non-hematologic toxicity:

A total of 43 of 68 patients in the ATRA + ATO group (63%) and 4 of 69 patients in the ATRA + CT group (6%) had Grade 3 or 4 hepatic toxic effects during induction or consolidation therapy (for patients in the 2 groups) or during maintenance therapy (for patients in the ATRA + CT group; $P < 0.001$). In all cases, the toxic effects resolved with temporary discontinuation of ATO, ATRA, or both or with temporary discontinuation of CT during the maintenance phase (for patients in the ATRA + CT group).

Prolongation of the QTc interval occurred in 12 patients in the ATRA + ATO group (16%) and in no patients in the ATRA + CT group ($P <0.001$). In 1 of the 12 patients with a prolonged QTc interval, ATO was permanently discontinued, and the patient went off protocol.

Evaluator's Comments: In this randomised, active-controlled, non-inferiority study involving 156 patients with newly diagnosed APL, the incidence of APDLS was similar in the ATRA+ATO and ATRA+CT groups (19% versus 16%). The incidence of Grade 3 - 4 neutropenia/ thrombocytopenia was significantly greater in the ATRA+CT group, but incidence of Grade 3 - 4 hepatotoxicity and prolongation of QTc intervals was significantly greater with the proposed ATRA+ATO combination treatment.

8.4.1.3. Dai et al, 2009

A total of 162 patients with newly diagnosed APL were enrolled in this open-label, non-randomised, single-centre study. Overall, 7 patients from Group A (ATRA + CT) and 6 patients from Group B (ATRA +ATO) did not enter consolidation and maintenance due to either early death (12 patients) or failure to achieve a CR (1 patient); 149 patients continued in the trial. After induction Group A was split into 2 groups, A1 receiving ATO in addition to ATRA and CT (as Group B1) and A2 continuing with ATRA plus CT alone. Both ATRA and ATO based treatments were well tolerated. During induction, therapy related hyperleukocytosis and neutropenia were observed in both Groups A and B (Table 26). APLDS or retinoic acid-like syndrome (fever, pulmonary infiltrates, tachypnoea and fluid retention) rarely occurred in the patients of this cohort (2 patients of Group A, 3 patients of group B). Patients with APLDS were treated with methylprednisolone and withdrawal of ATRA and As_2O_3. No patient died of this complication.

Table 26: Dai et al, 2009. Toxicity profile

	Remission induction		Postremission	
	group A (n = 72)	group B (n = 90)	group A2 (n = 45)	group A1+B1 (n = 104)
Hepatotoxicity				
Grade 1	8 (11.1)	33 (36.7)	4 (8.9)	13 (12.5)
Grade 2	4 (5.6)	15 (16.7)	2 (4.4)	5 (4.8)
Grade 3	2 (2.8)	7 (7.8)	0	4 (3.9)
Grade 4	0	1 (1.1)	0	0
Total	14 (19.4)	56 (62.2)*	6 (13.3)	22 (21.2)#
Skin reaction	10 (13.9)	14 (15.6)	5 (11.1)	8 (7.7)
Headache	13 (18.1)	18 (20.0)	6 (13.3)	14 (13.5)
Dryness of lips	30 (41.7)	41 (45.6)	15 (33.3)	38 (36.5)
Fluid retention	5 (6.9)	21 (23.3)*	0	14 (13.5)#
Cardiac arrhythmia	0	0	0	0
Differentiation syndrome	2 (2.8)	3 (3.3)	0	0

Figures in parentheses are percentages. * $p < 0.05$, vs. group A; # $p < 0.05$, vs. group B. Toxicity profile of group A2 was documented at the first consolidation course; group A1+B1: patients from groups A1 and B1 were merged into 1 group, in which patients received an As_2O_3-containing regimen for postremission therapy, toxicity profile was documented at the first course of As_2O_3 administration following CR.

During induction, hepatotoxicity occurred more frequently in Group B (ATRA + ATO) than in Group A (ATRA alone; P < 0.05). ATO was discontinued in 8 patients with Grade 3 or 4 hepatotoxicity for a mean period of 15 days. A total of 7 patients recovered and proceeded to complete the ATO course, 1 patient entered CR and did not receive any further ATO for induction. The incidence of liver dysfunction resulting from ATO administration decreased significantly in patients who had achieved CR (P < 0.05, Group A1 + B1, versus Group B).

A high incidence of fluid retention was noted in patients who received ATO for induction (Group B), compared to patients who received the regimen without ATO (P < 0.05, versus Group A), or patients who received ATO for consolidation and maintenance (P < 0.05, versus Group A1 + B1).

No event of cardiac arrhythmia or pathological prolongation of QT interval was noted. As the side effects of As_2O_3 were moderate and reversible, particularly in CR patients, some patients received intravenous As_2O_3 administration for maintenance on an outpatient basis with monitoring CBCs and liver function.

There were 12 early deaths, during induction: 9 were attributable to ICH, 2 to infection and 1 to pulmonary haemorrhage. Causes of death during induction were similar in both groups, with no patients dying of APLDS.

Evaluator's Comments: In this open-label, single centre study involving 162 patients with newly diagnosed APL, incidence of early death was similar during induction and there were no deaths due to APDLS which had a low incidence. However, incidence of hepatotoxicity and fluid retention was higher in patients treated with ATO.

8.4.2. Safety results from other published studies

8.4.2.1. Shen et al, 2004:

In this open-label, randomised, controlled, multicentre study, 61 newly diagnosed patients with APL without prior exposure to any anti-leukemic therapy were randomised to 3 treatment groups (ATRA+ATO), ATRA alone or ATO alone.

Out of a total of 61 subjects, only 4 failed to achieve CR, dying of intracerebral haemorrhage (ICH) on Days 1, 2, 8, and 15 respectively. Five subjects in Group 1 relapsed within 13 months

after achieving CR (26.3%). Three of these patients achieved second remission with ATO based re-induction therapy whereas the remaining 2 died of ICH. Two subjects in Group 2 relapsed within 1 year after achieving CR (11.1%). One patient achieved second remission with ATO based re-induction therapy and the other achieved second remission with the combined ATO and ATRA regimen. No patients in Group 3 had relapsed at the time the results were published

Skin reaction, dryness of mouth, headache were more commonly observed in treatment groups containing ATRA while hyperleukocytosis and hepatic dysfunction were more common with ATO (Table 27).

Table 27: Adverse events: Shen et al, 2004

	Group 1 ATRA	Group 2 ATO	Group 3 ATRA & ATO
Cases (n)	*20*	*20*	*21*
Skin reaction	4 (21%)	0	2 (10%)
Dysrhythmia	0	0	0
Gastrointestinal reaction	0	1 (5.6%)	1 (5%)
Dryness of mouth	11 (57.9%)	2 (11.1%)	12 (60%)
Headache	4 (21%)	1 (5.6%)	2 (10%)
Hyperleukocytosis	10 (52.6)	12 (66.7%)	14 (70%)
Liver Dysfunction			
Grade 1	4	7	8
Grade 2	0	2	3
Grade 3	1	2	2
Grade 4	0	0	0

Examination of whole peripheral BCC show earlier recovery of platelet counts (> 100 x 10^9/L) in Group 3 (median, 22 days) over Group 1 (median, 32 days, P = 0.03) as well as Group 2 (median, 22 days, P = 0.031) whereas both the recovery time of haemoglobin and that of WBC counts were found similar among the three groups. Combination therapy (Group 3) did not increase the frequency of hyperleukocytosis as compared with monotherapy groups[33] No patients developed adult respiratory distress syndrome (ARDS).

Overall, 29 patients experienced liver dysfunction, in 19 it returned to normal within 1 week, while in the remaining 10 it had recovered in 1 - 2 weeks. Hepatotoxicity was closely monitored and ATO was reduced to half the dose (0.08 mg/kg/day) and symptomatic therapy commenced for patients with Grade 0 - 1 liver dysfunction. In patients with grade 2 - 4 liver dysfunction ATO was withdrawn.

8.4.2.2. Powell et al, 2010:

This open-label, multicentre study enrolled 481 newly diagnosed patients with APL who were randomised to the non-ATO arm (no ATO prior to consolidation) and 244 patients were randomised to the ATO arm (2 courses of ATO prior to consolidation).

