CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-248

MEDICAL REVIEW/STATISTICAL REVIEW

Medical Officer and Biometrics Review
Division of Oncology Drug Products

NDA # 21248
Medical Officer: Steven Hirschfeld, MD PhD
Medical Officer: Amna Ibrahim, MD
Drug name: Arsenic Trioxide
Generic name: Arsenic Trioxide
Proposed trade name: Trisenox
Chemical name: Arsenic Trioxide

Submission: 3/28/00

Review completed: 9/13/00

Sponsor: Cell Therapeutics
Pharmacologic Category:
Proposed Indication(s): Second line therapy for acute promyelocytic leukemia
Dosage Form(s) and Route(s) of Administration: intravenous preparation
NDA Drug Classification: 1 S
Related Drugs: none
Related Reviews: Statistical Review dated:
Biopharmaceutics dated:
Pharmacology/Toxicology dated:
Chemistry review dated:
Division of Scientific Investigations review dated:

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1. Abstract and Summary

This as a clinical review of NDA submission 21248, Trisenox (arsenic trioxide), which is being proposed for second line therapy for patients with acute promyelocytic leukemia. The review is divided into several sections that describe the data sources, provide background material, describe and analyze the data submitted, summarize the findings, and make a regulatory recommendation. The purpose of this review is to provide a basis for a regulatory decision by the FDA

NDA 21248 describes studies that used infusions of arsenic trioxide to treat patients with refractory or relapsed acute promyelocytic leukemia (APL). There was one single arm multicenter study for 40 patients with relapsed or refractory acute promyelocytic leukemia, a Phase I study using doses ranging from 0.06 mg/kg to 0.2 mg/kg that enrolled 12 patients with relapsed or refractory acute promyelocytic leukemia of which 2 received the recommended dose of arsenic trioxide of 0.15 mg/kg, and additional safety data on 47 patients who had a variety of malignancies. The outcome of the 40 patients in the Phase 2 study with relapsed or refractory APL was that using intent to treat analysis and protocol defined criteria, 28 achieved complete remission following an induction course of arsenic trioxide. Of the 28 patients, 25 received a consolidation course of arsenic trioxide. The remissions had a range of 45 to 412 days prior to receiving subsequent therapy of either additional arsenic trioxide (16 patients) or bone marrow transplant (10 patients). An additional 6 patients were considered possible responders, but the response was inadequately documented based on protocol criteria.

An historical control cohort of 27 patients at a single institution treated with oral all trans retinoic acid (ATRA), an approved therapy for relapsed APL, had a response rate of 22 % .

The majority of patients experienced adverse events consistent with administration of oral ATRA. The most common adverse events experienced by more than 40% of patients were headache, nausea and emesis, fever, hemorrhage, pain, diarrhea, dry skin, hypomagnesemia, stomatis, asthenia, and hypokalemia. The most common severe (Grade 3 or 4) adverse events were fever, hemorrhage, hyperglycemia, headache, ATRA syndrome , and sepsis. ATRA syndrome was described in 9 patients (23%) with one patient having two episodes. Severe ATRA syndrome was described in 3 patients (8 %), with none of the patients subsequently discontinuing arsenic trioxide. A total of 2 patients discontinued arsenic trioxide and 3 patients died within 30 days of their last dose.. Arsenic trioxide, consistent with published reports on the cardiac effects of arsenic, caused prolongation of the QT corrected interval greater than 500 msec in 28 % of the 99 patients included in the safety database. One patient had an asymptomatic dysrhythmia that was temporally related to the administration of Amphotericin B. Amphotericin B is known to cause electrolyte abnormalities, which may have been a contributing factor. There were no deaths attributable to cardiac events.

Based on the data submitted, infusional arsenic trioxide, with appropriate monitoring, appears to be safe and effective for the therapy of relapsed or refractory APL.

2. Material Reviewed

Sponsor submitted materials: NDA Volumes 1 through 12
Sponsor submitted review aids consisting of data tables as SAS transport files converted by the FDA to Microsoft Access tables
Literature search on background materials in CancerLit and Medline databases under the following search terms:
Acute promyelocytic leukemia, acute myelocytic leukemia, acute promyelocytic leukemia + therapy, acute myelocytic leukemia + therapy, arsenic trioxide + therapy + human, arsenic+ therapy + human

3. Chemistry/Manufacturing Controls

Arsenic (As) is an intermediate element between metals and non-metals, with an atomic number of 33 and a molecular weight of 74.9 daltons. Arsenic ranks 20th in abundance of elements in the earth's crust. It is primarily found in rocks complexed with iron, sulfur, or oxygen as arsenopyrite (FeAsS), realgar (As_2S_2), orpiment (As_2S_3), or arsenic trioxide (As_2O_3). Elemental arsenic can exist in either a trivalent or pentavalent form, and sublimes from solid to gas at 613 degrees Centigrade (C). Arsenic trioxide (mol. wt. ~ 198 daltons), which is the primary form of arsenic from natural weathering as well as the major arsenic byproduct of metal smelting, is the chemical basis for most industrial uses of arsenic. The trioxide can exist in three forms, distinguished by the relative arrangement of the oxygen and arsenic atoms and thus the subsequent three-dimensional structure. All forms of arsenic trioxide begin to sublime at 135 C, melt at about 300 C and boil at about 460 C. Arsenic trioxide is slightly soluble in water with a solubility of 1.2 g per 100 g of water at 25 degrees C (about 60 mM) and 5.6 g (about 280 mM) at 75 degrees C.

For further details of the manufacture and chemistry, see the associated FDA chemistry review of arsenic trioxide.

4. Pharmacology/Toxicology

No formal animal studies were submitted with the application. A review of the published literature is provided in detail in the associated FDA pharmacology/toxicology review. In brief, there are data to raise concern that arsenic trioxide may cause fetal harm when administered to a pregnant woman. Studies in pregnant mice, rats, hamsters, and primates have shown that inorganic arsenicals cross the placental barrier when given orally or by injection. The reproductive toxicity of arsenic trioxide has been studied but primarily within a narrow scope of organogenesis. . An increase in resorptions, neural-tube defects, anophthalmia and microphthalmia, were observed in rats administered 10 mg/kg of arsenic trioxide on gestation day 9 (approximately 10 times the recommended human daily dose on a mg/m^2 basis). Similar findings occurred in mice administered a 10 mg/kg dose of a related trivalent arsenic, sodium arsenite, on gestation days 6, 7, 8 or 9 (approximately 5 times the projected human dose on a mg/m^2 basis). Intravenous injection of 2 mg/kg sodium arsenite on gestation day 7 (the lowest dose tested) resulted

in neural-tube defects in hamsters (approximately equivalent to the projected human daily dose on a mg/m^2 basis).

Carcinogenicity or impairment of fertility studies have not been conducted with arsenic tiroxide by intravenous administration. Arsenic trioxide, has been classified by the U.S. Environmental Protection Agency (EPA) as having "sufficient" human evidence for potential carcinogenicity. Arsenic trioxide and trivalent arsenite salts have not been clearly demonstrated to be mutagenic to bacteria, yeast or mammalian cells. Arsenite salts are clastogenic *in vitro* (human fibroblasts, human lymphocytes, Chinese hamster ovary cells, Chinese hamster V79 lung cells). Trivalent arsenic produced a small increase in the incidence of chromosome aberrations and micronuclei inbone marrow cells of mice.

There is much information about human toxicity of arsenic, which is further addressed in Section 6.1 of this review. For further details on the pharmacology and toxicology, see the associated FDA pharmacology/toxicology review.

4. Human pharmacology, pharmacokinetics and pharmacodynamics

There were multiple questions raised by the FDA review about the assay methods used to [redacted] The half-life appeared to be about 4 days; however, critical details on the metabolites, molecular species, and disposition in different populations were incomplete. Further studies, as outlined in the FDA biopharmaceutics review, will be requested of the sponsor as a Phase 4 commitment. For further details, see the biopharmaceutics review.

5. Financial Disclosure

The Financial Disclosure Rule states that for NDAs or sNDAs submitted on or after February 2, 1999, the applicant must disclose whether the following financial arrangements were made with the investigators:

- Compensation affected by the outcome of the clinical studies
- Significant equity interest in the sponsor of a covered study (exceeds $50,000 during the time the investigator conducts the study and for 1 year following completion)
- Proprietary interest in the tested product (patent, trademark, copyright, licensing agreement)
- Significant payments of other sorts (payments to the investigator or the institution of > $25,000, exclusive of study costs during the time the investigator conducts the study and for 1 year following completion)

If these arrangements have been made, the applicant must disclose the arrangements and state what has been done to minimize the potential for bias.

The Final Rule, published 12/31/98, states that for studies completed prior to 2/2/99, applicants are not required to collect information on significant equity interests and must submit information on significant payments of other sorts only if the payments were made on or after 2/2/99.

Requirements for Financial Disclosure were discussed with the applicant during the pre-NDA meeting on 1/6/00. The study was completed in July 1999, and therefore was subject to the financial disclosure requirements.

