CHILDREN'S ONCOLOGY GROUP
The world's childhood cancer experts

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CHILDREN'S ONCOLOGY GROUP

AAML1331

A Phase III Study for Patients with Newly Diagnosed Acute Promyelocytic Leukemia (APL) using Arsenic Trioxide and All-Trans Retinoic Acid

A COG Groupwide Phase III Study

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[redacted]

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AGENT	NSC#	IND#
Arsenic Trioxide (ATO)	706363	Commerical
Tretinoin (ATRA)	122758	Commercial
Cytarabine	63878	Commercial
Dexamethasone	34521	Commerical
Hydrocortisone	10483	Commercial
Idarubicin	256439	Commerical
Leucovorin	3590	Commerical
Methotrexate	740	Commerical
Mitoxantrone	301739	Commerical

SEE SECTIONS 13, 14 AND 15 FOR SPECIMEN SHIPPING ADDRESSES.

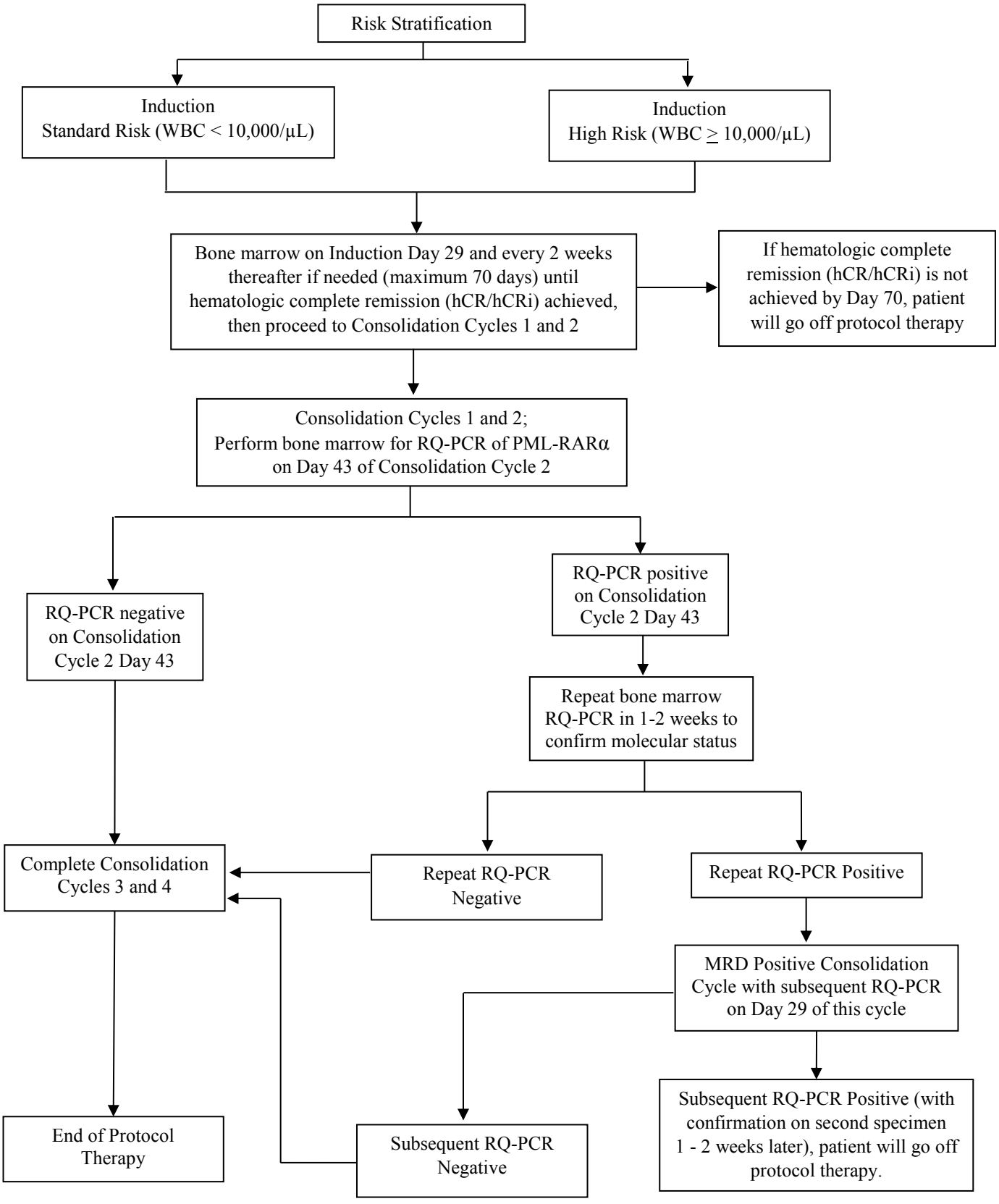
ABSTRACT

The use of all-trans retinoic acid (ATRA) in combination with anthracyclines (AIDA regimen) has achieved remission rates over 90% and event free survival (EFS) greater than 70% for children with APL. The addition of arsenic trioxide (ATO) further decreases the risk of relapse for APL patients as evidenced by randomized data from patients ≥ 15 years old enrolled on the North American Leukemia Intergroup CALGB 9710 trial. In a previous Children's Oncology Group (COG) APL trial (AAML0631), ATO Consolidation cycles were incorporated and total anthracycline dose reduced compared to prior AIDA based regimens. In a continuing evolution of APL treatment, a number of adult trials have utilized ATO in combination with ATRA and have successfully achieved excellent outcomes while significantly reducing, and even eliminating, anthracyclines and other conventional chemotherapy. This pediatric study will be based upon the MD Anderson Cancer Center (MDACC), GIMEMA-SAL-AMLSG APL0406, and Australasian APML4 studies utilizing ATRA and ATO. The Italian AIDA 0493 trial remains the most mature and has the best reported outcomes for a pediatric APL population, and thus will serve as the pediatric historical comparator.

In this Phase III trial, patients will be stratified into risk groups based on their presenting white blood cell (WBC) count (< 10,000/μL is standard risk and ≥ 10,000/μL is high risk). All patients will receive daily ATRA and ATO during Induction. High risk patients will also receive 4 doses of idarubicin during Induction. Patients who are confirmed to have a hematologic complete remission at the end of Induction, will subsequently receive 28 weeks of Consolidation therapy with ATRA and ATO. Since there is no Maintenance therapy, the total duration of treatment will be reduced from approximately 30 months to approximately 8 months. Following 2 ATO cycles in Consolidation, patients will have a bone marrow evaluation to confirm molecular remission by real-time quantitative polymerase chain reaction (RQ-PCR) testing of PML-RARα. Based on the adult experience with this regimen, PCR positive disease at this Consolidation time point will be rare. The rare patients with PCR positive disease will receive an additional chemotherapy cycle (mitoxantrone, cytarabine and ATRA).

Several important corollary studies, including assessment of FLT3 mutations, minimal residual disease (MRD) by RQ-PCR testing, and coagulopathy, as well as a quality of life study to determine the neurocognitive effects of this treatment, are important components of this clinical trial.

EXPERIMENTAL DESIGN SCHEMA



1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To eliminate exposure to conventional chemotherapy (including anthracyclines), for patients with standard risk APL, through use of ATO and ATRA based therapy while achieving an event free survival (EFS) that is not inferior compared to historical controls.

1.1.2 To significantly reduce exposure to conventional chemotherapy, and in particular, anthracycline exposure, for patients with high risk APL, through use of ATO and ATRA based therapy while achieving an event free survival that is not inferior compared to historical controls.

1.2 Exploratory Aims

1.2.1 To analyze the clinical impact of FLT3 mutations in pediatric APL.

1.2.2 To correlate clinical outcomes with the kinetics of reduction in PML/RARα transcript level by quantitative RT-PCR (RQ-PCR) in bone marrow and peripheral blood samples from diagnosis to time points during therapy.

1.2.3 To monitor incidence of coagulopathy complications, utilizing standardized conventional supportive care, and correlate with a battery of coagulation testing.

1.2.4 To evaluate the neurocognitive outcomes of patients treated on this protocol using patient-completed, performance-based measures of neuropsychological functioning and parent questionnaire report.

2.0 BACKGROUND

The use of ATRA and ATO in the treatment of APL has greatly improved the outcome for patients with APL, such that it is now the most curable subtype of AML. Historically, AIDA (ATRA and anthracycline) based treatment regimens relied upon large cumulative doses of anthracyclines to achieve cure resulting in long term risk of cardiac toxicity, second malignancy and infertility, and more immediate risk of myelosuppression, with concomitant risk of infection. Recent trials, including the now closed COG trial AAML0631, have evaluated lower doses of anthracyclines in conjunction with ATO Consolidation cycles. Recently several large adult trials, which utilized little or no conventional chemotherapy, have demonstrated that APL may be cured with ATO and ATRA alone. Pediatric patients in particular may benefit from an anthracycline-reduced or free regimen given the expected duration of life following APL cure. Thus, this trial aims to study the efficacy of an ATO and ATRA regimen in pediatric patients with APL.