During induction phase, APLDS was reported in 177 patients (37%), 162 of whom received DEX. No cases of APLDS were reported during consolidation. A total of 19 patients (8%) in each treatment arm died during induction therapy. There were no treatment related deaths during consolidation. Maximum hematologic adverse events due to consolidation treatments were 16% Grade 3 and 67% Grade 4 on the standard arm, and 21% Grade 3 and 54% Grade 4 on the As_2O_3-containing arm. Maximum no hematologic adverse events due to consolidation treatments were 30% Grade 3 and 5% Grade 4 for the standard arm, and 41% Grade 3 and 5% Grade 4 for the As_2O_3-containing arm. During consolidation the greatest difference in Grade 3 non-hematologic toxicity was headache at 3%in the non- As_2O_3 arm compared with 7% in the As_2O_3 arm, with smaller differences in electrolyte abnormalities (1% versus 3%) and nausea

[33] (Group 1 vs group 3, *P* = 0.557; Group 2 vs group 3, *P* = 0.825; Group 1 vs group 2, *P* = 0.385)

(3% versus 4%). No Grade 3 or 4 cardiac toxicities due to QTc prolongation were observed on the As_2O_3 arm. No patients experienced the APL differentiation syndrome during consolidation.

Evaluator's Comments: It was difficult to interpret safety results from this study as details were not available regarding types of hematologic or non-hematologic AEs. The limited information provided in the publication has been included in summary above.

8.4.2.3. Ravandi et al, 2009:

Overall, 82 patients with newly diagnosed untreated APL were enrolled in this open-label; single centre, non-randomised, uncontrolled study and were treated with ATRA and arsenic trioxide (ATO) with or without gemtuzumab ozogamicin (GO) but without traditional cytotoxic chemotherapy. Patients were identified by risk with high-risk presenting with a WBC count > 10 x 10^9/L and low-risk presenting with WBC count < 10 x 10^9/L. Most severe AEs occurred during induction and were related to the disease and its complications (Table 28). In 5 patients GO was substituted for ATO in consolidation due to cardiac AEs. APLDS occurred in 13 patients (11 of 65 patients on regimen A and 2 of 17 patients on regimen B; not significant) and was successfully managed by withholding ATRA, and administering corticosteroids; ATO was not discontinued. Presenting WBCs did not predict the development of APLDS which occurred in 8 of 56 (14%) low risk patients versus 5 of 26 (19%) high-risk patients (P = 0.57).

Table 28: Ravandi et al, 2009. Adverse events reported

Adverse event	Grade 3	Grade 4
Esophagitis	1	-
Rash	1	-
Headache	5	-
Atrial arrhythmia	3	-
Elevated liver enzymes	2	-
Back pain	1	-
Myocardial infarction	1	1
Subarachnoid haemorrhage	1	-
Constipation	1	-
Renal failure	4	-
Respiratory failure	-	1
GI bleed	-	1
Muscle weakness	1	-
Cerebral infarct	2	1
Bone pain	1	-
Nausea	1	-

Evaluator's Comments: There was only very brief description of safety results in the publication which has been summarised above.

8.4.2.4. Lou et al, 2013:

A total of 137 newly diagnosed APL patients were included, stratified by risk category according to their pre-treatment WBC counts: 45 high-risk patients with WBC count > 10 x 10^9/L and 92 low-risk patients with WBC count < 10 x 10^9/L.

Nine patients died during induction therapy. Of these 9 early deaths, 4 were attributable to ICH, 2 were due to pulmonary haemorrhage, 1 to disseminated intravascular coagulation (DIC), 1 to infection, and 1 to APLDS. Eight early deaths occurred within the first week of treatment with a median time from diagnosis to death of 4 days. One patient died during consolidation therapy due to an intracranial bleed. Hyperleukocytosis (WBC >10 x 10^9/L) developed in 104 of 137 patients, with the peak WBC counts ranging from 10.1 to 166.6×10^9/L (median, 50.1× 10^9/L),

occurring at 1 - 23 days (median 8.8 days) after commencing therapy. In addition, 40 of 137 patients had an increase in their peak WBC counts to more than 50 x 10^9/L, including 6 early deaths.

Evaluator's Comments: There was only very brief description of safety results in the publication which only focussed on effects on WBCs. Details of non-hematologic AEs related to hepatotoxicity or prolongation of QTc interval were not provided.

8.4.2.5. Pei et al, 2012:

A total of 73 newly diagnosed patients were enrolled in this Phase III, open, uncontrolled single centre study in which a combination regimen of ATRA and ATO was used for induction and a sequential regimen of ATRA, ATO and CT was used for consolidation and maintenance in patients who achieved CR. The DD dimer of all patients was higher than 1000 ng/mL before treatment and a rapid normalization of coagulopathy was observed in 69 evaluable responders, with a median of 8 days (range 4 – 19).

The main side effect of ATRA was hyperleukocytosis and the median time of the WBC reaching a peak 187 x 10^9/L was 12 days (range, 8 – 18). All cases with hyperleukocytosis returned to normal when treated with CT. APLDS was diagnosed in 4 patients, but no patients died of this complication. Overall, 35.6% (26/73) patients developed tolerable and reversible liver dysfunction. Among those patients, 23 patients showed Grade 1 - 2 liver damage and liver abnormality returned to normal within 1 - 2 weeks without termination of ATO therapy. Grade 3 hepatotoxicity occurred in the remaining 3 patients; which required both withdrawal of ATO and hepatoprotection for 2 weeks. No incidence of Grade 4 hepatotoxicity was observed.

Other side effects, including dry mouth, chapped skin, headache, and gastrointestinal tract reactions, such as nausea, vomiting and abdominal distention were mild and treated symptomatically.

Overall both ATRA and ATO based treatments were tolerated well. Hepatotoxicity and leukopenia was observed more frequently in consolidation than in induction therapy. Higher incidence of fluid retention was also found.

Two of 69 patients treated with ATO developed arrhythmia (sinus tachycardia, without QTc prolongation) during post-remission therapy, but the symptom disappeared spontaneously after completion of treatment cycles. No other events of cardiac arrhythmia or pathological prolongation of QT interval were noted. All of the side effects observed in treatment with ATO were mild to moderate so all patients in this cohort received a whole course of ATO treatment.

All patients except the 4 who died in induction therapy, were alive on long-term follow-up. One of the potential safety issues associated with the treatment regimen was long-term toxicity related to multiple exposures to both ATO and CT. Systematic physical examinations and laboratory studies[34] to screen for possible toxic effects were made in all CR patients at the end of treatment courses and at 6-month intervals following treatment. Evaluations by independent haematologists at final follow-up showed that all patients were in generally good condition.

8.4.2.6. Gore et al, 2010:

The open-label, uncontrolled, multicentre study involving 45 newly diagnosed, untreated patients with APL evaluated whether the addition of ATO to first-line CT could reduce the total amount of CT administered to patients without affecting the EFS. The median age was 50 years (range 19 - 70) and according to the Sanz prognostic score risk was low in 36%, intermediate in

[34] The tests included whole blood counts with morphological observation of peripheral blood cells, electrolyte panels with blood urea nitrogenand creatinine, urinalysis, liver function test, evaluation of serum tumor markers (CEA, AFP, CA-199, CA-125), electrocardiograms (ECGs), echocardiograms, and chest X-rays.

29%, and high in 32% of subjects. Of the 45 subjects who received induction therapy, 41 completed the cycle and 37 received consolidation therapy (including ATO) (Figure 21).

Four patients died during induction, 1 before therapy was initiated. One patient developed cardiomyopathy after induction and declined further intensive therapy (proceeding to maintenance therapy) and 1 patient completing consolidation therapy declined further study participation due to a prolonged QT interval. Pre-treatment and post-induction ECGs were obtained in 29 patients. Ejection fraction (EF) was the focus for identification of anthracycline-induced cardiomyopathy. In the 29 patients, EF decreased by a mean of 11.1% +3.6% (P <0.005), 13 patients (45%) had a reduction in EF of at least 10% after induction, 6 patients (21%) experienced an EF reduction of more than 20% (range 23 – 67%) and the lowest EF was 20% in a 71 year old female with no prior cardiac history. Endomyocardial biopsy results for 2 patients were diagnostic for anthracycline-associated cardiomyopathy.