Disclosures

Form 3454 was submitted with the application.

- Compensation affected by the outcome of the clinical studies

  None stated or apparent

- Proprietary interest in the tested product (patent, trademark, copyright, licensing agreement)

  A at the major study site, has an equity interest in the company, received consultation fees, will receive royalties and has a patent on the preparation of arsenic trioxide.

- The study was completed in July 1999.

Reviewer's assessment

- Analysis and publication of the study results and submission of an application are based on the completion date of July 1999. Although follow-up continues, patient accrual is complete and the majority of events have occurred.
- The endpoints for the study were bone marrow morphology and hematologic counts. These are objective measures that are read by technicians in laboratories and hematopathologists according to standard procedures. They are not readily amenable to manipulation or interpretation. The reviewer does not believe that the financial interests of could have affected the outcome, although should have been recused from participating in the study. There are no patients listed in the study roster that are attributable to therefore it is not likely that financial interests affected study outcome.
- Technically, a clinical investigator is defined as the spouse or offspring of an investigator as well as the investigator him/herself. The applicant did not include spouses and offspring in the submitted list. The reviewer believes it is unlikely that these individuals had significant proprietary interests that could alter the outcome of the submitted studies.
- The submitted information seems to be adequate and the reviewer believes it to be in compliance with financial disclosure requirements.

6. Clinical Background

6.1. Relevant human experience with arsenic

Documented human experience with arsenic dates from the beginnings of recorded history. In ancient Greece and Rome, arsenic was used as a chemical reagent, as therapeutic agent and poison. Hippocrates, for example, recommended it as a treatment

for ulcers while the Roman emperor Caligula was reported to be interested in producing gold from arsenic sulfide.

Historically arsenic compounds have been used in the manufacture of glass to improve clarity, as a hardening agent for lead, and as a yellow pigment in paints and fireworks. More recently arsenic has been a major constituent of the poisonous gases used in military campaigns during World War I (lewisite and adamsite), as a component of some insecticides, as a wood preservative, for a time as a component of flame retardant, and most recently in the manufacture of semiconductors. The starting compound for most industrial uses is arsenic trioxide, which is easily volatilized during the purification of many heavy metals and then recovered and further purified. Arsenic compounds are often found as impurities in coal, and must be reduced according to the United States Clean Air Act

Arsenic is toxic to plants and animals. Arsenic poisoning has been well described in literature, most notably in Flaubert's *Madame Bovary* (which led to a public trial for the author due to the level of detail in the book), and has been associated with the deaths of historical figures such as Napoleon Bonaparte, Brigham Young and Karen Blixen as well as being a favored weapon of family serial killers in the United States. In the 20th century arsenic poisoning was treated lightly in Joseph Kesserling's play *Arsenic and Old Lace* which became a film directed by Frank Capra and starring Cary Grant, yet arsenic remains a major health threat, primarily via contaminated drinking water, to millions of people. There are people in Styria (part of Austria) who were reported in the 19th century to have incorporated arsenic as part of their dietary regimen and thus built up tolerance for quantities that would otherwise be fatal when taken orally. The bodies of these "arsenic eaters" were reported to be well preserved after death, leading to legends of their ability to return to life at night.

Acute arsenic toxicity can cause

- gastrointestinal symptoms of severe abdominal pain, vomiting, diarrhea and hemorrhagic gastroenteritis due to transmural inflammation of the mucosa which can be accompanied by hepatic necrosis
- capillary leak, pulmonary edema, hypotension, and shock due to vascular endothelial injury which in turn can lead to renal failure and adult respiratory distress syndrome
- progressive neuropathy similar to Guillain-Barré syndrome

all of which can be fatal.

Chronic arsenic toxicity often results in changes in the skin and adnexa. There is deposition in the dermis which may be diffuse or may have a flecked appearance due to multiple non-pigmented areas interspersed among areas that are grayish brown. Other cutaneous manifestations include keratoses of the palms and soles and lines in the nail beds known as Mee's stripes. Arsenic can be chemically identified in the collagen of hair and nail clippings. Less common is gangrene of the legs and feet, known as blackfoot disease, which is a result of chronic vasospasm.

There are several published reports of cardiac dysrhythmias including torsade de pointes, ventricular tachycardia, ventricular fibrillation and sudden death associated with acute arsenic poisoning. In addition, arsenic has been described to cause myocarditis.

The German chemist Robert Wilhelm Bunsen discovered in 1834 the first known antidote for arsenic poisoning, hydrated iron oxide. Current antidotes are directed at chelation using

- dimercaprol (British anti-Lewisite or BAL) which is given 3 to 4 mg/kg IM q8h until symptom resolution or, for severe exposures, the dose may be increased to 6 to 7 mg/kg IM q8h on the first day followed by
- D-penicillamine given orally or
- Meso-2,3 dimercaptosuccinic acid (DMSA) given intravenously or orally or
- 2,3-dimercaptopropanesulphonate sodium (DMPS) given intravenously or orally

The latter two chelators have a broader therapeutic index and are more water soluble than BAL; therefore, both are available in formulations for oral dosing, but are considered less effective for short term therapy, thus BAL is still considered the therapy of choice for acute intoxication that is life threatening. There are no randomized comparative studies on therapy for acute arsenic toxicity, but there are case reports of successful recovery from acute ingestion using DMPS or DMSA without BAL.

Since the 1820s, arsenic has been recognized as a potential environmental co-carcinogen for some human malignancies, especially for skin and lung cancers. Nevertheless, for much of the nineteenth century arsenic, chiefly in the form of solution of potassium arsenite (Fowler's solution), was a standard remedy for many diseases. According to an 1887 report of the Pathological Society of London, hyperpigmentation keratoses, ulcerating lesions on the palms and soles, and epithelial malignancies were described in patients with extensive arsenic exposure for the treatment of psoriasis. Several case reports in the medical literature describe fatal dermatologic malignancies associated with chronic arsenic exposure. A mortality analysis on a cohort of patients given Fowler's solution (potassium arsenite) for periods ranging from 2 weeks to 12 years between 1945 and 1969 described an apparent excess of skin cancer but there was no overall excess mortality from other cancers. These data suggest that there may be a susceptible subgroup of patients at risk for malignancies that can be identified from dermatological manifestations.

Arsenic preparations were recognized for their potential beneficial effects throughout the history of therapeutics. Medical texts of the 17th century formally incorporated arsenic based preparations, and in 19th century America, several arsenic compounds were registered in the pharmacopoeia. In 1909 Paul Ehrlich developed the arsenic based preparation salvarsan (sometimes known as the "Magic Bullet" or compound 606), which had relatively selective anti spirochete effects. Arsenic based preparations have also been generally well tolerated in the treatment of congenital syphilis, although granulocytic aplasia and dermatitis have been reported. The discovery of penicillin led to the replacement of arsenic or other heavy metal therapy for syphillis.

Organic arsenic preparations such as melarsoprol are still in use for the treatment of African trypanosomiasis involving the central nervous system and other protozoal infections.

Arsenic has been also used to treat hematologic disease due to its affect on increasing hemoglobin in some forms of anemia and to decrease the white blood cell count in some types of leukemia. A 1931 publication in the Journal of the American Medical Association, reported 9 of 10 of patients with chronic myelogenous leukemia (CML) treated with potassium arsenite solution to have temporary normalization of white cell count, an increase in red cell count and resolution of hepatosplenomegaly.

In traditional Chinese Medicine arsenic-compounds have been used with the principal of using one toxin to treat another. Applications included diseases such as psoriasis,

syphilis, rheumatological conditions, root canal disease, and asthma. Preparations are typically an inorganic arsenic salt such as the sulphide or the trioxide combined with other ingredients including herbs to form a paste or solution. Some preparations have been analyzed and found to contain concentrations of arsenic ranging from 25 to 107,000 ppm or approximately 1.25 mg/L to 5 g/L. The United States Environmental Protection Agency (EPA) considers exposure greater than 50 micrograms/L in drinking water or about 1 ppm as cause for concern. For acute ingestions the EPA threshold for systemic toxic effects is about 50 micrograms/kg/day or about 3.5 milligrams for a 70 kg adult. The risks inherent in the variability of arsenic content in the Chinese preparations is illustrated by a report on arsenic poisoning in 74 patients in Singapore who took an anti-asthmatic preparation imported from China. Most victims (70%) had evidence of toxicity in skin (91%), the nervous system (51%), the gastrointestinal system (23%) or blood (23%). Nearly 40% of the patients had taken the preparation for less than six months, but the others had a longer history of exposure ranging from one to 15 years. Six patients (8%) developed a skin malignancy.

In early 1970s, some Chinese physicians with an interest in the integration of traditional Chinese medicine with western practice were studying cancer treatments. An analysis of several traditional preparations showed that arsenic compounds were a common component. Purification of the active ingredient yielded arsenic trioxide, which was then systematically tested in a variety of cancers. The most striking results were obtained in the treatment of relapsed acute promyelocytic leukemia (APL) with a remission rate reported to be 90%. The use of arsenic trioxide for the treatment of relapsed acute promyelocytic leukemia has been replicated in several published reports in North America and Europe.