2.1 Historical Controls

Outcomes in the treatment of both adult and pediatric APL improved greatly with the addition of ATRA to traditional cytotoxic chemotherapy.[1-5] Children treated on the first North American intergroup trial (INT0129) had a significantly improved DFS if they

received ATRA during Induction and/or Maintenance compared to those who received only conventional chemotherapy (DFS 48% vs. 0%).[5]

The Italian GIMEMA-AIEOP AIDA 0493 trial has one of the largest (n = 107) and most mature datasets in children with APL. The treatment regimen used in this trial included ATRA and idarubicin (Induction), cytarabine plus idarubicin/mitoxantrone/etoposide/6-thioguanine (Consolidation) and ATRA, 6MP and methotrexate (Maintenance). The CR rate was 96%, 10-year overall survival (OS) was 89%, and 10-year EFS was 76%.[6] On AIDA0493, patients with high risk disease (WBC count at diagnosis ≥ 10,000/μL) had a 10-year EFS of 59% compared to 83% for patients with standard risk APL. The publication of this pediatric data included long term follow-up with EFS estimates at 10 years; molecular relapses were censored in that analysis. For the AIDA 0493 study, EFS estimates that include molecular relapses as an event were 91.3% at 2 years for standard risk patients and 71.1% at 3 years for high risk patients (personal communication, Anna Maria Testi, MD).

The COG's most recent clinical trial for patients with newly diagnosed APL was AAML0631. Treatment included Induction with idarubicin and ATRA, two Consolidation cycles with ATO and ATRA, a Consolidation cycle with mitoxantrone/high dose cytarabine/ATRA, a Consolidation cycle with idarubicin and ATRA, and for high risk patients an additional Consolidation cycle with idarubicin/high dose cytarabine/ATRA. All patients received Maintenance with mercaptopurine/methotrexate/ATRA. One hundred and one patients (66 SR and 35 HR) were evaluable for outcome. The 2-year event-free survival (EFS) was 97% for SR APL and 83% for HR APL.[7]

The EFS for SR patients in AAML0631 was non-inferior to that of patients in the AIDA 0493 historical control, which used a significantly higher anthracycline dose and did not include ATO consolidation. AAML0631 was not statistically designed to allow a formal comparison of outcome for HR APL patients treated on the AAML0631 and AIDA 0493 regimens. However, the survival rate was higher on the AAML0631 trial and the incorporation of ATO with decreased anthracycline can be considered a new standard of care for these HR APL pediatric patients. Therefore while AAML1331 was initially designed to compare outcomes to ADIA 0493 during a time when the AAML0631 outcomes were not yet known, amendment 2 of the protocol now includes a comparison of outcomes between AAML1331 and AAML0631.

2.2 Arsenic Trioxide (ATO) in the Treatment of APL

ATO administered as a single agent has shown excellent efficacy for patients with relapsed APL, prompting further study of ATO in newly diagnosed patients. ATO appears to have even greater anti-tumor activity than ATRA in the treatment of APL since durable remissions have been achieved with ATO therapy alone.[8-10] Two studies have shown CR rates of approximately 86% and a 5-year OS rates of 64% - 74% utilizing ATO as a single agent for newly diagnosed APL in adults and children.[11,12] The North American APL intergroup study C9710 randomized patients ≥ 15 years old to two Consolidation cycles with ATO while all patients received a chemotherapy backbone including ATRA, daunorubicin and cytarabine (Induction), two cycles of ATRA and daunorubicin (Consolidation) and Maintenance with ATRA, 6MP and methotrexate. This study demonstrated an improved EFS and OS for patients who received ATO compared to those who did not (3-year EFS 80% vs. 63%, $p < 0.0001$, and 3-year OS 86% vs. 81%, $p = 0.059$, respectively).[13] Supported by these results, the COG AAML0631 study incorporated two

ATO Consolidation cycles into a backbone of anthracycline and high dose cytarabine chemotherapy while reducing the total anthracycline dose by 38 - 45% compared to earlier AIDA regimens. The ATO containing cycles were well tolerated and there were fewer infectious related complications during those cycles compared to the cycles with anthracyclines and high dose cytarabine.[7]

2.3 ATO and ATRA Regimen

There is evidence that combining ATRA with ATO produces results superior to ATO alone.[14,15] Investigators at the University of Texas – MD Anderson Cancer Center (MDACC) developed a regimen for newly diagnosed APL combining ATO and ATRA without any traditional cytotoxic chemotherapy.[16] Patients received ATO and ATRA daily for the first month of therapy as Induction, and subsequently received 28 weeks of Consolidation consisting of cycles of ATO (4 weeks every 8 weeks for 4 cycles) and ATRA (2 weeks every 4 weeks for 7 cycles). Patients with presenting WBC ≥ 10,000 also received a dose of gemtuzumab ozogamicin on Day 1 of Induction. Utilizing this regimen they achieved excellent outcomes with CR 98%, 5-year EFS 86% and 5-year OS 88%.[16,17] WBC ≥ 10,000 at diagnosis (high risk disease) continued to predict a worse outcome with this regimen. The Italian and German cooperative groups (GIMEMA-SAL-AMLSG) conducted a Phase III randomized trial (APL0406) of adult patients with standard risk APL comparing ATO/ATRA per the MDACC regimen to the Italian AIDA 2000 regimen. They demonstrated that ATO/ATRA was not inferior to AIDA therapy; patients in the ATO/ATRA arm vs. the AIDA arm achieving CR 97.4% vs. 95% (P = 0.12), 2-year EFS 97% vs. 86.7% (P = 0.03) and 2-year OS 98.7% vs. 91.1% (P = 0.03), respectively.[18,19] This data was recently updated to include outcomes through September 2013 and the EFS for the ATO/ATRA arm remained excellent at 97.5% with 3 events including 1 death in CR and 2 relapses. With this longer follow-up, the relapse rate (RR) is only 2%, which is significantly lower than the RR of 9.5% for patients treated with AIDA chemotherapy (P = 0.048) (presentation by Giuseppi Avvisati, 6th International Symposium on Acute Promyelocytic Leukemia, Rome).

In Australia and New Zealand (Australasian Leukaemia and Lymphoma Group), APL patients with both standard and high risk disease on study APML4 were treated with an Induction regimen including daily ATRA along with 4 doses of idarubicin given on Days 2, 4, 6, and 8 followed by daily ATO on Days 9 - 36. In Consolidation, Cycle 1 included daily ATO and ATRA for 28 days and Cycle 2 included ATO 5 days weekly for 5 weeks and ATRA 7 days on and 7 days off during the 5 weeks. This course was followed by 24 months of Maintenance with ATRA, mercaptopurine and methotrexate. This regimen achieved a 2-year OS of 93.2% and Failure Free Survival (FFS) of 88.1%.[20] Recently updated data including 5-year survival estimates demonstrate continued excellent results with low relapse risk even among patients with high risk disease. For high risk disease, the 5-year OS is 87% and 5-year EFS is 83%. Cumulative incidence of relapse at 5 years was similar between patients with standard risk disease and high risk disease (4.5% and 5.3%, respectively). (Presentation by Harry Iland, 6th International Symposium on Acute Promyelocytic Leukemia, Rome) All survival endpoints were significantly superior in APML4 compared to the prior APML3 trial which did not include ATO (APML3 regimen included ATRA, idarubicin and 2 years of Maintenance chemotherapy).

The therapy on the current study will include ATRA and ATO in Induction and 28 weeks of Consolidation per the same regimen that demonstrated excellent results in adult patients in the MDACC trial and APL0406. In place of gemtuzumab ozogamicin, as used on the

MDACC trial for high risk patients, AAML1331 will include four doses of idarubicin similar to the Induction regimen from APML4, which resulted in a low relapse risk for high risk patients.

2.4 Cardiac Toxicity in APL Therapy

Many APL treatment regimens rely upon high cumulative doses of anthracyclines. It is well known that anthracycline exposure places patients at risk for significant cardiac toxicity.[21,22] The risk increases with higher cumulative doses (especially over 300 mg/m^2), and the risk is higher when children are exposed at a young age.[23] On the European APL93 and APL2000 trials a total of 26 children and 58 adolescents were treated. The treatment regimens included a total of 495 mg/m^2 of daunorubicin. Three children experienced significant cardiac toxicity, including one patient with fatal heart failure during Consolidation, one patient who developed heart failure 6 years after completion of therapy and was managed with medical therapy, and one patient who relapsed and received additional mitoxantrone and auto-transplant prior to developing heart failure requiring a heart transplant.[24] On the AML intergroup C9710 trial, there were 2 deaths attributed to cardiac toxicity among 56 children (personal communication, James Feusner, MD).

A goal of AAML1331 is to further improve long-term outcomes and quality of life for survivors of childhood APL. For standard risk patients, no anthracyclines will be used in their treatment. For high risk patients, the cumulative dose of anthracycline will be reduced to 48 mg/m^2 of idarubicin (approximately 192 mg/m^2 daunorubicin equivalents). The current study will include repeated cycles of ATO, which is known to prolong the QTc during treatment. On the recently closed AAML0631, children received ten weeks of ATO (given as two courses of five weeks each) and QTc prolongation was monitored closely on the trial. Twenty four patients had prolonged QTc during their ATO cycles, but all were Grade 1 or 2, transient, and did not require dose adjustment.[7]

2.5 Rationale for Elimination of Chemotherapy Maintenance Cycles

The role of Maintenance chemotherapy in APL has been tested in several studies with variable results. Two recent randomized studies failed to demonstrate a significant benefit for the addition of Maintenance. The AIDA 0493 trial initially randomized patients to 4 Maintenance arms including mercaptopurine and methotrexate (6MP/MTX), ATRA alone, 6MP/MTX alternating with ATRA, or observation without Maintenance. Early results suggested a benefit to ATRA containing Maintenance prompting amendment of the trial. In long term follow-up, however, there was no difference in the Maintenance arms including the observation only group.[25] Similarly, on the North American Intergroup C9710 study, initial Maintenance arms were ATRA versus observation until the study was amended to compare ATRA versus ATRA plus 6MP/MTX, based in part on the early immature results of AIDA 0493. Among the 50 patients enrolled prior to amendment, there was no difference in observation versus ATRA Maintenance. Long term follow-up has shown no difference in outcomes for ATRA versus ATRA plus 6MP/MTX for patients receiving ATO Consolidation.[26]

The excellent results reported for adult patients in the MDACC trial and for standard risk patients on the APL0406 trial were attained using ATO/ATRA Induction followed by 28 weeks of Consolidation without additional Maintenance cycles. The current study uses the same schedule without Maintenance. For high risk patients, the APML4 regimen

resulted in a low relapse risk using idarubicin in Induction, two Consolidation cycles with ATO and 24 months of low dose oral chemotherapy Maintenance. The data from AIDA 0493 and C9710 suggest that Maintenance chemotherapy may not improve survival, and the latter study indicates that this is particularly true when ATO Consolidation is included. The current study will use idarubicin in Induction similar to APML4. However, rather than Maintenance chemotherapy, Consolidation will be extended to 28 weeks including a total of 16 weeks of post-Induction ATO versus 9 weeks of post-Induction ATO administrations in APML4.