After consolidation 22 patients had repeat ECGs. EF showed an average EF decrement of 12.8%+ 4.6 compared to baseline (P = 0.01), 6 patients had a decrease from baseline of >20% or greater (27%, range 24 – 54%). The systematic monitoring of EF before and after induction therapy in this study showed that this parameter decreased by > 20% in 21% of patients after only 180 mg/m^2 of anthracycline.

Evaluator's Comments: The reduction in EF observed following relatively low exposure to anthracycline raises the question of whether ATRA may sensitize the myocardium to anthracycline toxicity. The anthracycline used in this study was daunorubicin (60mg/m^2/day). There was no information on safety results related to haematological toxicity, APDLS or hepatotoxicity.

8.5. Safety results in the published single agent studies

8.5.1. Ghavamzadeh et al, 2006, 2011:

Ghavamzadeh et al, 2006 reported results of an open, uncontrolled, single centre study involving 111 APL patients (94 newly diagnosed). Sixteen patients died (14.4%) during induction with ATO and median time to death was 20 days (range 2 - 55). Causes of death included APLDS with pulmonary haemorrhage and/ or acute respiratory distress syndrome (n = 8), cerebral haemorrhage (n = 3), cardiac arrest (n = 2), disseminated aspergillosis (n = 1) and disease progression/ did not achieve CR (n = 2). Hyperleukocytosis during treatment (defined as WBC count > 10 x 10^9/L) occurred in 65 patients (58.6%) with median time to onset of 10 days (range 2 - 22). There was no significant difference in WBC counts at disease onset between patients with and without hyperleukocytosis and no increase in early mortality of treatment. No observation of relationship between hyperleukocytosis and APLDS, remission rate, and relapse rate was made; OS and DFS were not significantly different for patients with and without hyperleukocytosis. However, the death rate was significantly higher in patients with APLDS (P < 0.006).

In the longer term follow-up (Ghavamzadeh et al, 2011) involving 197 patients with newly diagnosed APL, 29 patients died (14.7%) during induction with ATO. Patients who died of pulmonary haemorrhage displayed symptoms of rapidly progressive dyspnoea, bloody sputum, pulmonary haemorrhage, and respiratory failure. These cases were attributed to APLDS. In 3 patients who were rescued by activated factor VII and supportive care, ATO was then reduced to half dose and continued until CR. Increases in liver enzymes were observed. AST and/or ALT increased to more than the upper limit of normal in 35% of cases. Bilirubin increased to more than 3 mg/dL in 3 cases. Liver abnormalities usually resolved with continued ATO therapy with minimal treatment interruption and/or dose reduction. Renal failure was noted in 7 patients (4%) requiring temporary discontinuation of treatment; treatment was resumed later in 2 patients successfully, and substitution of ATO with ATRA and CT was needed in 1 patient to

complete the course of treatment. Two patients with nephrotic syndrome before treatment received ATO without complication. Among patients on long-term follow-up (> 2 years), no symptomatic cardiac, liver, renal toxicities or secondary malignancies were observed.

Evaluator's Comments: Treatment of newly-diagnosed APL with single agent ATO was associated with 14% incidence of early death during induction phase and high incidence of hyperleukocytosis (58%) and hepatotoxicity (35%).

8.5.2. Matthews et al, 2006:

This was an open, uncontrolled, single centre study to evaluate the management of 72 newly diagnosed PML-RARα-positive APL patients on a regimen of single-agent ATO for remission induction, consolidation, and maintenance. After completion of scheduled therapy, patients were followed up once in 3 months for the first 2 years and once in 6 months for the next 3 years; total median follow-up was 25 months (range 8 – 92 months). There were 10 deaths during induction therapy, 7 of which were early deaths secondary to ICH bleeds. Three additional patients died prior to achieving a CR, on Days 20, 23, and 49, secondary to uncontrolled sepsis, IC bleed, and a differentiation syndrome, There were no sudden deaths attributable to a cardiac event. A total of 8 patients (11.1%) received an anthracycline in induction[35]. Hydroxyurea was administered to 53 (73.6%) patients for high-risk leukocyte count at presentation or leukocyte response following administration of ATO. Hydroxyurea was administered for a median period or 11 days (range 2 – 31 days) and a medium cumulative dose of 12 g (range 1 - 40.5 g).

Of the 62 patients who achieved CR, therapy was discontinued in 2 patients; 1 patient due to persistent neutropenia (relapsed on Day 572) and other patients due to recurrent Grade 3 transaminitis. Both patients were subsequently treated with a combination of ATRA + CT. An additional patient from this group had an isolated CNS relapse detected during a second maintenance course. Of the remaining 59 patients, who completed the consolidation and maintenance course as scheduled, only 4 patients required hospital admission during this period.

Admissions were for febrile neutropenia, acute onset diarrhoea, non-neutropenic fever, and hepatitis (Table 28). Of the 60 patients who received consolidation, 4 developed transient (< 1 week) Grade 3 - 4 neutropenia and only 1 of these patients developed febrile neutropenia. In all these cases ATO was discontinued briefly and restarted without recurrence of cytopenia. The non-hematologic toxicities in the majority of patients were mild, frequently reverted on continuing ATO, and in the rest the toxicities were reversible on discontinuation of ATO for 1 - 2 weeks.

APLDS occurred in 5 (6.9%) patients. The average time to onset was 13.2 days (range 6 - 21 days) from the start of induction. The syndrome occurred in patients who had leukocytosis at diagnosis or a leukocytic response to ATO. No cases occurred during consolidation or maintenance.

Hepatotoxicity was seen in 21 (29%) patients; in the majority (16/21), it was Grade 1/2 and reverted to normal on continuing As_2O_3 as per the protocol. Of the 5 patients who developed Grade 3/4 hepatotoxicity, in 4 patients, rechallenging with As_2O_3 once the hepatotoxicity had resolved did not lead to recurrence of the abnormality. There were no documented acute hepatic failures or cases with hepatic decompensation, though one patient had persistent Grade 1 toxicity up to 6 months after completion of therapy. There was no effect of hepatotoxicity on EFS or OS.

[35] Indications for anthracycline included: differentiation syndrome (2 cases), high leukocyte count at presentation or rapid leukocyte response (6 cases).

Only one patient developed an arrhythmia (supraventricular tachycardia, without QTc prolongation), which occurred on day 4 of induction; this was associated with symptoms but reverted without treatment. Arsenic trioxide was discontinued for a day and subsequently administered as per the protocol without any further cardiac events. One other patient developed a retrosternal discomfort during induction and the ECG showed transient nonspecific T-wave inversions. In this patient, the regimen was continued without a break and completed uneventfully.

Evaluator's Comments: APDLS occurred in only 5 (6.9%) patients which was lower than has been previously reported. It is possible that the use of hydroxyurea to control the leukocytic response contributed to this lower incidence. The low incidence of cardiac-related toxic events in this series of newly diagnosed cases of APL could potentially be due to absence of exposure to anthracyclines or other cardiotoxic agents prior to this therapy and the attention to maintenance of electrolyte levels within the normal range. Furthermore, it is possible that transient QTc prolongations were missed due to lack of cardiac monitoring.

8.5.3. Matthews et al, 2010

This paper provides the long-term follow-up data that was collected in July 2009 from the same 72 patients reported in Mathews et al 2006.

Hepatotoxicity (data includes treatment period and long-term follow-up): Grade 1 – 2: 24 patients (33.3%), occurred mainly in induction and was mainly associated with elevated levels of liver enzymes; Grade 3 – 4: 5 patients (6.9%) ATO was discontinued for a mean period of 18.2 days (range 7 – 28 days) in these patients additional patients developed acute hepatitis B (1 in consolidation and 1 in maintenance) ATO was discontinued for 4 weeks and restarted uneventfully after the acute phase of hepatitis had resolved. There was no evidence of hepatic compromise/ decompensation in patients in the period evaluated for long-term follow-up. In 4 asymptomatic patients, there was persistent mild elevation of liver enzymes (> 2-fold normal levels), at the last follow-up visit, for which no other aetiology could be identified. Follow-up data on the cohort of patients showed an additional 3 patients had developed hepatotoxicity during maintenance therapy. Out of a total of 72 patients, DNA samples were available for 63 patients. An association of hepatotoxicity with the homozygous mutant of the MTHFR A1298C polymorphism was present in 23 patients (36.5%), absent in 38 (60.3%), and in 2 patients (3%) not evaluable due to early death.