6.2. Current Therapy for acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) is one of the acute myeloid leukemias classified by the French American British nomenclature. The classification is based upon morphological criteria of the abnormal cells and their granularity. APL is designated M3 and M3v for variant. Genotypically the cells have a characteristic translocation at t15:17 or, less commonly, t11:17 and clinically the disease often presents with disseminated intravascular coagulation (DIC). Two fusion proteins that function as oncogenes have been described in the disease. One is the ProMyelocytic Leukemia protein (PML) and Retinoic Acid Receptor (RAR) alpha fusion (t15:17) and the other is the Promyelocytic Leukemia Zinc Finger protein (PLZF) and RAR alpha fusion (t11:17). They both bind nuclear co-repressors and recruit histone deacetylase activity to promoters of retinoic acid target genes, but the PML-RAR fusion is sensitive to retinoids while the PLZF-RAR is relatively resistant. The biological effect of either fusion protein is to block differentiation of the myelocytes at the promyelocyte stage.

There are estimated to be 1200 to 1500 new cases in the United States annually. Therapy is directed at achieving remission (induction) and then sustaining the remission (consolidation). Current practice is to use cytotoxic chemotherapy, typically cytarabine plus an anthracycline plus oral all trans-retinoic acid (ATRA) to achieve remission and then furtner courses of chemotherapy for consolidation.

Effective chemotherapy based induction regimens include the following:

dose-intensive cytarabine-based induction therapy.
cytarabine + daunorubicin.
cytarabine + idarubicin
cytarabine + daunorubicin + thioguanine
mitoxantrone + etoposide

An additional maintenance phase of oral ATRA or chemotherapy or both has been reported to improve long term outcomes. Reported remission rates depend upon several prognostic factors that include age, initial white count, and platelet count. Another major factor that impacts on outcome is the dose intensity of the anthracycline. In APL patients given oral ATRA as monotherapy, remission rates are reported to be 70->90% for newly diagnosed patients and relapsed patients who are either ATRA naïve or have not received ATRA for 6 to 12 months.

Table 1 Reported Response Rates for oral ATRA in Patients with Relapsed APL who are ATRA naive

Number of Patients	Response Rate	Reference
6	100 %	Liang et al., *Anticancer Drugs* (1993)
14	71%	Castaigne et al, *Blood* (1993)
22	82%	Ohno et al, *Leukemia* (1994)
17	82%	Cortes et al, *Cancer* (1994)
30	83%	Warrell et al, *Leukemia* (1994)
15	100%	Meloni et al, *Blood* (1997)
8	87%	Castagnola et al. *Haematologica* (1998)

The mechanism of action of ATRA is to differentiate the abnormal myelocytes. This process can result in a sudden increase in the total white cell number and a release of the granular contents that in turn would increase the concentration of mediators of inflammation. The clinical manifestations of the increase in mediators of inflammation are fever, edema, pulmonary infiltrates, pleural effusions, pericardial effusions, hypotension, and renal failure. A combination of any three of these symptoms is termed ATRA syndrome, and is a known complication of therapy with ATRA. A large series described by De Botton et al. of 413 newly diagnosed APL patients treated with ATRA and cytotoxic chemotherapy found an incidence of 64 patients or 15%. Fifty-five or 86% of these patients achieved complete remission, 13 (20%) required intubation, and 2 (3%) required dialysis. Kaplan-Meier estimates at 2 years of relapse rate were higher (32 $\pm$ 10% vs. 15 $\pm$ 3%) and overall survival (68 $\pm$ 7% vs. 80 $\pm$ 2%) were lower for patients who experienced ATRA syndrome than those who did not.

Daily administration of ATRA results in decreasing plasma concentrations over time due to an inducible increase in catabolism of the drug and the upregulation of retinoic acid binding proteins. This results in a relative resistance. Retinoid resistance is presumed to occur through the recruitment of histone deactylase by the fusion proteins, with the PLZF protein being more effective than the PML protein. The presumed effect of the histone deacetylase is an alteration in the gene expression pattern resulting in the observed changes in metabolism and binding protein profile. The clinical consequence is that ATRA is not sustained at effective concentrations and therefore does not result in a durable remission

unless used in conjunction with other drugs. A further consequence is that retreatment with ATRA may be less effective than initial treatment.

About 20 to 30% of patients either do not acnieve remission or relapse from combination ATRA and cytotoxic chemotherapy. Current practice is to retreat using ATRA with or without chemotherapy. Remission rates are variable, and are presumed to be dependent upon time from the last previous dose of ATRA with a longer time being more favorable. The evidence to support this impression has not been tested in randomized controlled studies, but nevertheless the effect is generally accepted. The focus of most research in APL is to identify effective treatments for the minority of patients who relapse or are refractory to current first line therapy.

6.3. Information from related INDs and NDAs

[redacted] one NDA that have been filed with the FDA for arsenic trioxide. [redacted]

Table 2 Applications for arsenic trioxide submitted to the FDA

Application Number	Sponsor	Date Submitted
[redacted]		
N021248	Cell Therapeutics	3/28/00

There are currently 8 approved therapies that are labeled either for acute promyelocytic leukemia specifically (tretinoin and mitoxantrone) or for various types of acute myelogenous leukemia that include acute promyelocytic leukemia. Six of the 8 are available as intravenous infusions. The currently approved therapies are summarized in the following table:

Table 3 Approved Therapies for Acute Promyelocytic Leukemia (APL) or Acute Myelogenous Leukemia (AML)

NDA Number	Trade Name	Generic Name	Dosage Form	Indication	Sponsor	Approval Date
016793	Cytosar	Cytarabine	Injection	AML	Pharmacia & Upjohn	4/17/69
050467	Adriamycin	Doxorubicin	Injection	AML	Pharmacia & Upjohn	8/7/74
012141, 012142	Cytoxan	Cyclophosphamide	Injection, Oral	AML	Bristol Myers Squibb	11/16/59
019297	Novantrone	Mitoxantrone	Injection	1st line AML	Immunex	12/23/87
050661	Idamycin Inj.	Idarubicin	Injection	AML	Pharmacia & Upjohn	9/27/90
020438	Vesanoid	Tretinoin (ATRA)	Oral	2nd line APL	Roche	11/22/95
050731	Cerubidine	Daunorubicin	Injection	AML	Wyeth Ayerst	12/19/79
012429	Thioguanine	6-thiogauanine	Oral	AML	Glaxo Wellcome	1/18/66

6.4. Foreign experience

Arsenic trioxide is not approved in any country for any indication, although it is used in China.

6.5. Regulatory History

The initial[ ]was filed by PolarRx Pharmaceuticals on 2/19/98 and became effective on 3/19/98. The End of Phase 2 meeting occurred on April 14, 1998.

MEETING OBJECTIVES:

1. PolaRx Biopharmaceuticals, Inc. would like to obtain concurrence from the Division that the proposed plan is adequate to support a New Drug Application (NDA) filing.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. PolaRx Biopharmaceuticals, Inc. proposes to conduct one pivotal phase 3 clinical study (Study No. PLRXAS01) to demonstrate the safety and efficacy of arsenic trioxide for the treatment of acute promyelocytic leukemia (APL).

   Does the FDA agree?

   FDA Response:

   - Given a suitable definition of poor prognosis patients* and a high enough CR rate, an uncontrolled study would be adequate. (* prior chemotherapy and ATRA in the past 12 months)
   - We would prefer a data base of at least 50-100 patients. We would consider an NDA data base of 35 APL patients and the remaining non-APL patients if the results are adequate.
   - If the data are equivocal and the data base is small, this will not be sufficient.

- Other therapy given after induction of remission with arsenic will confound analysis of duration of remission.
- For patients with better prognosis, we recommend a randomized trial. Alternatively, the study could be redesigned to be a randomized controlled study comparing standard relapse or refractory therapy, e.g. reinduction with all trans retinoic acid plus cytarabine as an active control versus arsenic trioxide. For statistical analyses, use a two-sided test.

PolaRx Response: PolaRx is not planning a randomized trial.

- Patients should be followed until death for any long term toxicity effects. Subsequent therapy should be reported.
- The criteria for serious toxicity should be explicitly defined. Amend the criteria for non-hematologic toxicity of grade 4 to grade 3 for neurotoxicity, cardiac toxicity, weight loss, and allergy.

PolaRx Response: PolaRx will evaluate and respond.

- Clarify whether the Common Toxicity Criteria version 2 will be used.

PolaRx: No, the old version will be used.

- Clarify the plan for patients who fail to attain remission.

PolaRx: No plans to retreat with arsenic trioxide.

- Clarify on what day remission will be determined, i.e. will it be the last day that all the criteria are met?

PolaRx: Yes. The definition of CR will include the 30 day duration.