2.6 Risk Stratification Based on WBC

The risk criteria first published by Miguel Sanz based on WBC and platelet counts have proven to be predictive in pediatric patients.[6] Standard risk disease (including both low and intermediate risk groups by Sanz criteria) includes patients with an initial WBC < 10,000 at diagnosis. High risk disease includes patients with WBC ≥ 10,000. On the AIDA 0493 study, pediatric patients with high risk disease had a worse EFS compared to those with standard risk disease. Early Induction deaths due to differentiation syndrome and coagulopathy occur more frequently in patients with high risk disease. The risk of relapse is also higher in patients with high risk disease. In this trial, therapy for high risk APL will differ from standard risk APL in that it will include 4 doses of idarubicin early in Induction. The goal of idarubicin for patients with high risk disease is to decrease risk of relapse as well as to decrease the white blood cell count (due to the associated early complications seen with uncontrolled leukocytosis).

2.7 Differentiation Syndrome Prophylaxis and Treatment

Steroid prophylaxis has been incorporated into APL trials to prevent the development of APL differentiation syndrome (DS), a potentially fatal complication of APL treatment. Both ATRA and ATO are differentiating agents in APL treatment, and when used together in Induction therapy there is potential for significant DS symptoms, especially in high risk patients. Therefore, prednisone was used as prophylaxis in all patients on the Australasian study, APML4, on Days 1 - 10 of Induction, as well as on the Italian-German study, APL0406, on Day 1 through the end of Induction. Patients on these studies who developed symptoms of DS were treated with dexamethasone. There were no deaths due to DS of 124 patients treated on APML4 versus 4 deaths due to DS of 101 treated patients in APML3. On APL0406 there were no deaths due to DS on the ATO/ATRA arm and 2 DS related deaths on the AIDA chemotherapy arm (out of 156 treated patients all of whom were standard risk). In this trial, patients who developed symptoms of DS were switched to dexamethasone IV. While 47% of patients developed leukocytosis (WBC > 10,000) during Induction therapy, all these patients were successfully managed with protocol specified hydroxyurea for therapy-induced leukocytosis. On the Spanish PETHEMA study, LPA99, prednisone prophylaxis was also given to all patients on Days 1 - 15 of Induction. On the subsequent study LPA2005, dexamethasone was given Days 1 - 15 at 2.5 mg/m^2 twice daily to patients with WBC > 5,000/µL. This approach resulted in similar rates of severe and moderate DS (24% on LPA99 vs. 28% on LPA2005, P = 0.12) and similar low rates of death (1.4% on LPA99 vs. 1.0% on LPA2005, P = 0.55).[27]

On the current study, high risk patients will receive DS prophylaxis with dexamethasone 2.5 mg/m^2/dose PO or IV, twice daily for 14 days. For patients with standard risk APL, if the WBC count rises above 10,000/µL during Induction, hydroxyurea and dexamethasone prophylaxis will be started to control the leukocytosis and reduce the risk of DS. Guidelines

for the management of DS are provided for those patients who develop symptoms of DS (see Section 5.1).

2.8 CNS Directed Therapy in APL

The incidence of CNS relapse in APL is low. The PETHEMA trials LPA96 and LPA99 did not include CNS prophylaxis and demonstrated a 1.1% 3-year incidence of CNS relapse.[28] A literature review of pediatric APL patients found a < 1% incidence of isolated CNS relapse in pediatric patients with standard risk APL who were treated without CNS prophylaxis.[29] Regimens with single agent ATO (including studies in India and Iran) and combined ATO and ATRA (including the MDACC trial, APML4 and APL0406) have all achieved low CNS relapse rates without use of prophylactic intrathecal chemotherapy. ATO is able to cross the blood brain barrier with CSF levels up to 50% of serum levels[30]. These data indicate that there is no role for prophylactic intrathecal chemotherapy in the majority of APL patients. However, a specific group of patients at risk for CNS relapse was identified on PETHEMA studies in Spain. CNS hemorrhage in Induction, which was a rare event with incidence of 2.7%, was a significant risk factor for CNS relapse (5-year cumulative incidence of CNS relapse of 18.7%).[28]

Prophylactic intrathecal chemotherapy will not be used on the current study with the exception of patients with a documented CNS bleed. These rare patients will receive triple intrathecal chemotherapy at the end of Induction and every 4 weeks during Consolidation for 6 doses as prophylaxis against CNS relapse. Patients with CNS symptoms concerning for CNS disease will have a lumbar puncture performed once coagulopathy is resolved. If a patient has CNS disease, the recommended treatment will include twice-weekly triple intrathecal chemotherapy until the CSF is cleared plus two additional twice-weekly treatments. Following the twice-weekly treatments, these patients with documented CNS disease will have additional triple intrathecal chemotherapy every 4 weeks during Consolidation on the same schedule as for patients with a CNS bleed.

Data from patients with CNS relapse APL suggests that triple intrathecal therapy (ITT) is effective for treatment of CNS disease.[28,31,32] There is little data about the efficacy of IT cytarabine alone in the treatment of APL CNS disease. Thus the current study will utilize ITT with dosing similar to that used on the CCG 2961 study for AML patients. During Induction for patients with CNS disease receiving twice weekly treatments, a dose of leucovorin will be given 24 hours after each ITT treatment to prevent systemic myelosuppressive effects of repeated methotrexate dosing.

2.9 PCR Monitoring of Bone Marrow

Quantitative RT-PCR (RQ-PCR) provides several advantages in the diagnosis of APL by providing a very sensitive and specific diagnostic test that establishes the breakpoint specific transcript for monitoring for persistent MRD or for surveillance to detect relapse. A panel of primers that covers the various breakpoints in the PML-RARα fusion gene transcript is used. An internal housekeeping gene, used to standardize the transcript level and determine the quality of the RNA, decreases false negative results.[33] Thus, PCR testing has become the "gold standard" for confirmation of the diagnosis of APL.[34] PCR testing can confirm the presence of the PML-RARα fusion gene and distinguishes this common type of APL from other rare variants (e.g., PLZF-RARα) that may not respond to ATRA treatment and should not be included on clinical trials utilizing ATRA as an essential component of therapy. The PCR testing is a very sensitive assay for detection of the

PML-RARα fusion gene transcript, which allows for detection of MRD and molecular relapse (the latter is recurrent disease detected by PCR prior to signs of full hematologic relapse).

MRD may be detected as a persistently positive PCR result during therapy. With chemotherapy, persistent PCR positive disease at the end of Consolidation (prior to Maintenance therapy) has been correlated with high risk of relapse.[33,35] On the COG study AAML0631, if a patient with standard risk disease was PCR positive at end of Consolidation Course 3, they received an additional course of Consolidation. However, no standard risk patient met this protocol specified criteria (personal communication, John Gregory, MD). Using an ATO/ATRA regimen that included 4 ATO Consolidation cycles, the MDACC trial included a recommendation for additional doses of gemtuzumab ozogamicin for patients with persistent PCR positive disease after 2 ATO Consolidation cycles. However, similar to the COG study, all patients were PCR negative at that time point on the trial.[16] Thus we would expect it to be rare for a patient on the current study to have PCR positive disease at Day 43 of Consolidation Cycle 2. In the unlikely event a patient has persistent disease at this time point, the proposed protocol specifies a course of mitoxantrone and high dose cytarabine (MA). The MA course has been used on recent (MRC-based) COG studies for AML patients. In the current AAML1031 study, this cycle is used as a second Induction course for patients who remain MRD positive at the end of the first Induction. Patients who remain PCR positive after the MA course will be taken off protocol therapy.

In the case of relapse, studies have demonstrated an advantage to detecting the disease at the molecular stage in bone marrow rather than at the later stage of overt hematologic relapse.[36,37] Greater disease burden carries increased risk for the potentially fatal complications of coagulopathy and differentiation syndrome. The sensitivity of RQ-PCR allows early detection of relapse, and it has been demonstrated that PCR positive disease (that has been confirmed with at least two tests) will invariably present as hematologic relapse in the absence of a therapeutic intervention.[38,39] Based on the sensitivity of RQ-PCR and the kinetics of the rise of PML-RARα transcripts during relapse, PCR testing on bone marrow samples is usually performed every 3 months.[40,41] RQ-PCR testing detects disease at a sensitivity of 1 in 10^4 cells in bone marrow, and the kinetics of relapse disease progression showed a median of 1.1 log fold increase in RQ-PCR transcript per month.[40] Thus, an interval of 3 months between testing generally allows detection of molecular relapse without sufficient time for the disease to progress to hematologic relapse between testing time points. This monitoring is continued for 2 - 3 years following Consolidation therapy since most patients relapse during this period. However, these serial bone marrow evaluations usually require sedation for pediatric patients. The cost and risks of these sedated procedures must be balanced with the benefit of such monitoring. With the ATO/ATRA regimen the risk of relapse for standard risk patients is expected to be very low. Thus the benefit of such post-therapy monitoring is likely outweighed by the risk and costs of the procedure. However, the relapse risk is greater in high risk patients, therefore, monitoring with serial bone marrow RQ-PCR testing every 3 months until 3 years from diagnosis is strongly recommended in the high risk cohort.