Despite counselling against pregnancy, a total of 7 patients had normal babies with no reports of abortions, foetal abnormalities, or stillbirths. There was no evaluation of fertility. However, there were no patients who requested any evaluation for an effect of study participation on fertility.

Arsenic retention is another major concern associated with use of ATO. Urine arsenic concentrations and arsenic contents in nails and hair, which are good indicators of long-term exposure and in vivo accumulation of arsenic, were analysed in 9 patients at the last follow-up visit, when all therapy had been completed 10 to 38 months previously. Although the arsenic levels in urine, hair, and nails from patients who had ceased treatment for less than 24 months were significantly greater than those in healthy controls, no significant difference was found between patients who had ceased treatment for more than 24 months and healthy controls. The urine arsenic concentrations in patients who had ceased treatment for more than 24 months were all below the safe limit of 200ug/L set by the US Agency for Toxic Substances and Disease Registry (ARTSDR).

Evaluator's Comments: Interpretation of this long-term safety results was limited as details of methodology used to collect the follow-up data was not provided.

8.5.4. Alimoghaddam, 2006:

This was an open, uncontrolled study to evaluate the clinical efficacy and anti-angiogenesis effect of ATO in 17 newly diagnosed APL patients. Hyperleukocytosis occurred in 14 patients. The median total WBC count during induction was 4.3 x 10^9/L (range 0.2 - 168 x 10^9/L). All patients developed hepatic toxicity as assessed by the elevation of one or more of the liver enzymes above normal values. The following laboratory abnormalities were observed: mild creatinine elevation (n = 3), coagulation abnormalities[36] (n = 16), high fasting blood sugars (n = 13) and hypokalemia (n = 1).

ATO dosage was reduced in 1 patient due to severe gastrointestinal disturbance and fever and was temporarily withdrawn in 1 patient due to severe pleuritic chest pain, dyspnoea and pulmonary effusions. The mean transfusion of FFP was 29.1 units (range 0 - 85), for platelets was 38 units (range 0 - 108), and for red blood cells was 11 units (range 0 - 55). The mean time for correction of thrombocytopenia was 25 days.

Evaluator's Comments: There was a high incidence of hyperleukocytosis and hepatotoxicity in this small open-label study evaluating single agent treatment with ATO in 17 newly diagnosed patients with APL.

8.5.5. Safety results in studies involving children with APL (ATO as single agent):

Two publications (George, 2004 and Zhou, 2010) reported efficacy and safety of ATO as single agent therapy in a total of 30 newly diagnosed children (age < 15 years) with APL.

8.5.5.1. George, 2004:

In this study, hyperleukocytosis occurred during induction therapy in 6 (60%) patients at a mean interval of 9 days (range 2 - 15) after initiation of therapy. Median peak in WBC count in these 6 patients was 29 x 10^9/L (range 16.9 - 45.8). Hydroxyurea was administered with a mean duration of 12 days (range 4 - 18) with a median cumulative dose of 415 mg/kg (range 54 - 815). One patient was administered a single dose of anthracycline. ATO was temporarily discontinued in 3 patients for a mean of 3 days (range 2 - 5), but successfully restarted in all patients. DEX was not required. The median numbers of red cell and platelet units transferred during induction therapy were 3 (range 0 - 16) and 11 (range 0 - 27), respectively. Five patients (45%) developed coagulopathy during induction requiring the use of FFP over a mean duration of 4 days (range 2 - 6). No patients required transfusion during consolidation and maintenance therapy. No cardiac or hepatic toxicity was seen. Minor toxicities that resolved following cessation of therapy included ichthyosis (5 patients), hyperpigmentation of skin (5 patients) and mild reversible neuropathy (1 patient).

8.5.5.2. Zhou et al, 2010:

Leukocytosis was observed in 19 patients during induction including 13 patients with marked leucocytosis (with median WBC count of 34.7 x 10^9/L, range 21.9 - 251.7) with mean duration of leukocytosis of 16 days (range: 8 - 25 days), but only 3 patients had a dose reduction of ATO due to leukocytosis. APLDS-like respiratory distress was seen in 2 patients and both were treated successfully by controlling progressive leukocytosis with the use of hydroxyurea, temporary discontinuation of ATO, and the administration of DEX for 3 - 5 days. Other AEs of ATO during induction included: Asymptomatic QTc prolongation – 1 patient (5.3%), headache – 3 patients (15.8%), skin rash – 2 patients (10.5%), facial oedema – 1 patient (5.3%), peripheral nephropathy – 1 patient (5.3%), musculoskeletal pain – 3 patients (15.8%), hepatic toxicity – 3 patients (15.8%) and dryness of the mouth – 2 patients (10.5%). All non-hematologic toxicities were mild and resolved quickly on discontinuation of ATO. All 16 patients who proceeded with maintenance therapy developed Grade 1 neutropenia, but no febrile neutropenia occurred. Other AEs during maintenance included: Headache – 4 patients (25%), skin rash – 3 patients

[36] (platelet, fibrin degradation products or fibrinogen values)

(18.75) and peripheral neuropathy – 2 patients (12.5%). All toxicity was reversible and required no additional management.

At the final follow-up, all of the 15 patients remaining in CR were in generally good health. Neither chronic arsenic intoxication (including neurologic toxicity), nor second malignancy were observed.

In 9 patients the arsenic levels retained in urine, hair and nails from patients who had ceased treatment for less than 24 months were significantly greater than those in healthy controls. However, there was no significant difference found between patients who had ceased treatment for more than 24 months and healthy controls. The urine arsenic concentrations in patients who had ceased treatment for more than 24 months were all below the safe limit of 200 ug/L.

Evaluator's Comments: Safety results in above paediatric studies using single agent ATO showed similar adverse event profile to that observed in adults. However, number of patients and duration of follow-up was not adequate to assess long-term consequences in these patients.

8.6. Post-marketing experience

Arsenic trioxide is available in the USA since 2000, in Europe since 2002, in Australian market since 1998 and as registered medicinal product from May 2009. All patients treated with Phenasen in the clinical study were evaluated for safety during the study and at follow-up. Safety assessments were based on physical examination, vital signs (heart rate, blood pressure, respiration rate, and temperature), ECG, clinical laboratory measures and interviews for subjective complaints.

In Australia, [information redacted] (90.71 patient years) of Phenasen were sold since its initial registration (7 May 2009 to 6 May 2014). The sponsor has submitted 3 PSURs so far (Table 28). The TGA Database of Adverse Events Notifications (DAEN) was searched for Phenasen (ATO) and arsenic trioxide between 1 January 2001 and 17 April 2014 (report searched on 31 July 2014)). Only 4 reports (cases) had been reported, out of which only one report had an outcome of death, which was suspected to be related to Phenasen (including nervous system disorder and systemic mycosis). The adverse events reported in the first PSUR were: neutropenia, febrile neutropenia, diarrhoea, QTC prolongation, ventricular tachycardia, fatigue, alkaline phosphatase elevation, elevation of liver enzymes, palpitations, chest pain and peripheral oedema. In the second PSUR, the adverse events reported were: hyperleukocytosis, APLDS and renal insufficiency. In the third PSUR, one serious, unexpected (but not related) adverse event of 'stroke like episode' was received by Phebra from a physician. Three scientific literature articles were cited which reported serious adverse events of APLDS differentiation syndrome, cardiac toxicity, liver toxicity, renal toxicity intracranial haemorrhage and pulmonary fungal infection. All these adverse events, except for pulmonary fungal infection, have been observed in previous studies and are listed in the currently approved Phenasen Injection Product Information. No adverse event reports were received by Phebra during the period 7 May 2012 till 31 July 2014.