- We suggest that all marrow specimens could be read at a central facility by a pathologist blinded as to treatment and date.

2. A phase 1/2 study entitled, "Pilot Study of Arsenic Trioxide in Relapsed or Refractory Acute Promyelocytic Leukemia" (Study No. 97-66[ ]) is near completion at Memorial Sloan-Kettering Cancer Center. Eleven patients have been treated and have undergone detailed pharmacokinetic studies. No further biopharmaceutic studies are proposed for arsenic trioxide to support the NDA.

   Does the FDA agree?

   FDA Response:

   Clinical Pharmacology and Biopharmaceutics Comments:

   a. Please provide more detailed information from the Phase I/II pilot study listed in the briefing document.

b. Although urine is the major elimination route, the total amount of arsenic excreted daily in the urine accounted for approximately 1% to 8% of the total daily dose and the toxicity of a arsenical is related to the rate of its clearance from the body and to the extent of its tissue accumulation. Therefore, drug accumulation is a concern considering that the arsenic is a well-established carcinogen in humans. A mass balance study is recommended to demonstrate the disposition of the drug in humans.

c. Previous pharmacokinetic studies provided in the appear to be inadequate to assess the pharmacokinetic characteristics of the drug. We recommend that you provide the following information in filing Section 6 (Human Pharmacokinetics and Biopharmaceutics) of the NDA.

- Descriptive pharmacokinetics of all relevant species (C_{max}, T_{max}, AUC, terminal half-life, clearance, volume of distribution, etc.) across the recommended dosing range in the targeted population. For drugs demonstrating saturable protein binding at in vivo concentration, it may be necessary to measure free drug for pharmacokinetic assessment.
- Establish pharmacokinetic/ pharmacodynamic relationships for each species if possible.
- Investigate the ratio between trivalent and pentavalent or other forms of arsenic *in vivo*.
- Since dimethylarsenic acid is a major form of arsenic excreted in urine, investigate the activity and percentage of methylated metabolites, investigate the enzyme responsible for the metabolism, and characterize the pathway of metabolism of arsenic trioxide in humans.
- Investigate the pharmacokinetics of arsenic trioxide in special populations, such as subgroups with different gender, age, race, renal or hepatic functions.
- Investigate any potential drug interaction between arsenic trioxide and other possible coadministered drugs.
- Determine the plasma protein binding of the drug and its metabolites over the therapeutic range of concentrations.

d. Assay for the drug as well as its active metabolites should be validated in terms of its specificity, limit of quantitation, sensitivity, accuracy and precision including both intra-assay and inter-assay variability.

3. PolaRx Biopharmaceuticals, Inc. proposes that the clinical safety data to support the NDA will consist of the patients treated in Study No. PLRXAS01 and patient data obtained from Study No. 97-66.

   Does the FDA agree?

   FDA Response:

- Yes, given adequate number of patients in the pivotal studies.
- We encourage you to enroll pediatric patients.

PolaRx Response: Pediatric patients will be eligible.

Nonclinical Issues:

1. PolaRx Biopharmaceuticals, Inc. does not propose to conduct any nonclinical pharmacology, pharmacokinetic, or toxicity studies on arsenic trioxide to support the NDA.

   Does the FDA agree?

   FDA Response:

   We agree, provided a thorough summary of the literature is provided with key articles. The summary should focus on studies using the I.V. route and conducted with trivalent arsenic.

The Pre-NDA meeting occurred on January 5, 2000.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:
Clinical
1. PolaRx believes that complete remission in relapsed or refractory APL patients is a clinical benefit measure, and that the high percentage of complete remissions in the pivotal trial demonstrates substantial evidence of effect of arsenic trioxide. Does the Division consider the efficacy endpoints reached in Study . PLRXAS01 and 97-66 to be an adequate demonstration of the efficacy of arsenic trioxide in patients with APL to support filing an NDA?
FDA Response: Yes provided that the duration of the remission is recorded and considered clinically beneficial.
2. PolaRx believes that the efficacy and safety data from the pivotal (Study No. PLRXASOI) and pilot (Study No. 9766) APL trials are sufficient for the Division to consider the possibility of "full" or "standard" NDA approval. Does the Division concur?
FDA Response: Yes, provided the remission rate and duration are adequate and the patient population is one that is relapsed or refractory to other therapy.
3. Is the human safety data proposed in Section 9.5 adequate to demonstrate the safety of arsenic trioxide? Full safety on a total of 100 patients, 52 from APL studies and 48 from patients with other cancers will be included. Additionally, serious adverse events (SAEs) from an additional 14 patients from will be presented.
FDA Response: Yes, it appears that the size of the safety database may be adequate. Additionally, we are concerned about QT interval prolongation and risk of ventricular tachyarrythmias. Please provide a comprehensive evaluation of QT prolongation and torsade. Include your experience with this in APL and non-APL patients in the NDA. Please include AE information re: neuropathy, hematologic effects, and ATRA syndrome.
4. Does the Division consider the independent pathology review of bone marrow aspirates acceptable (Attachment 2)? This independent review will be used as supportive data, as the results from the pathologists at each investigational site will be the primary efficacy data for analysis.

FDA Response: Yes, the independent review is acceptable.

5. Will this NDA require the Division to seek the opinion of the FDA Advisory Committee before deciding on the approvability of the application?
FDA Response: The Division is not committed to bring every application before an advisory committee. The determination as to whether the application will be before an advisory committee will be made after a thorough examination of the NDA submission and internal discussion of the review issues.
6. Is it acceptable to the Division to submit Case Report Forms (CRFs) only for those subjects who either died on study or discontinued due to adverse reactions?
FDA Response: No, case report forms should be submitted for all APL patients.
7. Does the Division agree that the data from Study . 97-66 and PLRXASOI have a sufficient number of pediatric patients to satisfy the pediatric rule of December 2, 1998? Of the 6 pediatric patients (age range 5 to 15 years) from the two APL trials, the incidence of complete remission was 83%. There are no current plans to limit the lower age range of APL patients eligible to receive arsenic trioxide. A cautionary statement about use in pediatric patients is planned for inclusion in the prescribing information.
FDA Response: It is possible that upon review of the data, some pediatric information would be included in the labeling. It is likely that a broader representation of the pediatric population with 15 to 20 patients would be necessary in order to determine if there were dose adjustments or differences in safety profile that should be included in the product label.
Please note that the Pediatric Rule does not apply to Orphan Drug Designated Products, however, under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if this drug is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Request (PPSR), should be submitted so that we can consider issuing a Written Request.
Please refer to the "Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act" at Drug Information Branch (301) 827- 4573 or http://www.fda.gov/cder/guidance/index.htm.
Human Pharmacokinetics and Bioavailability
1. Three clinical trials of arsenic trioxide, including one in APL patients, have provided human pharmacokinetic data of arsenic trioxide. This data provides initial and repeated dose concentration-time data for arsenic trioxide after administration of(drug product formulated the same as the proposed commercial formulation (see Attachment 1). Is this level of human pharmacokinetic data sufficient for the NDA?
FDA Response: The format is appropriate, but the content is inadequate.
During the April 14, 1998 End-of-Phase 2 meeting, we made recommendations about the NDA contents. It is not clear if the following concerns will be addressed in Section 6 of the NDA (the letters and bullets are adopted from the meeting minutes):
b. Although urine is the major elimination route, the total amount of arsenic excreted daily in the urine accounted for approximately 1% to 8% of the total daily dose and the toxicity of a arsenical is related to the rate of its clearance from the body and to the extent of its tissue accumulation. Therefore, drug accumulation is a concern considering that the arsenic is a well-established carcinogen in humans. A mass balance study is recommended to demonstrate the disposition of the drug in humans.
Please provide a justification for not conducting a mass balance study in the NDA submission.
c. Previous pharmacokinetic studies provided( ) appear to be inadequate to assess the pharmacokinetic characteristics of the drug. We recommend that you provide the following information in filing Section 6 (Human Pharmacokinetics and Biopharmaceutics) of the NDA.

Descriptive pharmacokinetics of all relevant species (Cmax, Tmax, AUC, terminal half-life, clearance, volume of distribution, etc.) across the recommended dosing range in
the targeted population. For drugs demonstrating saturable protein binding at in vivo concentration, it may be necessary to measure free drug for pharmacokinetic assessment.

Establish pharmacokinetic/ pharmacodynamic relationships for each species if possible.

Investigate the ratio between trivalent and pentavalent or other forms of arsenic *in vivo*.

Since dimethylarsenic acid is a major form of arsenic excreted in urine, investigate the activity and percentage of methylated metabolites, investigate the enzyme responsible for the metabolism, and characterize the pathway of metabolism of arsenic trioxide in humans.

Investigate the pharmacokinetics of arsenic trioxide in special populations, such as subgroups with different gender, age, race, renal or hepatic functions.

Investigate any potential drug interaction between arsenic trioxide and other possible coadministered drugs.