2.10 Correlative Studies

2.10.1 FLT3 Mutations in Pediatric APL

The purpose of this study is to test the hypothesis that FLT3 mutations in pediatric APL are prognostic markers.

Analysis of an exploratory cohort of patients from prior COG studies has shown that 40% of pediatric APL patients have FLT3-ITD or FLT3-ALM.[42] This analysis also demonstrated that patients with FLT3 mutations (either FLT3-ITD or FLT3-ALM) were at increased risk of early death. In the current study, we will determine FLT3 mutation status and correlate this with patient characteristics (such as presenting WBC, coagulation study parameters, and APL M3v subtype), patient outcomes (including early death, EFS, DFS and OS), and in select cases assessments of pathway activation using phosphoflow. These analyses will provide important information for potential future trials examining FLT3 inhibitors in APL treatment.

2.10.2 Bone marrow and Peripheral Blood Minimal Residual Disease Testing in Pediatric APL

This study will test the hypothesis that RQ-PCR test results (either in bone marrow or peripheral blood) following an ATO based Induction can be prognostic for treatment outcome.

RQ-PCR for PML-RARα is used to monitor response to therapy and for post therapy (molecular) relapse. At defined time points during treatment, bone marrow testing by RQ-PCR will determine if patients will receive an additional molecularly refractory treatment course. This study will investigate additional research time points for peripheral blood (PB) RQ-PCR and bone marrow (BM) RQ-PCR to analyze whether the rate of clearance of BM and/or PB RQ-PCR while on therapy can predict risk for relapse.

In both pediatric ALL and AML, MRD at end of Induction therapy has proven to be one of the most important prognostic markers for outcome. In APL, PCR for the PML-RARα transcript is more sensitive than flow-based MRD. The PML-RARα PCR may remain positive at the end of Induction due to persistence of maturing myelocytes. A significant percentage of patients may have PCR detectable disease while at the same time having entered a morphologic remission. Therefore, this study will use hematologic complete remission as the criteria to move onto Consolidation therapy (the same as utilized in the model studies at MDACC and APL0406). Most patients who are PCR positive at end Induction will go onto achieve durable molecular remissions, and thus a positive test is not a specific marker of relapse risk. Earlier studies (not utilizing ATO therapy) suggested that the end Induction PCR was not prognostic for outcomes.[40,41] However, the use of ATO in Induction may change the kinetics of PML-RARα clearance as assessed by PCR. Indeed there is evidence that a negative or low normalized copy number (NCN) PCR result at end Induction may be a marker for low relapse risk when ATO is used in Induction. In a Chinese study, pediatric patients with high risk APL were treated with ATO and ATRA and those with standard risk disease were treated with ATRA alone or in combination with ATO. One third of patients (34.2%) had end Induction PCR of < 1 NCN. These patients who rapidly achieved molecular remission had a 100% DFS at 5 years compared to patients with end Induction PCR > 1 NCN who had DFS of 55.2% (P = 0.018).[43] A report of patients treated with ATO monotherapy in India also demonstrated that negative PCR testing at end Induction was associated with a lower relapse risk.[44] The current study will analyze end Induction PML-RARα PCR values and correlate NCN values with outcomes. The log-fold reduction in NCN from

diagnosis to end Induction will also be correlated with outcomes. Validation of a low NCN for PCR (or a certain log fold reduction) as a marker of low relapse risk could allow use of this response criteria in future studies to identify patients who could benefit from further treatment reductions and decreased relapse monitoring.

2.10.3 Early Death and Coagulopathy Complications in Pediatric APL

This study will test the hypothesis that a biomarker (elevation in thrombomodulin level) used alone or in combination with a clinical predictive score (the International Society on Thrombosis and Haemostasis (ISTH) DIC score), will correlate with bleeding and clotting events during Induction therapy of APL. Our specific aim is to compare sensitivity and specificity of thrombomodulin levels along with the ISTH DIC score in predicting Grade 3 or higher episodes of hemorrhage or thrombosis from diagnosis through end of Induction. Additionally we will test the hypothesis that global coagulation test results (thrombin generation parameters, fibrinolytic parameters, microparticles levels) used alone or in a stepwise combination with the ISTH DIC score and thrombomodulin levels will improve identification of APL patients at risk for adverse events of hemorrhage or thrombosis.

Early deaths and morbidity due to coagulopathy (both hemorrhage and thrombosis) remain a significant problem in APL.[45,46] The coagulopathy of APL is unique as there is activation of the coagulation cascade (due to expression of tissue factor and other procoagulants) with concomitant increase in primary and secondary fibrinolysis due to expression of annexin II on the APL blasts. Additionally, due to the secretion of various cytokines, there is increased vascular fragility. The exact outcome depends on the net balance between these mechanisms.

Some studies have shown that various clinical (low performance status) and laboratory parameters (elevated WBC count at presentation, low platelet count, or low fibrinogen level with elevation in PT) are able to predict those APL patients at higher risk for hemorrhagic complications.[47] The ISTH DIC score was developed in order to offer a standard approach with objective criteria for the diagnosis and severity of DIC. A score of ≥ 5 is correlated with overt DIC[48]. In one retrospective study an ISTH DIC score of ≥ 6 independently correlated with an increased risk of hemorrhagic early death.[49] We calculated the ISTH DIC score for patients enrolled in the AAML0631 study. Complete data for coagulation parameters (PT, fibrinogen level, D-Dimer levels) and clinically significant bleeding or thrombosis (Grade 3 or higher) during Induction were available for 76 of 102 patients. Amongst the 31 patients with an ISTH DIC score ≥ 6 there were 10 clinical adverse effects related to coagulopathy (including four early deaths) and amongst the 45 patients with an ISTH DIC score < 6, there were 4 clinical adverse effects related to coagulopathy (no deaths). The sensitivity of the ISTH DIC score in predicting coagulopathy events during Induction was only 66.7% and the specificity was 65.6% further underscoring the fact that although the ISTH DIC score may be valuable in predicting early hemorrhagic death, it has inherent limitations in identifying pediatric APL patients at risk for serious hemorrhage and thrombosis.

Traditional coagulation tests such as PT, aPTT and fibrinogen levels (as are used to calculate the ISTH DIC score) are limited as they cannot measure the unique contribution of fibrinolysis or the balance between procoagulation and fibrinolysis.

To implement specific interventions that prevent these serious events improved biomarkers are needed to accurately predict patients at risk for coagulopathy and differentiate patients at risk for either bleeding or thrombosis. Recently, measurement of soluble thrombomodulin (sTM) levels has been used for risk stratification and prognostic evaluation of septic patients with coagulopathy.[50,51] Also, recent advances in global coagulation assays that assess thrombin generation and measure the fibrinolytic potential of blood may be of additional benefit in identifying patients at risk for coagulopathy.

This study will determine the incidence of clinically significant bleeding and clotting events (defined as Grade 3 or higher) in pediatric and young adult patients receiving both ATRA and ATO in Induction. Data on APL related coagulopathy will be collected including results of local coagulation studies as well as central testing of soluble thrombomodulin levels, fibrinolytic parameters by the Clot Formation and Lysis (CloFAL assay), thrombin generation and APL associated microparticles. These data may provide a method to identify patients most at risk for lethal complications and also provide a framework on which to test novel interventions for control or prevention of coagulopathy (including investigational agents such as recombinant thrombomodulin) in future studies.

2.10.4 Neurocognitive Outcomes in Pediatric APL Treatment

The purpose of this correlative study, which is optional for subjects, is to longitudinally monitor cognitive side effects associated with this treatment.

Arsenic can enter the brain and have toxic effects on the central nervous system (CNS).[52] Chronic arsenic exposures via drinking water or industrial sources have been widely reported to be associated with impaired neurocognitive function in children.[53-59] However, little is known about the CNS effects of arsenic administration when used at therapeutic doses for the treatment of APL. There are case reports in adults suggesting that short-term exposure to high concentrations of arsenic can alter the verbal learning and memory, cause confusion and visual sensations, and adversely affect learning, memory and concentration.[60-63] Arsenic trioxide has been administered safely to children and adolescents with relapsed as well as newly diagnosed APL. Reports from studies in India, China and Australia/New Zealand have not noted any overt arsenic-related CNS toxicities in their pediatric populations.[11,14,20,64,65] Also, no significant CNS toxicity has been attributed to the arsenic containing Consolidation cycles on COG AAML0631 (personal communication John Gregory, MD). However, no research has been done using more sensitive and specific neurocognitive testing batteries to study the short-term and long-term neurocognitive impact in children with APL who are exposed to arsenic.

In most epidemiological studies, arsenic concentrations in drinking water between 100 µg – 300 µg/L will cause a significant neurocognitive delay in school aged children.[59] This concentration is roughly correlated with a blood arsenic concentration of 10 µg/L.[66] Since all the epidemiological studies published are cross sectional, the length of time required to develop neurocognitive delay at this concentration is unclear. In the Phase I pediatric clinical trial using arsenic at 0.15 mg/kg per dose, daily, as single agent, the median plasma arsenic maximum concentration was 0.28 µM (56 µg/L).[67] In the current study, all children with newly diagnosed APL will be treated with ATO at 0.15 mg/kg dose daily for a

minimum of 20 weeks. This is comparable arsenic exposure to previous APL studies. Since > 95% children are expected to have long-term survival, it is important to study the neurocognitive impact of arsenic exposure on the developing brain in these children.