Table 28: Summary of PSURs completed and submitted for Phenasen

PSUR No.	Date of PSUR	Data Lock Point	[redacted]	Patient years represented	No. of AEs reported§
PSUR#1	5 Aug 2010	6 May 2010		14.14	12
PSUR#2	4 Jul 2011	6 May 2011		18.44	0
PSUR#3	2 Jul 2012	6 May 2012		18.93	1

§ Does not include AEs identified in the published [redacted] each in PSUR#1and PSUR#2 and 3papers in PSUR#3)

It is noted that within the PSUR#1 SAEs from the APML4 clinical study that were considered possibly or probably related to Phenasen (ATO) were reported to Phebra. Additionally, 2 of the 3 published studies included in PSUR#3 have been included as supportive studies in this submission (Ghavamzadeh et al, 2011 and Alimoghaddam, 2006).

NB: The number of vials sold has been deleted (with a black box) from this table.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Liver toxicity

Hepatotoxicity was quite common following ATO treatment of newly diagnosed patients with APL, when used in combination with ATRA as well as single agent treatment. However, most cases of hepatotoxicity were managed with supportive care, ATO dose reduction, temporarily withholding ATO treatment or a combination of these options.

8.7.2. Haematological toxicity

Hyperleukocytosis was very common and managed with hydroxyurea during most studies. In some studies hyperleukocytosis was related to poor outcomes. Low platelet counts were associated with higher risk of early death during ATO induction treatment phase. However, aggressive monitoring of haematological function and supportive treatment with platelet infusions, etc may help to reduce adverse outcomes associated with ATO-related haematological toxicity.

8.7.3. Serious skin reactions

None.

8.7.4. Cardiovascular safety

Prolongation of QTc interval was quite common following ATO treatment of newly diagnosed patients with APL- both when used in combination with ATRA as well as single agent treatment. However, this could be managed with a 12-lead electrocardiogram performed at baseline and weekly during induction and consolidation therapy as well regular monitoring and correction of electrolyte abnormalities in patients receiving ATO therapy.

8.7.5. Unwanted immunological events

None.

8.8. Other safety issues

8.8.1. Safety in special populations

8.8.1.1. Intrinsic factors:

Iland et al 2012 (APML3), which is considered the control group for the APML4 study, made the following conclusions relating to WBC and platelets at diagnosis: - The WBC count at diagnosis

was strongly associated with an increased risk of early death, with a cut-off or 2.5 x 10^9/L or above being the most discriminatory account; no early deaths occurred among the 55 patients (0%) with a WBC <2.5 x 10^9/L, whereas a 8 of the 46 patients (17%) with a WBC >2.5 x 10^9/L died within 30 days (P <0.002). However, platelet count at diagnosis, age and FLT3 mutations were not associated with early death, neither was WBC at diagnosis when a cut-off of 10 x 10^9/L was used.

In Study APML4 the relationships between early deaths and both age and baseline WCC were analysed. Early death was associated with age greater than 70 years at baseline [age ≤ 70 years: 2/117 (2%) versus age 70+ years: 2/7 (29%); OR = 21.2; 95% CI: 1.30 to 350; P = 0.02], but not with WCC greater than 10 x 10^9/L at baseline [WCC ≤ 10 x109/L: 2/101 (2%) versus WCC > 10 x 10^9/L: 2/23 (9%); OR = 4.63; 95% CI: 0.32 to 67.3; P = 0.16]. However, an analysis of WCC ≤ 2.5 10 x 10^9/L was not conducted.

The impact of WBC on early death and APLDS was examined in a few of the other clinical studies. Ravandi et al (2009) noted that the presenting WBCs did not predict the development of APLDS with similar incidence in low risk (8 of 56, 14%) and high risk patients (5 of 26, 19%) (P = 0.57). However, Mathews et al (2006) noted that APLDS occurred in patients who either had leukocytosis at diagnosis or had a leukocytic response to ATO.

Ghavamzadeh et al, 2006 found that there was no significant difference in WBC counts at disease onset between patients with and without hyperleukocytosis, and no increase in early mortality of treatment. No association between hyperleukocytosis and APLDS was observed.

8.8.1.2. Extrinsic factors:

None of the RCTs provided any data on the effects of extrinsic factors such as use of alcohol or tobacco, or in relation to food/meals.

8.8.2. Safety related to drug-drug interactions and other interactions

There was no specific evaluation of drug interactions in the clinical studies. Caution is recommended when drugs that prolong the QTc interval (for example, certain antiarrhythmics, thioridazine) or lead to electrolyte abnormalities (for example, diuretics, amphotericin B) are used in conjunction with Phenasen. Arsenic trioxide should not be used concomitantly with ziprasidone or pimozide because of potential additive effects on prolongation of the QT intervals. The above concerns are adequately covered in the Precautions and Interactions sections of the proposed Phenasen Product Information.

8.8.3. Other safety issues

8.8.3.1. Use in pregnancy and lactation:

There are no data available on exposure of Phenasen in pregnant or breast-feeding women. There are no studies available on reproductive toxicity in animals.

8.8.3.2. Overdose:

There are no data available on overdose with Phenasen, although overdose and poisoning (particularly after oral administration) is well documented for arsenic in other forms. No subject in the clinical trials was reported to experience an overdose, or symptoms of overdose.

8.8.3.3. Drug abuse:

Not applicable. Phenasen has no psychotropic potential and does not induce dependency. It is not known to have performance enhancing effects.

8.8.3.4. Withdrawal and rebound:

Not relevant. No double-blind studies have been conducted/ published which may examine AEs occurring or increasing in severity after discontinuation of the active study drug. Phenasen is given in cycles of treatment to allow recovery from known adverse drug reactions, and to

reduce the amount of arsenic deposited/retained in tissues. Therefore there is no concern as to a reversal or rebound effect when treatment is completed.

8.8.3.5. Effects on ability to drive or operate machinery or impairment of mental ability:

Phenasen has no potential to affect the central nervous system and does not induce drowsiness or sedation.

8.9. Evaluator's overall conclusions on clinical safety

The demographic data for the patients in the APML4 trial, the APML3 maintenance cohort and other published studies were generally similar and consistent with the expected target patient population of newly diagnosed APL (Table 29). For the majority of the published studies, only brief description of safety results were available; AEs were not reported or analysed in terms of the MedDRA system, organ and class and it was not possible to analyse the AEs across all studies.

Table 29: Demographic data and baseline characteristics of the groups treated with ATO in combination with ATRA.

Characteristic	Lo-Coco (n=77)	Shen (n=21)	Powell (n=244)	Dai (n=104, Groups B, A1)	APML4 (n=124)	Ravandi (n=82; All)	Lou (n=137; All)	Pei (n=73)	Gore (n=45)
Age, years median (range) Age group No.(%) 15-60 >60	44.6 (19.1-70.2)	34 (14-62)	 207 (85) 37 (15)	B: 32 (14-67) A1: 29 (16-62)	44 (3-78)	47 (14-81) 23 (28)	38.4 (13-77) 4 (2.9)	37 (14-72)	50 (19-70)
Gender No. (%) Male Female	40 (52) 37 (48)	12 (57) 9 (43)	123 (50) 121 (50)	65 (59) 45 (41)	62 (50) 62 (50)	44 (54) 38 (46)	73 (53.3) 64 (46.7)	42 (58) 31 (42)	- -
WCC, $x10^9/L$	1.5 (0.3-10.0)	-	-	-	2.4 (0.1-85.8)	2.5 (0.4-195.0)	-	2.3 (0.6-62.6)	-
Platelet $x10^9/L$	31 (3-224)	-	-	-	22 (2-173)	32 (7-261)	-	23 (5-138)	-
Risk, No. (%) Low Intermediate High	33 (43) 44 (57) 0	- - -	- - -	- - -	33 (26) 67 (54) 23 (19)	26 56	- - 45	- - -	(36) (29) (32)
FLT3 mutation No./Total No. (%)	14/65 (22)	-	-	-	52 (44)	-	-	-	-

8.9.1. Safety of ATO as combination therapy with ATRA/CT in newly diagnosed APL:

The AE profile observed in newly-diagnosed patients with APL was similar to the known AE profile of ATO in relapsed ATO and no new or unexpected AEs were identified. The common AEs (>1% incidence) reported in the RCTs is summarised in Table 30. The safety results reported in the RCTs confirmed the expected AE profile as patients receiving ATRA alone or ATRA + CT had more frequent prolonged cytopenias, mucositis and infections, while groups given ATRA + ATO

had more frequent prolonged QTc and liver function abnormalities (Lo-Coco et al, 2013, Shen et al, 2004). All studies in newly diagnosed, previously untreated patients with APL reported early deaths most often during induction treatment with lower incidence during consolidation/ maintenance phases (Table 31).