Determine the plasma protein binding of the drug and its metabolites over the therapeutic range of concentrations. Please provide justification for any PK information not provided in the NDA as requested above.

Statistics

1. Because of the limited size of the open-label uncontrolled pivotal study, descriptive statistics will be used. The primary analysis for efficacy will be on all patients considered evaluable by having at least two weeks of treatment with arsenic trioxide. Does the Division consider the statistical treatment of the clinical data adequate?

FDA Response: Yes, however, statistics based on all patients enrolled should also be reported and all confidence interval calculations should be based on exact method due to small sample size.

Nonclinical Pharmacology and Toxicology

1. Does the Division consider the review of the literature on the nonclinical pharmacology, pharmacokinetics, and toxicology to be acceptable for fulfilling the requirements of the Nonclinical Pharmacology and Toxicology Sections of the NDA as previously agreed at the end-of-phase 2 meeting on April 14, 1998?

FDA Response:

As we agreed upon earlier (see minutes of the April 14, 1998 end of phase 2 meeting),
you will need to provide a thorough summary of the literature with key articles. The summary should focus on studies using the IV route and conducted with trivalent arsenic.

Other Questions

1. Does the Division agree that the archival copy of the NDA can be provided in paper format?

FDA Response: Yes, the archival copy may be provided in paper format.

2. PolaRx believes that arsenic trioxide can qualify for Fast Track Designation per Section 506
(21 USC 356). Does the Division concur?

FDA Response: Yes, it may qualify for Fast Track Designation.

6.5. Post-Marketing Experience

There is no post marketing experience.

6.6. Directions for Use

The intended use is for second line therapy for patients with relapsed or refractory acute promyelocytic leukemia. The intended dose is 15mg/kg intravenous as a 30 minute infusion given daily until remission is achieved.

7. Description of Clinical Data Sources

7.1. Study Type and Design/Patient Enumeration, Demographics, Extent of Exposure

There were data submitted from 2 single arm studies without concurrent controls that enrolled patients with relapsed or refractory APL patients. There were no other studies with concurrent controls submitted. The studies and the number of patients enrolled are listed in the following table.

Table 4 List of studies submitted by sponsor

Study	# of Patients
Phase II relapsed or refractory APL patients	40
Phase I relapsed or refractory APL patients	12
Patients with other hematologic malignancies	22
Patients with non-hematologic malignancies	27
Total	**99**

7.2. Literature

There are several published studies on the use of arsenic trioxide for the therapy of APL. The first publications in the last decade of the 20th century appeared in the early 1990's when an Ayurvedic preparation used India to control blood counts of patients with hematological malignancies was described. The report referred to studies published near the end of the 19th century on the use of arsenic in the United States and Europe for the therapy of acute myelocytic leukemia. Clinical reports from China in 1997 and 1997 described an infusion of arsenic trioxide as an effective therapy with 9 of 10 patients with relapsed or refractory APL treated achieving remission. In 1998 a report in the New England Journal of Medicine described similar results in 10 of 11 patients treated in New York. A subsequent report in the British Journal of Hematology described 4 of 7 patients with relapsed APL achieved remission, but 6 of the 7 had evidence of arsenic toxicity. The toxicity was fluid retention, neuropathy, and cardiac or pleural effusions. In 1999 the successful use of a combination of arsenic trioxide and ATRA was described in a case report of a patient with relapsed APL. The organic arsenical, melarsoprol, was used to treat 8 patients with various types of refractory leukemia, but it proved to have little efficacy and severe CNS toxicity. A 1999 report from China described the use of arsenic trioxide in both 11 newly diagnosed and 47 relapsed APL patients, with a similar remission rate (new onset 72% vs. 85% in relapsed) in both populations. Hepatic toxicity was observed in 7 of 11 newly diagnosed cases, including 2 deaths, while there was only elevation of transaminases in 33% of the relapsed patients and no deaths. Preliminary results of the Phase II study submitted to support the claim for this NDA were published in 1999 on 26 patients. Twenty-three (88%) achieved remission and 8 (31%) had retinoic acid syndrome.

7.3. Proposed indication

Second line therapy for patients with relapsed or refractory acute promyelocytic leukemia.

7.4. General Comments

There were three studies submitted to support the efficacy claim. They are:

- PLRXAS01: A phase II, single arm, multicenter study with a total of 40 patients with refractory or relapsed APL
- 97-66: A phase I, single arm, single institution study with a total of 12 patients with refractory or relapsed APL.
- A case series of 27 patients with relapsed or refractory APL from Memorial Sloan Kettering who received second line therapy with ATRA as a historical control.

7.5. Overview of Clinical Studies

The primary end point for all studies was Complete Remission and it was defined as *"Cellular bone marrow aspirate with < 5 % blasts; Peripheral blood WBC ≥ 3000 /mm^3 or ANC ≥ 1,500/mm^3 and platelet count ≥ 100,000/mm^3"*.
The marrow aspirate in 30 days should show continued remission

Secondary endpoint of PLRXAS01 is the duration of relapse free survival. It was defined as

"Beginning from the date upon which the complete remission has been attained to the date of clinical relapse (defined as presence of > 20% myeloblasts plus promyelocytes in the bone marrow or the appearance of frankly leukemic cells in the peripheral blood. Abnormalities confined to abnormal cytogenetics or molecular studies, absent from the previously defined clinical abnormalities will not constitute clinical relapse)".

Patients who receive additional antileukemic therapy will be censored from the relapse free survival analysis at the date on which the therapy is first administered.

Overall survival will be descriptively recorded and calculated from the first treatment date with arsenic trioxide up to the date of death from any cause. However, measurement of overall survival is not an efficacy endpoint of this study.

7.5.1. Reviewer's Trial # 1 — Sponsor's protocol # PLXAS01

7.5.1.1. Objective

To quote from the study protocol:

- *"To determine the proportion of patients with relapsed or refractory acute promyelocytic leukemia who achieve complete remission with the use of arsenic trioxide.*
- *To determine the duration of relapse free survival in patients with relapsed or refractory APL who have achieved a complete remission with arsenic trioxide therapy.*

- *To determine the pattern of clinical adverse experience when Arsenic trioxide is administered in patients with relapsed or refractory APL during induction and during complete remission".*

7.5.1.2. Design

This was an open label, nonrandomized, single arm phase II study

7.5.1.3. Population

Confirmed diagnosis of APL by bone marrow morphology, and by conventional cytogenetics for t(15:17) or RT-PCR assay for PML-α/RAR, or FISH analysis showing evidence of RAR-α or PML translocations. Relapse from or resistance to standard antileukemic therapy is defined as at least one course of induction chemotherapy using anthracycline antibiotics AND at least one course of induction or maintenance therapy using either ATRA or 9-cis retinoic acid. The patient needed an adequate hepatic and renal reserve as well as a negative pregnancy test and an informed consent. Concurrent chemotherapy, radiation, or investigational agents, patients with active uncontrolled infections, or with history grand mal seizures were not allowed

7.5.1.4. Endpoints

The primary endpoint of the study was complete remission and was defined as:

Cellular bone marrow aspirate with < 5 % blasts; Peripheral blood WBC ≥ 3000 /mm^3 or ANC ≥ 1,500/mm^3 and platelet count ≥ 100,000/mm^3".
The marrow aspirate in 30 days should show continued remission.

Secondary endpoint of PLRXAS01 is the duration of relapse free survival. It was defined as

"Beginning from the date upon which the complete remission has been attained to the date of clinical relapse (defined as presence of > 20% myeloblasts plus promyelocytes in the bone marrow or the appearance of frankly leukemic cells in the peripheral blood. Abnormalities confined to abnormal cytogenetics or molecular studies, absent from the previously defined clinical abnormalities will not constitute clinical relapse)".

Patients who receive additional antileukemic therapy will be censored from the relapse free survival analysis at the date on which the therapy is first administered.

Overall survival will be descriptively recorded and calculated from the first treatment date with arsenic trioxide up to the date of death from any cause. However, measurement of overall survival is not an efficacy endpoint of this study.

7.5.1.5. Planned Regimen

INDUCTION: Patients will receive a fixed dose of Arsenic Trioxide at 0.15 mg/kg daily for a cumulative maximum of 60 days to be diluted in dextrose water and infused over 2 hours. The treatment may be stopped early if there is complete disappearance in the bone marrow of leukemic myelo- and promyeloblasts by morphology, and < 5% of mononuclear cells are myeloblasts.
Dose Modifications: Treatment will be discontinued for significant hepatotoxicity (bilirubin, SGOT, ALP > 5 times the UNL), nephrotoxicity (creatinine > 4 mg/dl), significant neurological impairment (seizures, somnolence, impaired mentation, or severe peripheral neuropathy), or Grade 3 non-hematological events.
If there is a second recurrence of any of the toxicities after a 50 % dose reduction they will be removed from the study.

CONSOLIDATION: with one course for a total of 25 days would be administered for patients who entered remission, beginning 3 to 8 weeks after completion of induction therapy.