To evaluate neurocognitive functioning in children receiving ATO treatment for APL, we will use a brief battery of computerized tasks (patient-completed) and behavioral ratings (parent-completed) administered at two time points during treatment and three times following treatment, as well as a short battery of traditional performance-based measures administered at three time points following treatment completion.

The primary goal of this exploratory aim is to evaluate the neurocognitive outcomes of patients treated on this protocol using patient-completed, performance-based measures of neuropsychological functioning and parent questionnaire reports. Declines in neurocognitive functioning will be measured by CogState, BRIEF, and a psychologist-administered battery of tests in children with ATO-treated APL, as defined by a clinically meaningful decrease in mean scores apparent at 2 years off therapy in the following domains: working memory, executive function, visual motor, processing speed, visual attention, IQ, verbal learning, processing speed, and adaptive functioning.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*. At this time, however, enrollment onto APEC14B1 is NOT a prerequisite to enrollment on AAML1331.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site

registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.4 Timing

Study enrollment must take place within five (5) calendar days of beginning protocol therapy. If enrollment takes place before starting therapy, the date protocol therapy is projected to start must be no later than **five (5)** calendar days after enrollment.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.1.4.1 CLINICAL RQ-PCR Testing

Specimens for RQ-PCR of PML-RARα are required and must be obtained prior to Day 1 of protocol directed therapy (pre-treatment with ATRA allowed). These specimens must be sent to one of the approved labs for PML-RARα RQ-PCR testing but the cost is not covered by the study. It should be billed as a regular clinical lab through the institution/insurance/patient as appropriate. A list of approved labs is available on the protocol-specific web page of the COG website located at https://cogmembers.org/PROT/AAML1331/AAML1331ValidatedRQ-PCRLabsList.pdf

Results of the clinical RQ-PCR testing are not required to be completed prior to enrollment or initiation of therapy, but samples must be collected prior to the initiation of therapy or patient will be taken off study. (For Standard Risk patients see Section 4.2.2 and for High Risk patients see Section 4.8.2 for required studies to be obtained prior to starting protocol therapy.) Prior therapy, per Section 3.2.3, is allowed before drawing samples.

NOTE: This CLINICAL testing is separate from RESEARCH samples submitted for the optional MRD study. Details on the CLINICAL specimens can be found in Section 7.1. Details on the RESEARCH specimens for the optional MRD biology study can be found in Section 15.2. Results of that RESEARCH MRD testing are not returned to sites and do not take the place of the CLINICAL RQ-PCR testing that must occur at diagnosis.

3.1.4.2 Cytogenetics

Specimens for cytogenetics analysis are required and must be obtained prior to therapy initiation. For COG treatment sites, it is strongly recommended that they be sent to a COG-approved institutional cytogenetics laboratory. A listing of these laboratories, as well as methods of attaining COG approval for local cytogenetics laboratories without current COG approval may be found on the COG website.

Results of cytogenetics and FISH are not required to be completed prior to enrollment, but samples must be collected prior to the initiation of therapy.

Cytogenetic and FISH results should be sent to the appropriate central reviewer within 2 weeks from start of therapy. See Section 14 for specimen collection and data submission details.

3.1.5 Emergent Treatment

- A diagnosis of APL is a hematologic emergency and treatment with ATRA should be initiated without waiting for confirmatory genetic testing if there is a clinical suspicion of the diagnosis. Up to 5 days of ATRA pre-treatment, prior to start of protocol directed therapy, is allowed. Of note, if the patient is later determined to have non-APL AML they could remain eligible for the

COG study of non-APL AML (AAML1031) since ATRA pre-treatment is also allowed on AAML1031.

- In patients with standard risk disease (WBC < 10,000/µL), ATRA should be started at time of first suspicion of APL diagnosis and then ATO given (when available) on Day 1 of protocol directed therapy.

- In patients with high risk disease (WBC ≥ 10,000/µL at diagnosis), ATRA should be started at time of first suspicion of APL diagnosis. Idarubicin and ATO should be given on Day 1 of protocol therapy. If an institution does not have ATO available on Day 1 when idarubicin is given, it will not be a protocol violation to start protocol directed therapy with idarubicin and ATRA as long as the ATO is started within 48 hours of the first idarubicin dose.

3.1.6 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study.

3.2 Patient Eligibility Criteria

Important note: **The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.**

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

For Standard Risk patients see Section 4.2.2 and for High Risk patients see Section 4.8.2 for required studies to be obtained prior to starting protocol therapy.

3.2.1 Age

Patient must be ≥ 12 months and < 22 years of age at first diagnosis of APL.

3.2.2 Diagnosis

- Patients must be newly diagnosed with a clinical diagnosis of APL (initially by morphology of bone marrow or peripheral blood).

  Bone marrow is highly preferred but in cases where marrow cannot be obtained at diagnosis, peripheral blood will be accepted.

- If the RQ-PCR results are known at the time of study enrollment, the patient must demonstrate the PML-RARα transcript by RQ-PCR to be eligible.

NOTE: A lumbar puncture is not required in order to be enrolled on study nor are lumbar punctures recommended at the time of diagnosis. If the diagnosis of APL is known or suspected, diagnostic lumbar punctures in patients with neurologic symptoms should be deferred until any coagulopathy is corrected. If CNS disease is suspected or proven, a CT or MRI should be considered to rule out the possibility of an associated chloroma. If CNS disease is documented, patients are still eligible and will receive protocol directed intrathecal treatments.

3.2.3 Prior Therapy

- Patients may receive up to a maximum of 5 days of pre-treatment with ATRA prior to administration of protocol therapy.

- Treatment with hydroxyurea, corticosteroids (any route) and intrathecal cytarabine prior to beginning protocol directed therapy is allowed. However, it should be noted that lumbar puncture and intrathecal therapy at initial diagnosis of APL is not recommended due to the possible complications of coagulopathy.

Please see Section 4.1.3 for concomitant therapy restrictions for patients during treatment.

3.2.4 Exclusion Criteria

3.2.4.1 Secondary APL

Patients with secondary APL are excluded. This includes all patients with APL that may have resulted from prior treatment (chemotherapy or radiation).

3.2.4.2 Isolated Myeloid Sarcoma

Patients with isolated myeloid sarcoma (myeloblastoma, chloroma, including leukemia cutis) but without evidence of APL by bone marrow or peripheral blood morphology are excluded.

3.2.4.3 EKG Abnormalities

- Patients with a pre-existing diagnosis of a prolonged QT syndrome (even if QTc is normal at the time of APL diagnosis) are excluded due to the use of arsenic trioxide, which can prolong the QT interval.

- Patients with a baseline QTc of > 450 msec are excluded. Bazett's formula is to be used for measurement of the corrected QT interval: the QT interval (msec) divided by the square root of the RR interval (msec).

- Patients with a history or presence of significant ventricular or atrial tachyarrhythmia are excluded.

- Patients with right bundle branch block plus left anterior hemiblock, bifascicular block are excluded.

3.2.4.4 Renal Dysfunction

Patients with serum creatinine > 3.0 mg/dL and patients on active dialysis for renal dysfunction are excluded.

3.2.4.5 Prior Chemotherapy

Patients who have received treatment with any other cytotoxic chemotherapy prior to beginning protocol therapy (other than allowed in Section 3.2.3) are excluded.

3.2.4.6 Pregnancy and Breast Feeding

3.2.4.6.1 Female patients who are pregnant are excluded. Treatment under this protocol would expose an unborn child to significant risks. Patients should not be pregnant or plan to become pregnant while on treatment. **There is an extremely high risk of fetal malformation if pregnancy occurs while on ATRA in any amount, even for short periods.**

A pregnancy test prior to enrollment is required for female patients of childbearing potential.

3.2.4.6.2 Lactating females who plan to breastfeed their infants are excluded.

3.2.4.6.3 Sexually active patients of reproductive potential who have not agreed to be abstinent or use 2 forms of effective contraception during treatment through 1 month off therapy are excluded.

3.2.5 Regulatory Requirements

3.2.5.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.5.2 All institutional, FDA, and NCI requirements for human studies must be met.

3.3 Definitions

3.3.1 Initial CBC

The first CBC from the COG treating institution.

3.3.2 Standard Risk

Patients with a WBC < 10,000/μL on the initial CBC at diagnosis are defined as standard risk.

3.3.3 High Risk

Patients with a WBC ≥ 10,000/µL on the initial CBC at diagnosis are defined as high risk.

3.3.4 CNS Disease and CNS Bleed

3.3.4.1 CNS disease is defined as:

- Any number of blasts on a cytospin prep in an atraumatic (< 100 RBCs) lumbar puncture.*
- Blasts in a traumatic tap in which the WBC/RBC ratio in the CSF is twice that in the peripheral blood.*
- Clinical signs of CNS leukemia (such as facial nerve palsy or hypothalamic syndrome). Patients with retinal hemorrhage alone do not have CNS leukemia. Patients with documented CNS bleed and with neurologic symptoms that are fully attributable to the CNS bleed do not have CNS leukemia unless they meet one of the other criteria in this section (CSF or chloroma) but these patients do meet criteria for "CNS Bleed". See Section 3.3.4.2 below.
- Radiographic evidence of an intracranial, intradural mass consistent with a chloroma.

*NOTE: For patients who are diagnosed with CNS disease based on blasts in the CSF, we strongly recommend that you contact the COG APL investigator James "Jim" Feusner, MD to discuss central review of the CSF slides. Dr. Feusner can be contacted at jfeusner@mail.cho.org and he will provide shipping information upon contact.