Table 30: Common AEs reported in RTCs (occurring in ≥ 1 % of patients)

Study Identifier (Author)	Adverse Events	No. of Patients (%)		
		ATO	ATO + ATRA	ATRA or ATRA+CT
Lo-Coco et al[3] 2013, module 5.3.5.1.1	§ n=68 †n=69		*(n=77)*	*(n=79)*
	Haematologic:			
	Gr 3 or 4 neutropenia and/or		35 (46)	62 (79)
	Thrombocytopenia (>15 days),		45 (59)	70 (88)
	Hyperleukocytosis		35 (47)	19 (24)
	Non-haematologic:			
	Hepatic (Grade 3 or 4)		43 (63)§	4 (6)†
	Prolonged QTC interval		12 (16)	0
Shen et al[6], 2004 , module 5.3.5.1.2		*(n=20)*	*(n=20)*	*(n=21)*
	Haematologic:			
	Hyperleukocytosis	12 (67)	14 (70)	10 (53)
	Non-haematologic:			
	Hepatic (Grade 3 or 4)	2 (10)	2 (10)	1 (5)
	Dry mouth	2 (11)	12 (60)	11 (58)
	Headache	1(6)	2 (10)	4 (21)
Powell et al[5], 2010, module 5.3.5.1.3			*(n=244)*	*(n=237)*
	Haematologic			
	Grade 3		(21)	(16)
	Grade 4		(54)	(67)
	Non-haematologic			
	Grade 3		(41)	(30)
	Grade 4		(5)	(5)
	Headache (Grade 3)		(7)	(3)
	Nausea (Grade 3)		(4)	(3)
	Electrolyte abnormalities (Grade 3)		(3)	(1)
Dai et al[4], 2009 module 5.3.5.1.4			*(n=90)*	*(n=72)*
	Haematologic:			
	Hyperleukocytosis		'common'	'common'
	Non-haematologic:			
	Hepatotoxicity: Total		56 (62)	14 (19)
	Grade 1		33(37)	8(11)
	Grade 2		15 (17)	4(6)
	Grade 3		7(8)	2(3)
	Grade 4		1(1)	0
	Dry lips		41 (46)	30 (42)
	Headache		18 (20)	13 (18)
	Skin reaction		14 (16)	10 (14)
	Fluid retention		21 (23)	5 (7)
	Differentiation Syndrome		3 (3)	2(3)

Table 31: Deaths on treatment in RCTs

Study Identifier (Author)	Early deaths during induction	Deaths during consolidation	Deaths during maintenance
Lo-Coco et al. 2013 ATRA + CT ATO	4 4 0	4 3 1	8 (at 24 months) 7 1
Shen et al. 2004 ATRA + CT ATRA + ATO ATO	4 1 1 2	N/A	2
Powell et al. 2010	-	-	38 (19 each group)
Dai et al. 2009	12 (both groups)§	-	-
ALLG APML4	4	-	3
§ 7 from group A and 6 from group B did not enter consolidation; 12 were early deaths			

8.9.2. Safety results of pivotal Study APML4:

There were 7 deaths of which 4 were early deaths during induction period. Two of the early deaths were caused by intracerebral haemorrhage, with other causes of death reported as: myocardial ischaemia, cerebral oedema, infection (2 deaths due to Klebsiella pneumonia) and progressive AML. Overall, 91 of the 124 patients commencing induction treatment (73%) experienced SAEs. Of the 91 patients, 63 (69%) experienced more than 1 SAE; 1 patient experienced 11 SAEs The most common SAEs were: reduced neutrophils/ granulocytes, febrile neutropenia, elevated liver function tests and infection (with Grade 3 or 4 neutrophils) occurring in more than 10% of patients. Elevated GGT, prolonged QTc interval and APLDS occurred in more than 5% of patients. In general, consolidation was associated with considerably less toxicity than induction, and this was especially evident for hepatic, gastrointestinal, infective, and metabolic AEs. No APLDS was observed in consolidation phase. Compared with the first cycle of consolidation, biochemical hepatotoxicity and infections were also less frequent in the second cycle when ATO and ATRA were given on an intermittent schedule (weekdays only for ATO and alternate weeks for ATRA) (Table 22). Myelotoxicity associated with ATO was also schedule dependent, because Grade 3 - 4 neutropenia occurred in 69 of 112 patients in CON1, compared with 30 of 112 patients in CON2. No Grade 3 - 4 thrombocytopenia was seen in either cycle of consolidation. QTc prolongation was less frequent during consolidation than during induction, but the differences were not statistically significant. One episode of ventricular tachycardia occurred in a single patient during the first cycle of consolidation, but this was transient and was not associated with serious outcomes. Toxicities experienced by the 4 paediatric and adolescent patients (ages 3, 15, 16, and 17 years) were comparable with those seen in adult patients. During MNT therapy AEs were more frequent and more severe during the earlier cycles of MNT. There were no cases of CNS haemorrhage, 2 cases of gastrointestinal haemorrhage and 3 cases of pulmonary haemorrhage.

SAEs reported in the clinical studies included APLDS, ECG abnormalities, hyperleukocytoisis, neutropenia and thrombocytopenia. Lo-Coco et al (2013) reported APLDS in 15 (19%) of the ATRA + ATO patients and 13 (16%) of the ATRA + CT patients. It was considered severe in 5 patients from each group, and fatal in 2 patients from the ATRA + CT group. Powell et al (2010) noted that APLDS occurred in 177 patients (37%; 177/481) during induction, while in Dai et al (2009) only 5 patients (of the 162 patients) were reported to have had APLDS (3 in the ATRA + ATO group and 2 in the ATRA group) and none of these patients died. Overall, no new or unexpected SAEs were reported in the clinical studies.

Clinical laboratory data was not reported in most of the RCTs. However, based on the known hepatotoxicity of ATO increases in LFTs were noted. In the study published by Shen et al (2004) a total of 29 patients reported liver dysfunction (Grade 1 to 4). Only four patients in the ATO group had Grade 3-4 toxicity. Following dose reduction of ATO (Grade 1) and supportive

therapy or cessation of ATO (higher grades) the liver function of 19 patients returned to normal within 1 week and the remaining 10 patients within 1 - 2 weeks. ATO was not required to be stopped completely in any of the patients in this study.

While ECG was used to monitor QT interval most of the RCTs did not report details of ECG or vital signs data. Arsenic levels were not measured in any of the combination studies.

The adverse effect profile for ATO includes some unique toxicity. ATO can cause differentiation syndrome similar to ATRA. The occurrence of differentiation syndrome is limited to the induction cycle. In the pivotal APDLS study, incidence was 14% during induction but no deaths were attributable to APDLS. Similar results were observed in the other clinical trials. Monitoring for unexplained fever, dyspnoea, weight gain, pulmonary infiltrates, pleural or pericardial effusions, and leucocytosis during induction and management of differentiation syndrome by immediate initiation of high-dose corticosteroids (for example, dexamethasone 10 mg IV twice daily), supportive care and temporary discontinuation of ATO were useful.

ATO also can cause QT interval prolongation. In the APML4 study, incidence of QT prolongation >500ms was 14% but there were no instances of torsade de pointes or other serious arrhythmias. The prescribing information recommends that a 12-lead electrocardiogram be performed at baseline and weekly during induction and consolidation therapy. Levels of potassium, magnesium and calcium should be monitored and abnormalities should be corrected in patients receiving ATO therapy.

Other potential toxicities include liver function abnormalities, peripheral neuropathy, gastrointestinal effects, rash, hyperglycemia and myelosuppression. Most toxicity can be managed with supportive care, ATO dose reduction, temporarily withholding ATO treatment or a combination of these options.