7.5.1.6. Statistical considerations

The sample size is based on the following assumptions:
- 14 % of patients will not be evaluable for the protocol secondary to violations.
- It is required that the CR rate is at least 33% within a 95 % confidence interval.

If 35 patients are entered, then 30 should be evaluable for efficacy.
If a predicted 33% R.R is the minimum required within a confidence interval for the calculated potential response rate, then the study must generate at least an observed CR equal to at least 50 %.
Analysis of efficacy is based on the following:
Achieving a CR < 50 % will be interpreted as failure of trial to prove efficacy. The hypothesis to be tested is that the rate of CR meets or exceeds a 50% CR rate. For a 30 patient accrual, a lower limit of confidence interval will be $\geq$ 33%.
A patient will be considered adequately treated if he/she has received a minimum of 14 days of arsenic trioxide and lack of response can be reasonably assessed.
Relapse free survival is a secondary endpoint and will be analyzed using descriptive analysis. Relapse free survival and over all survival will be estimated using Kaplan-Mayer analysis.

7.5.1.7. Results

A total of 40 patients from the phase II study (PLRXAS01) were analyzed for efficacy. Specifics of all patients analyzed are given in table 5.

Table 5 Population enrolled/analyzed

Patient ID Number	Age	Gender	Race	Previous ATRA	Previous Chemo	< 1 year relapse	# of prior regimens	Prior BMT	Days since last ATRA
1013	24	F	C	Y	Ara/Daun	Y	2	N	9
1014	48	M	C	Y	Ara/VP/Dexr	Y	3	N	192
1015	36	F	C	Y	Adr/Ara/VP	?	2	Y	215
1016	45	M	C	Y	Ara/Daun	N	2	N	2
1017	20	F	C	Y	Ara/Daun	N	1	N	343
1018	46	M	H	Y	Dnxm/Dexrzxn/Ida /Mito/VP/POMP /Lipo ATRA	Y	3	N	204
1019	65	F	I	Y	Ara/Ida	N	1	N	332
1020	39	M	AA	Y	Ciss/Ara	N	2	Y	439
1021	72	M	C	Y	Daun/Ida/LDG-1057	N	2	N	368
1022	63	M	C	Y	Anthracycline/Ara	N	2	N	621
1023	38	M	C	Y	Ara/Daun/Moab/Ida	N	2	N	89
1024	37	M	C	Y	Ara/Ida	?	1	N	203
1025	43	M	C	Y	Ara/Ida/Hidac	?	1	N	391
1026	50	F	AA	Y	Ara/Ida	N	1	N	16
1027	44	F	C	Y	Ara/VP/Mit	N	1	N	22
1028	5	F	C	Y	Ara/Daun/VP/Fludr /Thiogn	?	4	N	7
1029	22	F	C	Y	Ara/Ida	?	2	N	28
1030	6	M	C	Y	Ara/Daun	N	2	Y	437
1031	51	F	C	Y	Ara/Mit/Cis	?	3	Y	380
1032	7	M	C	Y	Ara/Daun	N	1	N	47
1033	71	M	C	Y	Ara/Daun/Ida	?	1	N	148
1034	70	F	AA	Y	Mit/VP	N	2	N	905
1035	70	F	C	Y	Ara/Ida	?	1	N	27
1036	37	F	C	Y	Ara/Ida	N	1	N	450
1037	24	M	C	Y	Ida/Lipo ATRA	N	1	N	3
1038	43	F	H	Y	Ara/Daun	N	2	N	666
1039	42	F	C	Y	Ara/Daun/Moab	N	2	N	63
1040	48	F	AA	Y	Anthracycline	?	1	N	622
1041	15	F	C	Y	Ara/Daun	N	1	N	625
1042	73	M	C	Y	Mit	?	1	N	523
1043	52	M	C	Y	Ara/Daun	?	1	N	274
1044	28	F	C	Y	Ara/Ida	Y	1	N	390
1045	32	F	H	Y	Ara/Daun/Epi	?	2	N	344
1046	41	F	C	Y	Hidac	N	2	N	4
1047	20	M	H	Y	Ara/Moab/Ida	N	1	N	145
1048	23	F	C	Y	Ara/Ida	N	1	N	1089
1049	62	F	AA	Y	Ara/Ida/Mit	N	2	N	576
1050	19	F	C	Y	Ara/Daun	N	2	N	752
1051	37	F	C	Y	Arac/Daun	N	1	N	446
1052	16	F	C	Y	Ara/Daun	?	2	Y	431

Ara: Ara-c, Cis: cis-retinoic acid Daun: duanurubicin, VP: etoposide, Epi: epirubicin, Fludr: fludanbine, Hidac: high dose ara-C, , Ida: idarubicin, Lipo ATRA: liposomal ATRA,, Mit: mitoxantrone,: Moab: monoclonal antibody, Thiogn: thioguanine
AA: African American C: caucasian, H: Hispanic, I: Islander

- NB. Column "Days Since Last ATRA" is calculated from the time of ATRA administration in the previous diagnosis to the current relapse.

Table 6 Distribution of patients enrolled in relapsed APL protocol

Category	Total
Total Patients	40
Gender- Women	24
Gender- Men	16
Children < 16 years	5
Race/Ethnicity- Caucasian	32
Race/Ethnicity - Black	3
Race/Ethnicity - Hispanic	4
Race/Ethnicity - Other	1
APL History- No Prior ATRA	0
APL History- ATRA > 1 year	18
APL History- ATRA < 1 year	22
APL History- No Prior Anthracyclines	1
APL History > 1 prior regimen	21
APL History of 1 prior regimen	19
History of prior BMT	5
APL History < 1 year relapse	4
APL History > 1 year relapse	23
APL History unknown	13
Study sites	9

Table 7 Initial violations for relapsed APL protocols

Violations	Total	Pt ID
Patients with undocumented marrow status at baseline (cytogenetics or PCR)	1	1046
Patients without prior Anthracycline	1	1046
Patients without prior ATRA	0	0
Potentially fertile women missing documentation of required pregnancy test	0	0

Table 8 Patients who received ATRA within 21 days prior to ATO

PT ID	ATRA started prior cycle	ATRA stopped prior cycle	Response prior cycle	ATRA started current diagnosis	ATRA stopped current diagnosis	ATO started
1013	7/22/97	7/28/97	Responded	4/6/98	4/14/98	4/22/98
1016	12/31/96	2/3/97	Responded	6/11/98	6/22/98	6/23/98
1026	4/3/97	?/?/97	Not evaluable	6/11/98	8/20/98	9/4/98
1028	8/30/96	9/13/96	Not evaluable	9/4/98	10/1/98	9/15/98
1037	10/17/97	12/1/98	Progressed	10/17/97	12/1/98	12/3/98
1046	10/1/97	10/1/98	Responded	2/9/99	3/6/99	3/9/99

Table 9 Days on ATRA in patients who received ATRA within 21 days prior to receiving ATO

Pt ID	# of days ATRA given prior cycle	# of days ATRA given this cycle	Days between ATRA cycles	Days between ATRA and ATO
1013	7	9	253	9
1016	35	12	494	2
1026	Not known	71	Not known	16
1028	15	28	722	7
1037	N/A	411	N/A	3
1046	366	26	132	4

The patient 1046 had an undocumented marrow status at baseline. Evidence of APL was confirmed later on in the course of his disease. 1 patient did not receive an anthracycline in the past. One patient (1037) received ATRA only in the liposomal form. Patient 1036 received 14 or less doses of arsenic trioxide. Two patients (1038 and 1050) did not receive consolidation therapy since they went on bone marrow transplant after induction. 15 patients had not received ATRA within one year of starting ATO treatment, and theoretically could have responded to ATRA. Six patients i.e., 1013, 1016, 1026, 1028, 1037, 1046 started Arsenic within 21 days of stopping ATRA. They received 9, 12, 71, 28, 411 and 26 days of ATRA respectively. 5 of these patients were responders to arsenic trioxide. For 4 of these patients (1013, 1016, 1026, 1028) it is difficult to evaluate the contribution of ATO to their response because the response could still be due to ATRA. 1037 progressed on ATRA. For 1046, a bone marrow biopsy showed marked leukemia after 26 days of ATRA. A prespecified time interval between stopping ATRA and starting arsenic trioxide was not part of the protocol inclusion requirements.

7.5.1.8. Outcome

As can be seen from the table below, the difference in outcomes between intent to treat analysis and analysis excluding patient (1046) with major violations is small. In order to simplify the analysis, the calculations are performed on 'an intent to treat' analysis, unless otherwise stated.