3.3.4.2 CNS Bleed is defined as:

- Any radiographic evidence of hemorrhage into the brain parenchyma, spinal cord or subarachnoid, subdural or epidural spaces.
- Retinal hemorrhage alone is not a CNS bleed.

3.3.4.3 Method of Evaluating Initial Traumatic Lumbar Punctures:

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains blasts, the following algorithm should be used to diagnose CNS disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \quad \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis. Example: CSF WBC = 60/µL; CSF RBC = 1,500/µL; blood WBC = 46,000/µL; blood RBC = 3 X 10^6/µL:

$$\frac{60}{1{,}500} = \mathbf{0.04} \quad \mathbf{> 2X} \quad \frac{46{,}000}{3 \times 10^6} = \mathbf{0.015}$$

4.0 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Treatment on this study will consist of an Induction course to achieve an hCR/hCRi, followed by 28 weeks of Consolidation. There is no randomization in this study. Patients will be stratified into risk groups based on WBC at diagnosis. The standard risk group includes patients with WBC < 10,000/μL, and the high risk group includes patients with WBC ≥ 10,000/μL.

Induction therapy consists of daily arsenic trioxide and twice daily tretinoin for all patients. Patients with high risk APL will also receive 4 doses of idarubicin and prophylaxis dosing of dexamethasone to help prevent differentiation syndrome. All doses of therapy on the protocol should be calculated using actual (not ideal or adjusted) body weight.

Induction will last a minimum of 28 days. Beginning on Day 29 of Induction, patients will have bone marrow testing every 2 weeks as needed to confirm morphologic remission. Induction may last up to a maximum of 70 days. Once in morphologic remission, Consolidation therapy will start a minimum of 14 days after Induction and upon count recovery, whichever occurs later.

Consolidation therapy will be the same for patients with standard risk and high risk APL. Consolidation consists of 28 weeks of therapy including 2 weeks of tretinoin every 4 weeks (7 cycles of tretinoin) and 4 weeks of arsenic trioxide every 8 weeks (4 cycles of arsenic trioxide). After Week 14 of Consolidation (on Day 43 of Cycle 2) there is a bone marrow assessment to determine if patients are in molecular remission (RQ-PCR for PML-RARα). A clinical sample for RQ-PCR must be sent at that time. Patients not in molecular remission will receive an additional cycle of Consolidation chemotherapy (mitoxantrone, cytarabine and tretinoin) and will again be tested for molecular remission. Those patients in molecular remission will proceed with Cycles 3 and 4 of Consolidation therapy. Those patients not in molecular remission will go off protocol therapy.

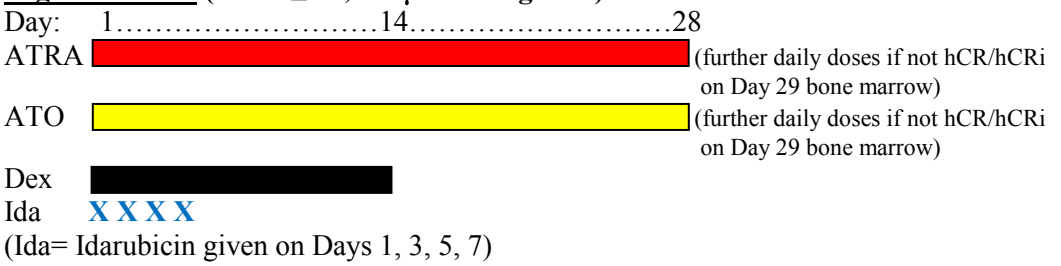
A schematic overview of the treatment plan follows:

ATRA= tretinoin
ATO= arsenic trioxide

Induction:
Standard Risk APL (WBC < 10,000/µL at diagnosis)

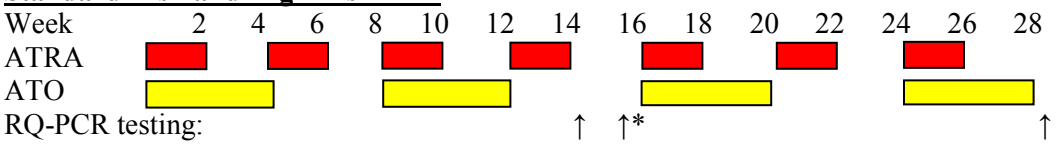
(Hydroxyurea and dexamethasone will be used to control leukocytosis if WBC rises to > 10,000/µL during Induction)

High Risk APL (WBC ≥ 10,000/µL at diagnosis)



(Ida= Idarubicin given on Days 1, 3, 5, 7)

Consolidation:
Standard Risk and High Risk APL



(*Only if Week 14 RQ-PCR of PML-RARα positive, repeat testing in 1-2 weeks. If repeat test is confirmed positive continue to MRD Positive Consolidation)

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

4.1.1 CNS Bleed and CNS Disease

CNS Bleed

Patients with documented CNS bleed will receive CNS prophylaxis to include triple intrathecal chemotherapy on Day 29 of Induction and 6 additional doses during Consolidation.

Note: routine (screening) imaging is not recommended, rather imaging should be performed for neurologic symptoms.

CNS Disease

Patients with CNS disease will receive twice weekly triple intrathecal chemotherapy until the CSF is cleared plus two additional twice weekly treatments during Induction (minimum of 4 and maximum of 6) and 6 additional doses during Consolidation.

Note: Evaluations of CSF for CNS disease at initial APL diagnosis are only to be performed in patients with neurologic symptoms at diagnosis consistent with CNS disease, and the lumbar puncture to investigate this is not to be performed in these patients until APL associated coagulopathy has resolved.

4.1.2 Supportive Care

Hospitalization is strongly recommended for at least the first 2 weeks of Induction (and until all coagulopathy or differentiation syndrome symptoms resolve).

4.1.2.1 Differentiation Syndrome:

For any patient with symptoms of differentiation syndrome, treatment will include dexamethasone. For more details on the diagnosis and management of differentiation syndrome including treatment dosing of dexamethasone, see dose modifications Section 5.1.

4.1.2.2 Coagulopathy

Patients with APL are at risk for life-threatening bleeding and thrombosis. Patients may experience these events despite only mild coagulation lab abnormalities. **During at least the first 7 days of therapy (or longer if needed until coagulopathy resolves),** aggressive blood product support should be employed as follows:

- Maintain platelet count above 50,000/μL. For patients with CNS hemorrhage maintain the platelet count above 100,000/μL until bleeding stable, coagulopathy improved and a minimum of 7 days from diagnosis of the bleed.
- Obtain stat CT scan of the head for any patient with neurologic symptoms consistent with possible intracranial bleed. If CNS bleed present, consider neurosurgery consultation for help in management.
- Transfuse cryoprecipitate to maintain fibrinogen above 150 mg/dL
- Transfuse fresh frozen plasma to maintain PT and PTT within normal range.
- Routine use of heparin or anti-fibrinolytics is not recommended.

4.1.2.3 Other Recommendations

i. Leukopheresis should be avoided, if possible, due to the concern of worsening of bleeding secondary to release of procoagulant substances during cell trauma of the procedure. Pre-treatment with hydroxyurea is allowed on this protocol (see Section 3.2.3).

ii. Routine use of prophylaxis against pneumocystis pneumonia is not necessary with this regimen.

iii. Growth factors such as GCSF, GMCSF and erythropoietin are not to be used routinely.

For COG Supportive Care Guidelines see:
https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines
under Standard Sections for Protocols.

4.1.3 Concomitant Therapy

An extensive number of medications have been reported to prolong the QTc interval that could potentially exacerbate the effect of ATO on the QTc interval. Caution should be taken when using any medications concomitantly with ATO. Since this list of medications can potentially change during the time this protocol is active, please refer to the following reference website for a current and complete list:
https://www.crediblemeds.org/everyone/composite-list-all-qtdrugs/

These medications should be avoided during ATO therapy if other options exist. If these agents are used, they should be discontinued in any patient with normal serum electrolytes, calcium and magnesium who is found to have a QTc > 500 msec. Forty-eight hours after discontinuation of the agent, if the QTc remains > 500 msec or the patient is unable to discontinue these medications, the ATO must be discontinued.

Azole antifungal medications may increase ATRA toxicity due to inhibition of cytochrome P-450 metabolism of ATRA, and thus toxicities (including pseudotumor cerebri and renal dysfunction) should be monitored closely during concomitant use.

4.2 Induction – Standard Risk APL

4.2.1a Induction Therapy Delivery Map – Standard Risk APL

Standard Risk APL is defined as WBC < 10,000/μL at diagnosis.

_____ Patient COG ID number _____ DOB

Induction lasts a minimum of 28 days and a maximum of 70 days See Section 4.2.3 for treatment details. This TDM is on 3 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 28 minimum. Continue up to Day 70 if not in hCR/hCRi.	**Total Dose:** 25 mg/m^2/day divided twice daily Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV daily over 2 hours*	0.15 mg/**kg**/day	1 - 28 minimum. Continue up to Day 70 if not in hCR/hCRi.	*May lengthen infusion to 4 hours if active vasomotor symptoms occur.
Triple Intrathecal Therapy (ITT) Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age / MTX / HC / ARAC 1-1.99 yrs / 8 mg / 15 mg / 30 mg 2-2.99 yrs / 10 mg / 25 mg / 50 mg ≥ 3 yrs / 12 mg / 35 mg / 70 mg	**If CNS Disease:** Twice weekly until CSF cleared plus 2 additional twice weekly treatments (minimum of 4 and maximum of 6 treatments) **If CNS Bleed:** Day 29 only	Only patients with CNS disease or CNS bleed will require intrathecal treatments (see Sections 3.3.4 and 4.2.3 for details).
Leucovorin (LCV)	PO/IV	10 mg/m^2/dose	**CNS Disease ONLY:** Leucovorin should be given 24 hours after IT methotrexate.	