The findings from the pivotal combination therapy studies confirm the distinct side effect profiles of ATRA combined with ATO and ATRA combined with CT. The ATRA + CT combination results in more frequent prolongation of cytopenias, mucositis, and infections, whereas the ATRA + ATO combination results in more frequent prolongation of the QTc interval and liver-function abnormalities. Hepatotoxic effects appeared to be manageable with temporary discontinuation of the study medication and subsequent dose adjustments; hydroxyurea was used to counteract hyperleukocytosis.

8.9.3. Safety of ATO as monotherapy in newly diagnosed APL:

In the Ghavamzadeh studies (2006, 2011) involving up to 197 patients with newly diagnosed APL, ATO monotherapy was associated with 14% incidence of early death during induction phase and high incidence of hyperleukocytosis (58%) and hepatotoxicity (35%). In the Matthews studies (2006, 2010), APDLS occurred in only 5 (6.9%) patients which was lower than has been previously reported. The low incidence of cardiac-related toxic events in this series of newly diagnosed cases of APL could potentially be due to absence of exposure to anthracyclines or other cardiotoxic agents prior to this therapy and the attention to maintenance of electrolyte levels within the normal range. Furthermore, it is possible that transient QTc prolongations were missed due to lack of cardiac monitoring, Interpretation of this long-term safety results was limited as details of methodology used to collect the follow-up data was not provided There was a high incidence of hyperleukocytosis and hepatotoxicity in this small open-label study evaluating single agent treatment with ATO in 17 newly diagnosed patients with APL (Alimoghaddam, 2006).

Safety results in the 2 paediatric studies (George, 2004 and Zhou, 2010) in 30 paediatric patients aged 4-15 years showed that treatment with TATO monotherapy in newly diagnosed APL showed similar adverse event profile to that observed in adults. However, number of patients and duration of follow-up was not adequate to assess long-term consequences in these patients.

The patients evaluated in the six ATO monotherapy studies were not representative of target patient population. ATO monotherapy is only indicated in newly diagnosed APL in patients in whom ATRA and /or CT is contraindicated. However, these patients were not specifically evaluated and in fact all patients in the ATO monotherapy studies were much younger (median age was 28-30years in 4 of these studies and 2 studies were in paediatric patients). Overall, the evidence for safety of ATO monotherapy in treatment of newly diagnosed APL was not adequate.

8.9.4. Overall safety conclusions:

Arsenic trioxide has been available for some time now in the treatment of Relapsed and Refractory APL. The three most clinically important adverse events associated with the use of Arsenic trioxide are 'Differentiation Syndrome (APLDS)', cardiac arrhythmias associated with electrolyte imbalance and hepatotoxicity. These adverse events are all well recognized; as the patients are treated in centres familiar with these issues and can be safely managed.

Arsenic retention is another major concern associated with use of ATO. Urine arsenic concentrations and arsenic contents in nails and hair, which are good indicators of long-term exposure and in vivo accumulation of arsenic, were analysed in very few patients mainly in the paediatric single dose studies. Although the arsenic levels in urine, hair, and nails from patients who had ceased treatment for less than 24 months were significantly greater than those in healthy controls, no significant difference was found between patients who had ceased treatment for more than 24 months and healthy controls. The urine arsenic concentrations in patients who had ceased treatment for more than 24 months were all below the safe limit of 200ug/L set by the US Agency for Toxic Substances and Disease Registry (ARTSDR).

Overall, the AE profile of ATO combination therapy in newly-diagnosed patients with APL was similar to the known AE profile of ATO in relapsed ATO and no new or unexpected AEs were identified. However, evidence for safety of ATO monotherapy in newly diagnosed APL in patients in whom ATRA and /or CT is contraindicated is not adequate.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Phenasen in the proposed usage are:

- Excellent response rates when used in combination with ATRA for newly diagnosed patients with APL. Results from the pivotal Phase II open-label Study APML4 in 125 newly diagnosed APL patients demonstrate that induction and consolidation treatment with ATO with ATRA/CT results in CR of 95% at end of induction with median time to relapse of only 53 days and observed annual relapse-free rates of 97.3% at 1 and 2 years and 95.4% at 3, 4 and 5 years. Furthermore, use of ATO in the consolidation cycle enabled reduced exposure to CT as it substituted IDA (which was used in Study APML3).
- Rapid onset of CR following combination treatment with ATRA+ATO with median duration to CR ranging from 25 to 53 days in the 4 main combination studies.
- May be used instead of chemotherapy in adults with newly diagnosed APL especially in patients not likely to tolerate chemotherapy
- Some evidence of efficacy when used as single agent in newly diagnosed patients with APL although efficacy appears to more evident in patients with low/ intermediate risk.
- Risks associated with ATO such APDLS and haemorrhagic complications can be managed by aggressive monitoring and supportive treatment with corticosteroids, hydroxyurea, platelet infusions, etc.

- Limited risk of myelosuppression, although long term risks of ATO such as hepatotoxicity, prolonged QTc interval, secondary cancers, etc) cannot be ruled out.

9.2. First round assessment of risks

The risks of Phenasen in the proposed usage are:

- APL differentiation syndrome.
- hyper-leukocytosis,
- hepatic toxicity
- Prolongation of QTc interval
- Chronic arsenic toxicity
- The risk of development of secondary cancers resulting from ATO exposure is not known.
- Greater risk of APDLS and early death was associated with high risk (especially WBC >10x109/L) compared to those with low/intermediate risk.
- The studies evaluating ATO monotherapy for newly diagnosed APL did not specifically evaluate target patients, that is, those in whom ATRA and/or chemotherapy was contraindicated. In fact majority of patients in the monotherapy studies were younger (median age 28 - 30 years) and 2 studies evaluated paediatric patients aged 4 - 15 years.

9.3. First round assessment of benefit-risk balance

The standard treatment for patients with newly diagnosed APL is the combination of ATRA and chemotherapy. Chemotherapy during induction and consolidation has typically consisted of an anthracycline, specifically daunorubicin or idarubicin with or without cytarabine. Some regimens have included a maintenance phase that consists of ATRA with oral methotrexate and mercaptopurine.

Prior to the introduction of ATRA, APL was among the most fatal subtypes of AML at presentation or during induction, primarily because of an associated complex and often catastrophic bleeding disorder. However, since the advent of ATRA in the late 1980s and arsenic trioxide (ATO) in the late 1990s, progress in the treatment of APL has changed its course from a highly fatal to a highly curable disease. Despite the dramatic improvement in the treatment outcome of APL, treatment failure still occurs due most often to early death. Relapse has become increasingly less frequent, most commonly occurring in patients with high-risk disease. A major focus of research for the past decade has been to develop a risk-adapted treatment strategy to reduce treatment-related morbidity and mortality in low- and intermediate- risk or older patients while targeting more intensive or alternative therapy to those patients at most risk of relapse.

Early detection of relapse is now possible by monitoring of the molecular marker of the disease, the PML-RARα fusion transcripts. Minimizing the toxicities of cytotoxic chemotherapy may further improve the outcome in APL, particularly for older adult patients, who account for 15% to 20% of patients with APL. In general, the CR rate for patients older than 60 years is significantly lower than that of younger patients. This is typically due to a higher incidence of early death owing to infection and bleeding. The outcome for this population can be improved by taking advantage of high sensitivity of the disease to anthracyclines and omitting cytarabine.

One Phase II study (APML4) and other controlled and uncontrolled studies (publications only) were submitted to support use of ATO in combination with ATRA and CT in newly diagnosed previously untreated APL. All efficacy and safety assessments were considered standard, widely used and generally recognised as reliable, accurate and relevant.

The APML4 trial from the Australasian Leukaemia and Lymphoma Group evaluated the combination of ATO, ATRA and idarubicin for induction therapy in 124 patients with newly diagnosed, previously untreated APL. Consolidation consisted of two cycles of ATRA and ATO alone, and maintenance consisted of 2 years of ATRA, methotrexate and mercaptopurine. The simultaneous administration of ATRA and anthracycline-based chemotherapy is currently considered the standard induction treatment in newly diagnosed patients with APL. With regards to the choice of anthracyclines, no prospective randomized trials have compared daunorubicin and idarubicin in APL. IDA was used in studies APML4 and Lo Coco, 2013, but DA was used in studies published by Dai (2009), Shen (2004) and Powell (2010).