Table 10 Clinical Outcome of ATO therapy

Pt ID	Outcome	Comments	Days to reach CR	Duration of CR	Survival (status) in days
1013	CR		34	564+	597+
1014	CR	Patient is dead	36	226	353
1015	No response	Residual disease	-	-	233
1016	CR		72	486+	557+
1017	CR		45	513+	557+
1018	CR		76	461+	535+
1019	No response	Residual disease	-	-	39
1020	CR		49	461+	509+
1021	CR	Pt is dead	73	262+	334
1022	CR		34	473+	506+
1023	CR(no response per sponsor)	Died after relapse	59	109	285
1024	Possible CR (no response per sponsor)	Refused treatment. No consolidation.Underwent BMT prior to confirmatory BM Biopsy	62	423+	484+
1025	CR		57	428+	484+
1026	CR		42	239+	280+
1027	CR		39	400+	438+
1028	No response	Residual disease	-	-	381+
1029	CR		28	403+	430+
1030	CR		55	362+	416+
1031	Possible CR	With inadequate disease related counts	69?	182	283
1032	CR		38	374+	411+
1033	No response	Lost to f/u	-	87	170
1034	Possible CR (No response per sponsor)	Confirmatory marrow done within 28 daysDid not receive consolidation.Died later from unknown cause	65	-	179

1035	CR		39	362+	362+
1036	No response	Pt died due to intracranial hemorrhage	-	-	16
1037	CR	Alive with recurrence	54	172	394+
1038	CR (No response per sponsor)	Pt did not f/u. & did not receive consolidation.Off-study BMBx 7.5 mo later in remission.	47	314+	360+
1039	CR		61	289+	349+
1040	CR	Alive with recurrence. Did not receive consolidation	61	215	309+
1041	CR		80	211+	290+
1042	-Possible CR	Confirmatory bone marrow biopsy not done	40?	290+	329+
1043	CR		53	264+	316+
1044	Possible CR	Continued low WBC	68?	242+	309+
1045	CR		62	248+	309+
1046	CR		85	171+	255+
1047	CR		49	234+	282+
1048	CR		28	282+	282+
1049	No response		-	-	63+
1050	CR		74	157	230
1051	CR		56	176+	231 +
1052	No response	Early termination because of adverse events	-	-	86

Table 11 Patients unable to maintain CR because of lowered Blood Counts

Pt ID	Lowered WBC
1023	X (lowered ANC)
1040	X
1043	X
1046	X
1048	X
1051	X

Table 12Characteristics of responders in relapsed APL protocol

Category	Responders	Initial # of pts.	%
Confirmed responders (intent to treat)	28	40	70
Confirmed responders (excluding violations)	27	33	81
Possible responders lacking documentation	5	40	13
Sum of confirmed and possible responders	33	40	83
Women responders (confirmed +possible)	19	24	79
Male responders (confirmed +possible)	15	16	94
Pediatric responders	3	5	60
Caucasian responders (confirmed +possible)	24	32	75
Hispanic responders (confirmed +possible)	4	4	100
Black responders (confirmed +possible)	3	3	100
No prior ATRA (confirmed +possible)	0	0	0
Of 34 responders, ATRA for > 1 year (confirmed + possible)	15 (10+5)	33	45
Of 34 responders, ATRA < 1 year (confirmed + possible)	19 (18+1)	33	58
Responders that relapsed during study period (confirmed +possible)	1	40	2
Responders that are alive and disease free (confirmed +possible)	21	40	53

Cytogenetics and Polymerase Chain Reaction Results

Cytogenetic conversion to no detection of the APL chromosome rearrangement was observed in 24 of 28 (89%) patients who met the response criteria defined above, in 5 of 5 (100%) patients who met some but not all of the response criteria, and 3 of 7 (43%) of patients who did not respond. Reverse Transcriptase – Polymerase Chain Reaction conversions to no detection of the APL gene rearrangement were demonstrated in 22 of 28 (79%) of patients who met the response criteria, in 3 of 5 (60%) of patients who met some but not all of the response criteria, and in 2 of 7 (29%) of patients who did not respond.

7.5.1.9. Follow-up

The range of follow-up for all patients was 16-597 days, with a median of 322 days.
On an intent to treat basis, there were a total of 28 of 40 (70%) patients who were complete responders. 24 of the 28 are still alive, 21 without recurrence, with a median duration of follow up of 356 days. 2 are alive with recurrence and 4 have died. Of the 5 'possible' responders, 3 are alive (survival range: 309 - 484 days) and 2 have died (survival range: 179 – 283 days).

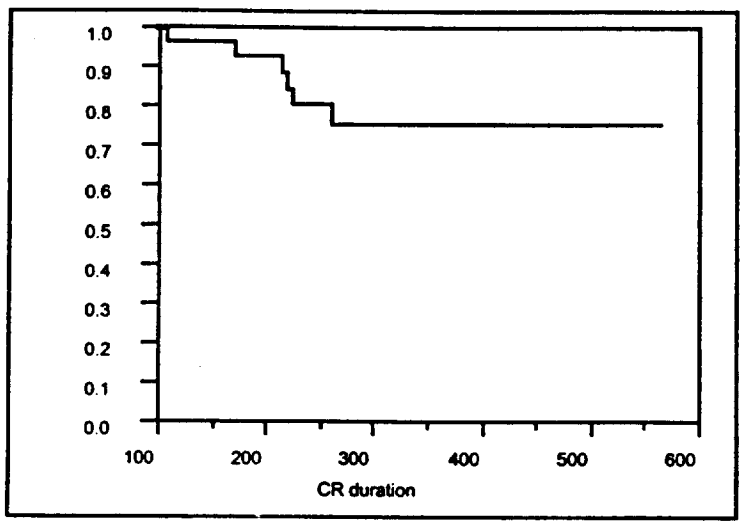
If the major violations are excluded, i.e., patients who have not received anthracyclines prior to ATRA (N:1), and counting patients who have received ATRA within 21 days of starting ATO as a violation (N:6),), the total number of patients falls to 33, with 23 CR's (69%), 5 possible CR's (15%).
According to the sponsor, in this set of patients, there were 28 of 40 (70%) responders .

Five patients (1023, 1043, 1046, 1048and 1051) reached CR level WBC's or/ANC. These were not maintained for 28 days. Since their bone marrow biopsies continued to show response after 28 days, and because there can be multiple reasons for decreased blood counts other than leukemia, these were counted as complete responders. Their survival in days was 285, 316+, 255+, 282+ and 231+ respectively. They all received either maintenance, and/or BMT after induction and consolidation with arsenic trioxide.

Table 13 Extent of exposure to Arsenic Trioxide

Patients	Range of # of dosages	Median # of dosages	25th percentile	75th percentile
All	14-101	52	62	40
Responders	29-85	53	63	49
Nonresponders	14-70	34	41	24

Graph 1- Kaplan-Meier Curve of CR Duration



N.B. Value of ordinate was 1.0 from 0 to 100 days

Graph 2- Kaplan-Meier curve for CR duration censored for BMT

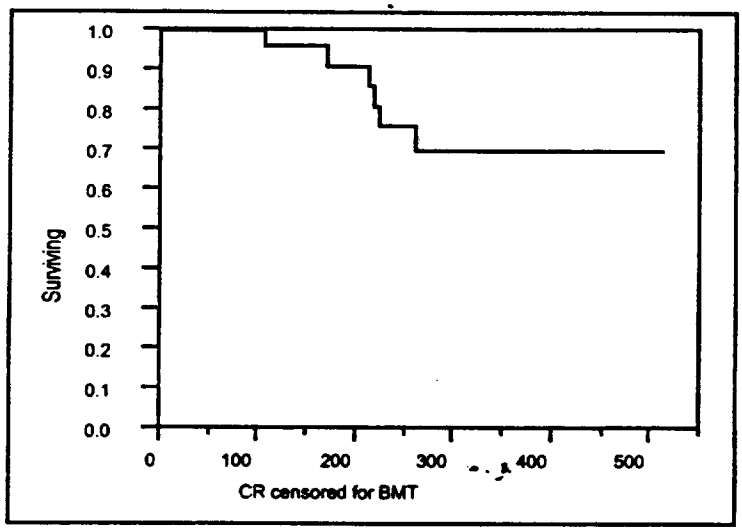


Table 14 Time to CR

	Range in days	Median in days
Days to reach CR	28-85	53
Days to reach marrow remission	27-91	44

Table 15 Distribution of responders among study sites

Site	Enrolled	% total pts	CR	% of responders	Response Rate
MSKCC	14	35	11	41%	79%
GTUH	7	18	3	8%	43%
USC	4	10	1	3%	25%
Northwestern Univ. Med. Cr.	4	10	3	8%	75%
MDACC	3	7.5	3	8%	100%
Dana Farber	3	7.5	2	5%	66%
Cleveland Clinic	2	5	2	5%	100%
Stanford Univ.	1	2.5	1	3%	100%
Fred Hutchinson	2	5	1	3%	50%

Patients receiving further treatment

31 patients received further treatment in the form of Bone Marrow Transplant (15/32), and/or maintenance with Arsenic trioxide (18/32). 2 patients received both.