Ht _____cm **Wt _____kg** **BSA _____m^2**

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations.

Date Due	Date Given	Day	ATRA mg mg	ATO mg	ITT mg (MTX) mg (HC) mg (ARAC)	LCV mg	Studies
			Enter calculated dose above and actual dose administered below				
		1	_____mg _____mg	____mg	***Only for patients with CNS disease (not CNS Bleed)*** *give ITT twice weekly as directed (see Section 4.2.3 for details).* ***Caution:*** *Most patients will not need intrathecal treatment. Lumbar puncture is recommended only for patients with neurologic symptoms consistent with CNS disease and should not be performed until coagulopathy resolves.*		a-r*, s*, t*
		2	_____mg _____mg	____mg			f, h, l
		3	_____mg _____mg	____mg			f, h, l
		4	_____mg _____mg	____mg			f, h, l
		5	_____mg _____mg	____mg			f, h, l
		6	_____mg _____mg	____mg			f, h, l
		7	_____mg _____mg	____mg	Date CNS disease diagnosed: _____		f, h, l
		8	_____mg _____mg	____mg	Date Given: _____		b, f, h, j, l, m, t*
		9	_____mg _____mg	____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)		
		10	_____mg _____mg	____mg		_____mg	
		11	_____mg _____mg	____mg	Date Given: _____		
		12	_____mg _____mg	____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)		
		13	_____mg _____mg	____mg			
		14	_____mg _____mg	____mg		_____mg	
		15	_____mg _____mg	____mg	Date Given: _____		b, f, h, j, l, m, t*
		16	_____mg _____mg	____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)		
		17	_____mg _____mg	____mg			
		18	_____mg _____mg	____mg	Date Given: _____	_____mg	
		19	_____mg _____mg	____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)		
		20	_____mg _____mg	____mg			
		21	_____mg _____mg	____mg		_____mg	
		22	_____mg _____mg	____mg	Date Given: _____		b, f, h, j m
		23	_____mg _____mg	____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)		
		24	_____mg _____mg	____mg			
		25	_____mg _____mg	____mg	Date Given: _____	_____mg	
		26	_____mg _____mg	____mg			
		27	_____mg _____mg	____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)		
		28	_____mg _____mg	____mg		_____mg	
		29	*A bone marrow evaluation is performed on Day 29. If hCR/hCRi is achieved, proceed to Consolidation (see Section 4.3). If hCR/hCRi is not achieved on Day 29, continue with Induction (see Page 2 of this TDM). A bone marrow evaluation is done every 2 weeks until hCR/hCRi is achieved. When hCR/hCRi is achieved, proceed to Consolidation (see Section 4.3).* _____mg _____mg	____mg	***Day 29: Only for Patients with CNS Bleed (not CNS Disease):*** mg (MTX) _____mg (HC) _____mg (ARAC)		b, c, f, h, j, l, m, o, s*, t*

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Induction – Standard Risk

4.2.1b Induction Therapy Delivery Map Continued – Standard Risk APL

Standard Risk APL is defined as WBC < 10,000/μL at diagnosis.

Patient COG ID number _____ DOB _____

Induction lasts a minimum of 28 days and a maximum of 70 days See Section 4.2.3 for treatment details. This TDM is on 3 pages

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 28 minimum. Continue up to Day 70 if not in hCR/hCRi.	**Total Dose:** 25 mg/m^2/day divided, twice daily Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV daily over 2 hours*	0.15 mg/**kg**/day	1 - 28 minimum. Continue up to Day 70 if not in hCR/hCRi.	*May lengthen infusion to 4 hours if active vasomotor symptoms occur.
Triple Intrathecal Therapy (ITT) Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age / MTX / HC / ARAC 1-1.99 yrs / 8 mg / 15 mg / 30 mg 2-2.99 yrs / 10 mg / 25 mg / 50 mg ≥ 3 yrs / 12 mg / 35 mg / 70 mg	**If CNS Disease:** Twice weekly until CSF cleared plus 2 additional twice weekly treatments (minimum of 4 and maximum of 6 treatments). **If CNS Bleed:** Day 29 only	Only patients with CNS disease or CNS bleed will require intrathecal treatments (see Sections 3.3.4 and 4.2.3 for details).
Leucovorin (LCV)	PO/IV	10 mg/m^2/dose	**CNS Disease ONLY:** Leucovorin should be given 24 hours after IT methotrexate.	

Ht _____cm **Wt _____kg** **BSA _____m^2**

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations.

Date Due	Date Given	Day	ATRA mg / mg	ATO mg	ITT mg (MTX) / mg (HC) / mg (ARAC)	LCV mg	Studies
			Enter calculated dose above and actual dose administered below				
		30	_____mg _____mg	_____mg			
		31	_____mg _____mg	_____mg			
		32	_____mg _____mg	_____mg			
		33	_____mg _____mg	_____mg			
		34	_____mg _____mg	_____mg			
		35	_____mg _____mg	_____mg			
		36	_____mg _____mg	_____mg			b, f, h, j, m
		37	_____mg _____mg	_____mg			
		38	_____mg _____mg	_____mg			
		39	_____mg _____mg	_____mg	***Only for patients with CNS disease (not CNS Bleed)*** *give ITT twice weekly as directed (see Section 4.2.3 for details).*		
		40	_____mg _____mg	_____mg			
		41	_____mg _____mg	_____mg			
		42	_____mg _____mg	_____mg			
		43	_____mg _____mg	_____mg			b, f, h, j, m, o
		44	_____mg _____mg	_____mg	***Caution:*** *Most patients will not need intrathecal treatment. Lumbar puncture is recommended only for patients with neurologic symptoms consistent with CNS disease and should not be performed until coagulopathy resolves.*		
		45	_____mg _____mg	_____mg			
		46	_____mg _____mg	_____mg			
		47	_____mg _____mg	_____mg			
		48	_____mg _____mg	_____mg			
		49	_____mg _____mg	_____mg			
		50	_____mg _____mg	_____mg			b, f, h, j, m
		51	_____mg _____mg	_____mg			
		52	_____mg _____mg	_____mg			
		53	_____mg _____mg	_____mg			
		54	_____mg _____mg	_____mg			
		55	_____mg _____mg	_____mg	**NOTE: A MAXIMUM OF 6 TREATMENTS OF INTRATHECAL THERAPY SHOULD BE ADMINISTERED DURING INDUCTION**		
		56	_____mg _____mg	_____mg			
		57	_____mg _____mg	_____mg			b, c, f, h, j, m, o
		58	_____mg _____mg	_____mg			
		59	_____mg _____mg	_____mg	**ALL DOSES WILL BE RECORDED ON PAGE 1 OF THIS TDM.**		
		60	_____mg _____mg	_____mg			
		61	_____mg _____mg	_____mg			
		62	_____mg _____mg	_____mg			
		63	_____mg _____mg	_____mg			
		64	_____mg _____mg	_____mg			b, f, h, j, m
		65	_____mg _____mg	_____mg			
		66	_____mg _____mg	_____mg			
		67	_____mg _____mg	_____mg			
		68	_____mg _____mg	_____mg			
		69	_____mg _____mg	_____mg			
		70	_____mg _____mg	_____mg			o
			A bone marrow evaluation is done every 2 weeks until hCR/hCRi is achieved. When hCR/hCRi is achieved, proceed to Consolidation (see Section 4.3). If hCR/hCRi is not achieved by Day 70, patient will go off protocol therapy.				

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.2.2 Required Observations in Induction – Standard Risk APL

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. Obtain other studies during Induction as indicated.

a. History
b. Physical Exam with VS: weekly
c. Ht, Wt, BSA: Days 1, 29 and 57
d. Performance status
e. Pregnancy test: Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.
f. CBC, differential, platelets: daily during Week 1, then at least once weekly
g. Urinalysis
h. Electrolytes including Ca^{++}, Mg^{++}, K^{+} and creatinine: daily during Week 1, then at least once weekly
i. Uric Acid
j. AST, ALT, Total Bilirubin (and Direct Bilirubin if Total Bilirubin is >2 mg/dL): Once weekly
k. Cholesterol triglycerides
l. PT, PTT, fibrinogen, D-Dimer: daily during Week 1, then on Days 8, 15 and 29 (more frequently if needed for active coagulopathy)
m. ECG for QTc monitoring: Weekly
n. Echocardiogram or MUGA
o. BMA for morphology: At diagnosis and Day 29 and every 2 weeks thereafter as needed until hCR/hCRi
p. BMA for flow cytometry, cytogenetics & FISH: At diagnosis
q. BMA for clinical RQ-PCR of PML-RARα: At diagnosis. This clinical testing is separate from research samples submitted for the optional MRD study; this **mandatory** clinical testing is not free of charge (cost is not covered by the study), but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing; a list of approved labs is available on the protocol-specific web page of the COG website.
r. FLT3 (optional)*: bone marrow (or peripheral blood if bone marrow is unavailable) at diagnosis. See Section 15.1 for details.
s. Research MRD (optional)*: bone marrow and peripheral blood at diagnosis and Day 29 of Induction. See Section 15.2 for details. Results of this research testing will not be returned to sites. This research testing does not take the place of the mandatory RQ-PCR clinical testing that must be done at the time of initial diagnosis (see observation "q" above).
t. Coagulopathy (optional)*: peripheral blood at diagnosis (if available), Day 1, Day 8, Day 15 and Day 29 of Induction. See Section 15.3 for details.