In the APML4 study, the complete remission rate was 95%, DFS at 2 years was 97.5% and therapy was generally well tolerated. Additionally, the patients' exposure to an anthracycline was reduced while maintaining the positive outcomes expected in this population. The study by Lo-Coco et al, (2013) shows that a combination of ATRA and ATO given for induction and consolidation therapy is at least not inferior and is possibly superior to standard ATRA and anthracycline based CT for adults with newly diagnosed, low-to-intermediate-risk APL. The observed advantage in the 2-year event-free survival (which was primary efficacy endpoint) with ATRA + ATO compared to ATRA +CT (97% versus 86%) appears to be due mainly to lower mortality from causes other than relapse, probably as a consequence of reduced severe hematologic toxicity together with similar antileukemic efficacy. The study reported CR in all (100%) ATRA+ATO patients after a median 32 days of induction. Dai et al (2009) reported high rates of RFS, with combination treatment, while patients receiving ATRA alone had significantly higher relapse rates and lower RFS. The estimated OS of 85% reported by Ravandi et al (2009; with a median 99 weeks follow up) is in line with the results from other studies.

The study reported by Powell et al (2010) involving 481 patients with newly diagnosed APL shows that addition of As_2O_3 to consolidation therapy to regimens using ATRA and anthracycline based CT improves EFS with similar results reported by Gore (2010). Overall, there was adequate evidence to support use of ATO in combination with ATRA and/ or CT in newly diagnosed, previously untreated patients with APL.

The proposed dosing regimen for ATO as combination therapy for newly diagnosed APL was used in the 3 pivotal studies discussed in section 7.1.1 (APML4 study. Lo Coco, 2013 and Dai, 2009). Results from the large study involving 481 newly diagnosed patients with APL (Powell, 2010) demonstrated that As_2O_3 given as initial consolidation therapy is safe and improves event-free, disease-free, and overall survival for newly diagnosed patients with APL. Similar results were observed in Gore et al 2010. However, both studies did not use As_2O_3 for remission induction

As a single agent, ATO can induce CR in 85 - 86% of patients with untreated newly diagnosed APL, comparable with that achieved by ATRA-based therapy [Ghavamzadeh et al. 2006; Mathews et al. 2006]. The most benefit from ATO monotherapy during induction and consolidation is observed in patients with the WBC counts of < 5000/µl and platelet counts > 20,000/µl at diagnosis with an event-free survival (EFS) of 100% at 3 years. However, the outcome of patients with WBC >5000/µl at diagnosis appears to be inferior to a similar subset treated with ATRA plus chemotherapy, with an EFS of only 67% and a higher early death rate of 14.4% mostly from haemorrhagic complications [Mathews et al.2006]. Therefore, therapy with single-agent ATO does not appear sufficient for many patients as a frontline therapy. Furthermore, due to risk of early mortality during remission induction phase with ATO treatment, it is important to determine the subgroups of patients likely to benefit from ATO monotherapy. The sponsors proposed that ATO be used as single agent therapy in newly diagnosed APL in patients in whom ATRA and/or chemotherapy is contraindicated. However, the patients evaluated in the six monotherapy studies did not represent this target patient population (2 of 6 studies included only paediatric patients aged 4-15 years and median age of patients in other studies was only 28 - 30 years). Patients with contraindications to ATRA and/

or chemotherapy are more likely to be elderly patients with comorbidities, but these patients were not evaluated in any of the submitted single agent ATO studies.

The AE profile observed in newly-diagnosed patients with APL was similar to the known AE profile of ATO in relapsed ATO; that is, no new or unexpected AEs were identified. The common AEs (> 1% incidence) reported in the RCTs is summarised in Table 30. The safety results reported in the RCTs confirmed the expected AE profile as patients receiving ATRA alone or ATRA + CT had more frequent prolonged cytopenias, mucositis and infections, while groups given ATRA + ATO had more frequent prolonged QTc and liver function abnormalities (Lo-Coco et al, 2013, Shen et al, 2004). The majority of AEs were managed with reduction of the dose of ATO, discontinuation of treatment, or through supportive care. Arsenic levels in urine, hair and nails were only measured in the paediatric studies and did now show significant accumulation although long-term follow-up was not available.

Due to overall effectiveness of ATO and its ability to minimize administration of chemotherapy, ATO has a potential role in the treatment of newly diagnosed, previously untreated APL. However, ATO administration has its own administration and toxicity issues that must be considered (hepatotoxicity, prolonged QTc interval, APDLS, etc) although many of these can be managed with aggressive monitoring and supportive treatment or ATO dose reduction or temporary withdrawal.

The benefit-risk balance of Phenasen is unfavourable given the proposed usage, but would become favourable if the changes recommended are adopted.

10. First round recommendation regarding authorisation

It is recommended that the submission be rejected for the proposed extended indication for Phenasen: 'For the induction of remission and consolidation in patients with previously untreated Acute promyelocytic leukaemia (APL) in combination with all-trans retinoic acid (ATRA) and chemotherapy unless ATRA and/or chemotherapy is contraindicated.'

Approval for a modified indication for use as combination therapy in previously untreated patients with APL may be granted subject to incorporation of changes suggested in section 10 and adequate response to questions in section 11.

However, the evidence to support efficacy/ safety of Phenasen as single agent in newly diagnosed, previously untreated patients with contraindications to ATRA and/ or chemotherapy is not adequate.

11. Clinical questions

11.1. Pharmacokinetics

None.

11.2. Pharmacodynamics

None.

11.3. Efficacy

11.3.1. Question 1:

'For the induction of remission and consolidation in patients with previously untreated Acute promyelocytic leukaemia (APL) in combination with all-trans retinoic acid (ATRA) and chemotherapy unless ATRA and/or chemotherapy is contraindicated.'

Evaluator's Comments: The sponsors have not specified that arsenic trioxide be used as single agent in the wording of the indication although it is implied as suggested by the proposed PI 'Dosing and administration' section. It has not been specified if ATO could still be used with either ATRA or chemotherapy depending on which treatment was contraindicated. Could the sponsors please provide clarification on this issue.

11.3.2. Question 2:

The proposed indication also implies that single agent treatment with ATO is to be used in patients with previously untreated APL if ATRA and/ or chemotherapy is contraindicated. However, the published studies submitted to support this did not specifically evaluate this patient population. Two of the 6 ATO monotherapy studies were conducted in paediatric patients aged 4-15 years and the median age in the other studies was 28-30 years with very few patients over 50 year. Patients with contraindications to ATRA and chemotherapy are more likely to be elderly patients with comorbidities, but these patients were not evaluated in any of the submitted single agent ATO studies. Furthermore, it appears that patients at low/ intermediate risk showed better results compared to those with high risk and this was shown in both Ghavmazadeh 2011 and Matthews, 2006 reports. Due to risk of early mortality during remission induction phase with ATO treatment, it is important to determine the subgroups of patients likely to benefit from ATO monotherapy. Could the sponsors justify use of ATO as single agent in patients with newly diagnosed APL with contraindications to ATRA and/or chemotherapy.

11.3.3. Question 3:

In module 2 (Clinical summary of efficacy), page 14 of 92) states the following:-

Induction Regimen. During induction Group 1 received ATRA 25 mg/m^2/day orally, Group 2 received ATO 0.16 mg/kg/day iv and Group 3 received both ATRA 25 mg/m^2/day orally and ATO 1.16 mg/kg/day iv concurrently.

Evaluator's Comments: There seems to be a typo as the last line should read Group 3 received both ATRA 25 mg/m^2/day orally and ATO 0.16 mg/kg/day IV concurrently.

11.3.4. Question 4:

The Table 2.7.3.-49 from the clinical summary in Module 2 [not in this AusPAR] had errors in reporting results of the Lou et al, 2013 study. The results observed in the high risk and low/ intermediate risk groups have been misrepresented. Could the sponsors provide clarification on this.

11.4. Safety

Nil.

12. Second round evaluation of clinical data submitted in response to questions

Not applicable.

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Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au