Maintenance therapy was administered to the responders of PLRXAS01 in another study, PLRXAS02. In this study, a maximum of 4 courses of arsenic trioxide was to be administered, using the same regimen as in the prior study. The first course was planned to begin within 3 - 6 weeks after completing preceding course of therapy in protocols PLRXAS01. All treatments in this protocol were to conclude within 12 months of starting treatment on PLRXAS01.

Responders receiving therapy after induction and consolidation: Twenty-eight patients were eligible for maintenance with arsenic trioxide according to the extension protocols described above.16 patients received maintenance treatment. Two underwent BMT after receiving maintenance with arsenic trioxide. Twelve patients who were eligible for arsenic trioxide maintenance did not receive it. Eight patients underwent a bone marrow transplant and did not receive maintenance therapy. No reason was given for the remaining four patients who were eligible for, but did not receive maintenance with arsenic trioxide.

Table 16 Days from CR to further treatment:

Treatment	Median	Range
Maintenance arsenic trioxide	75	63 -105
Any (BMT or Maintenance)	85	45 - 412

Patients receiving Bone Marrow Transplant: 15 patients out of 40 underwent bone marrow transplant. 11 of these were in responders' group, 2 were in possible responders' group and 2 were in the non-responders' group. Median time to BMT after CR was 148 days (approximately 4.9 months), with the range being 45 (1024 was a possible CR and not included in CR)– 412 days. The details of these patients are included in the table below.

Table 17 Management of patients following ATO treatment

Pt ID	Response	Further treatment	Days from CR to next treatment	CR Duration	Survival
1013	CR	BMT	412	564+	597+
1014	CR	Main.	90	226	353
1015	No Response	BMT	-	-	233
1016	CR	Main.	71	486+	557+
1017	CR	Main.	75	513+	557+
1018	CR	Main.	78	461+	535+
1019	No Response	-	-	-	39
1020	CR	-		461+	509+
1021	CR	Main.	104	262+	334
1022	CR	Main.	77	473+	506+
1023	CR	Main.	74	109	285
1024	Possible CR	BMT	16	423+	484+
1025	CR	Main.	69	428+	484+
1026	CR	Main.	89	239+	280+
1027	CR	Main+BMT	85, 247	400+	438+
1028	No Response	BMT	-	-	381+
1029	CR	Main.	105	403+	430+
1030	CR	Main.	67	362+	416+
1031	Possible CR	Main.	63	182+	283
1032	CR	BMT	148	374+	411+
1033	No Response	-	-	87	170
1034	Possible CR	-		-	179
1035	CR	Main.	71	362+	362+
1036	No Response	-	-	-	16
1037	CR	Main.	71	172	394+
1038	CR	-		314+	360+
1039	CR	BMT	129	289+	349+
1040	CR	-		215	309+
1041	CR	BMT	57	211+	290+
1042	Possible CR	Main.	93	290+	329+
1043	CR	BMT	202	260+	316+
1044	Possible CR	BMT		242+	309+
1045	CR	Main.	104	248+	309+
1046	CR	BMT	45	171+	255+
1047	CR	Main+BMT	65, 161	234+	282+
1048	CR	BMT	92	282+	282+
1049	No Response	-	-	-	63+
1050	Possible CR	BMT		157	230
1051	CR	BMT	52	176+	231+
1052	No Response	-	-		86

Main.: Maintenance; BMT= Bone Marrow Transplant

Historical controls:

As a control, the sponsor submitted data from 27 patients with relapsed or refractory APL from Memorial Sloan Kettering Cancer Center who were treated between July 1990 and July 1996.. The data is limited in information and does not include significant information such as bone marrow biopsy results, drugs involved in prior treatments, dosages and laboratory data.

Table 18 Summary of data from historical control

Time from last dose of ATRA	No. of Pts	CRs (%)	Median Survival, months
< 1 M	3	0 (0%)	4.3
< 6M	6	1 (17%)	6
6 < 12 M	10	1 (10%)	1.4
12 < 18 M	1	0 (0%)	6.8
>= 18 M	7	4 (57%)	39
	27	6 (22%)	

7.5.1.9.1. Safety outcomes in APL patients treated with ATO

The majority of patients experienced adverse events consistent with administration of differentiating therapy for APL. The most common adverse events experienced by more than 40% of patients were headache, nausea and emesis, fever, hemorrhage, pain, diarrhea, dry skin, hypomagnesemia, stomatis, asthenia, and hypokalemia. The most common severe (Grade 3 or 4) adverse events were fever, hemorrhage, hyperglycemia, headache, APL differentiation syndrome , and sepsis. APL differentiation syndrome was described in 9 patients (23%) with one patient having two episodes. Severe APL differentiation syndrome was described in 3 patients (8 %), with none of the patients subsequently discontinuing arsenic trioxide. A total of 2 patients discontinued arsenic trioxide and 3 patients died within 30 days of their last dose. The data are displayed and summarized in the following tables.

ECG Changes

Cardiac dysrhythmias have been reported with arsenic use. In this study, QT prolongation greater than 500 msec as measured by prolongation of the absolute QT or QT corrected interval (QTc) on an electrocardiogram was seen in 16 (40%) of patients. One patient, 1026, had a prolonged QTc of 618 msec which became asymptomatic torsade de pointes while receiving amphotericin B for a fungal infection. Amphotericin B is known to produce electrolyte abnormalities, which are a risk factor for cardiac dysrhythmias. Three days prior to this episode the serum potassium was 2.9 mEq/dL and the serum magnesium was 1.6 meq/dL The dysrhythmia resolved spontaneously and the patient was treated with correction of electrolytes. All the QT and QTc prolongation are Grade I (asymptomatic) on the National Cancer Institute Common Toxicity Criteria version 2.

Almost 470 separate ECG records were reviewed and compared for changes in QTc during therapy with arsenic trioxide during induction therapy and then during consolidation therapy. There was no trend to increasing prolongation of QTc in patients with repeated exposure, either within a treatment course or from one treatment course to the next (induction to consolidation). QT and QTc returned to baseline following cessation of arsenic trioxide. The effects of arsenic trioxide on QT and QTc prolongation in this limited study seem to be reversible

Table 19 Number of patients experiencing adverse events and severe adverse events

Adverse Events (any grade) Occurring in ≥5% of 40 Patients with APL who Received TRISENOX™ at a dose of 0.15 mg/kg/day

System organ class / Adverse Event	All Adverse Events, Any Grade		Grade 3 & 4 Events	
	n	%	n	%
General disorders and administration site conditions				
Fatigue	25	63	2	5
Pyrexia (Fever)	25	63	2	5
Edema -General	16	40		
Rigors	15	38		
Chest pain	10	25	2	5
Injection site Pain	8	20		
Pain- Non specific	6	15	1	3
Injection site erythema	5	13		
Injection site edema	4	10		
Weakness	4	10	2	5
Hemorrhage	3	8		
Weight gain	5	13		
Weight loss	3	8		
Drug hypersensitivity	2	10	1	3
Gastrointestinal disorders				
Nausea	30	75		
Anorexia	9	23		
Appetite decreased	6	15		
Diarrhea	21	53		
Vomiting	23	58		
Abdominal pain (lower & upper)	23	58	4	10
Sore throat	14	40		
Constipation	11	28	1	3
Loose Stools	4	10		
Dyspepsia	4	10		
Oral blistering	3	8		
Fecal Incontinence	3	8		
Gastrointestinal hemorrhage	3	8		
Dry mouth	3	8		
Abdominal Tenderness	3	8		
Diarrhea hemorrhagic	3	8		
Abdominal distension	3	8		
Metabolism and nutrition disorders				
Hypokalemia	20	50	5	13
Hypomagnesemia	18	45	5	13
Hyperglycemia	18	45	5	13

Adverse Events (any grade) Occurring in ≥5% of 40 Patients with APL who Received TRISENOX™ at a dose of 0.15 mg/kg/day

System organ class / Adverse Event	All Adverse Events, Any Grade		Grade 3 & 4 Events	
	n	%	n	%
ALT increased	8	20	2	5
Hyperkalemia	7	18	2	5
AST increased	5	13	1	3
Hypocalcemia	4	10		
Hypoglycemia	3	8		
Acidosis	2	5		
Nervous system disorders				
Headache	24	60	1	3
Insomnia	17	43	1	3
Parasthesia	13	33	2	5
Dizziness (excluding vertigo)	9	23		
Tremor	5	13		
Convulsion	3	8	2	5
Somnolence	3	8		
Coma	2	5	2	5
Respiratory				
Cough	26	65		
Dyspnea	21	53	4	10
Epistaxis	10	25		
Hypoxia	9	23	4	10
Pleural effusion	8	20	1	3
Post nasal drip	5	13		
Wheezing	5	13		
Decreased breath sounds	4	10		
Crepitations	4	10		
Rales	4	10		
Wheezing	4	10		
Hemoptysis	3	8		
Tachypnea	3	8		
Rhonchi	3	8		
Skin & subcutaneous tissue disorders				
Dermatitis	17	43		
Pruritus	13	33	1	2
Ecchymosis	8	20		
Dry Skin	6	13		