*Only obtain in patients who have consented to participation in this component of the trial.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.2.3 Induction Treatment Details – Standard Risk APL

ATRA should be started at the time of first suspicion of APL diagnosis and ATO given (when available) on Day 1 of protocol directed therapy.

Induction for standard risk APL consists of daily ATO and twice daily ATRA. Induction lasts at least 28 days (ATRA pre-treatment without ATO is not included in the 28 days). A bone marrow evaluation is performed on Day 29. Patients should remain on daily ATO/ATRA therapy while awaiting results of the Day 29 bone marrow hCR/hCRi assessment.

If hCR/hCRi is achieved per the Day 29 bone marrow, patients stop daily induction therapy and proceed to Consolidation. If hCR/hCRi is not achieved, patients continue with Induction up to a maximum of 70 days, and a bone marrow evaluation is done every 2 weeks until hCR/hCRi is achieved. This end Induction determination of hematologic complete response is not dependent on results of genetic testing (such as cytogenetics, FISH or RQ-PCR testing). Patients who appear not to have achieved hematological complete remission after Day 43 of Induction may benefit from consultation for a rapid pathology review beginning with the Day 57 marrow sample (See Section 13 for details).

Induction ends with the confirmation of an hCR/hCRi and after a minimum of 28 days of induction. When hCR/hCRi is achieved the patient proceeds to Consolidation Cycle 1 (see Section 4.3). Following completion of Induction, Consolidation starts a minimum of 14 days from the end of Induction or when blood counts have recovered (ANC ≥ 1,000/μL and platelets ≥ 100,000/μL), whichever occurs later.

Tretinoin (ATRA): PO divided BID
Days: 1 - 28 minimum. Continue beyond Day 28 if not in hCR/hCRi up to a maximum of 70 days (See Section 10.2 for response criteria and definition of hCR/hCRi).
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients). Guidance for administration of tretinoin by parents/caregivers can be found in Appendix III.
Note: If the patient received pre-treatment with ATRA prior to starting Day 1 of protocol directed therapy (see Section 3.2.3), these pre-treatment doses are not considered part of the required 28 days minimum of induction protocol therapy.

Arsenic Trioxide (ATO): IV daily over 2 hours (may lengthen infusion to 4 hours if active vasomotor symptoms occur)
Days: 1 - 28 minimum. Continue beyond Day 28 if not in hCR/hCRi up to a maximum of 70 days (See Section 10.2 for response criteria and definition of hCR/hCRi).
Dose: 0.15 mg/**kg**/day (no maximum dose)

Indications for intrathecal therapy

CNS Bleed
Patients with documented CNS bleed will receive CNS prophylaxis to include triple intrathecal chemotherapy at Day 29 of Induction. See table below for age-based dosing.

CNS Disease
Patients with CNS disease (see Section 3.3.4 for definition) will receive twice weekly triple intrathecal chemotherapy (with a minimum interval of 48 hours between treatments) until the CSF is cleared plus two additional twice weekly treatments (minimum of 4 and maximum of 6 treatments). During Induction, patients with CNS disease will also receive a 10 mg/m^2 dose of leucovorin, 24 hours after each of the twice weekly triple intrathecal therapies.

Age-based dosing of triple intrathecal therapy:

	Triple Intrathecal Therapy (ITT)		
Age	Methotrexate	Hydrocortisone	Cytarabine
1 - 1.99 years	8 mg	15 mg	30 mg
2 - 2.99 years	10 mg	25 mg	50 mg
≥ 3years	12 mg	35 mg	70 mg

4.2.3.1 Management of Leukocytosis during Induction

If the WBC rises above 10,000/µL during the first 28 days of Induction, hydroxyurea and dexamethasone should be started to control the leukocytosis and reduce the risk of differentiation syndrome symptoms. If the patient develops actual symptoms of differentiation syndrome, refer to Section 5.1 for recommendations on diagnosis and management of differentiation syndrome including treatment dosing of dexamethasone. Dosing is as follows:

Dexamethasone:
Days: As needed only if WBC rises above 10,000/µL; discontinue when WBC falls below 10,000/µL.
Dose: 2.5 mg/m^2/dose twice daily PO/IV
Note: This is prophylaxis dosing of dexamethasone.

Hydroxyurea:
Days: As needed only if WBC rises above 10,000/µL; discontinue when WBC falls below 10,000/µL.
Dose:
For WBC ≥ 10,000/µL: 30 mg/**kg**/dose (maximum, 1,000 mg/dose) PO four times daily.

See Section 5.0 for Dose Modifications based on Toxicities.

4.3 Consolidation Cycle 1 – Standard Risk APL

4.3.1 Consolidation Therapy Delivery Map Cycle 1 – Standard Risk APL

Consolidation Cycle 1 starts a minimum of 14 days after end of Induction therapy or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.

_____ Patient COG ID number

_____ DOB

Consolidation Cycle 1 lasts 8 weeks. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 14 and 29-42	**Total Dose:** 25 mg/m^2/day divided twice daily. Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV over 2 hours*	0.15 mg/**kg**/day	1 - 5, 8 - 12, 15 - 19, 22 - 26	*May be extended to 4 hours see Section 4.3.3 for additional details
Triple Intrathecal Therapy (ITT) Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age / MTX / HC / ARAC 1-1.99 yrs: 8 mg / 15 mg / 30 mg 2-2.99 yrs: 10 mg / 25 mg / 50 mg ≥3 yrs: 12 mg / 35 mg / 70 mg	15 and 43	Only patients with documented CNS disease or CNS bleed will require intrathecal treatments (see Sections 3.3.4 and 4.3.3 for details).

Ht _____cm Wt _____kg BSA _____m^2

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations

Date Due	Date Given	Day	ATRA _____mg _____mg	ATO _____mg	ITT _____mg (MTX) _____mg (HC) _____mg (ARAC)	Studies
			Enter calculated dose above and actual dose administered below			
		1	_____mg _____mg	_____mg	***Only patients with CNS disease or CNS bleed will require intrathecal treatments*** *(see Sections 3.3.4 and 4.3.3 for details)*	a – g, h*
		2	_____mg _____mg	_____mg		
		3	_____mg _____mg	_____mg		
		4	_____mg _____mg	_____mg		
		5	_____mg _____mg	_____mg		
		6	_____mg _____mg			
		7	_____mg _____mg			
		8	_____mg _____mg	_____mg		c, d, e, f
		9	_____mg _____mg	_____mg		
		10	_____mg _____mg	_____mg		
		11	_____mg _____mg	_____mg		
		12	_____mg _____mg	_____mg		
		13	_____mg _____mg			
		14	_____mg _____mg			
		15		_____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)	c, d, e, f
		16		_____mg		
		17		_____mg		
		18		_____mg		
		19		_____mg		
		---	---	---		
		22		_____mg		c, d, e, f
		23		_____mg		
		24		_____mg		
		25		_____mg		
		26		_____mg		
		---	---	---		
		29	_____mg _____mg			a, c, e
		---	↓			
		42	_____mg _____mg			
		43			_____mg (MTX) _____mg (HC) _____mg (ARAC)	
		---	---	---		
		56				
		57	*Proceed to Consolidation Cycle 2 (see Section 4.4) on Day 57 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later*			

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Consolidation Cycle 1 – Standard Risk

4.3.2 Required Observations in Consolidation Cycle 1 – Standard Risk APL

a. Physical Exam with VS: Every 4 weeks b. Ht, Wt, BSA c. CBC, differential, platelets: Weekly while receiving ATO and on Day 29. d. Electrolytes including Ca^{++}, Mg^{++}, K^{+} and Creatinine: Weekly while receiving ATO. e. Total bilirubin (and direct bilirubin if total is > 2 mg/dL), AST, ALT: Weekly while receiving ATO and on Day 29. f. ECG for QTc monitoring: Weekly while receiving ATO. g. Cholesterol, triglycerides h. Neurocognitive Testing (optional)*: CogState and BRIEF on Day 1 of Consolidation Cycle 1 (+/- 2 weeks). See Section 16 for details.

*Only obtain in patients who have consented to participation in this component of the trial.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.3.3 Consolidation Cycle 1 Treatment Details – Standard Risk APL

Consolidation Cycle 1 lasts 56 days.

Tretinoin (ATRA): PO divided BID
Days: 1 - 14 and 29 - 42
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients).

Arsenic Trioxide (ATO): IV over 2 hours (may lengthen infusion to 4 hours if active vasomotor symptoms occur)
Days: 1 - 5, 8 - 12, 15 - 19 and 22 - 26
Dose: 0.15 mg/**kg**/day (no maximum dose)

NOTE: Some patients may require infusion in a clinic setting (i.e. unable to arrange home infusion) and holidays may result in intermittent clinic closure. Therefore it is permissible for patients to miss doses of ATO on those days at the discretion of the treating physician. It is suggested that patients not miss more than 2 doses in a 4 week period (10% of doses). If more than 2 doses are missed in a 4 week period due to holidays, then make-up doses (following Day 26) may be administered at the discretion of the treating physician.

Indications for intrathecal therapy

Intrathecal Triple Therapy (ITT): Only for patients with documented history of CNS bleed or CNS positive disease.

Days: 15 and 43
Dose: Age based dosing as follows:

	Triple Intrathecal Therapy (ITT)		
Age	Methotrexate	Hydrocortisone	Cytarabine
1 - 1.99 years	8 mg	15 mg	30 mg
2 - 2.99 years	10 mg	25 mg	50 mg
≥ 3 years	12 mg	35 mg	70 mg

Proceed to Consolidation Cycle 2 on Day 57 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later. See Section 4.4 for details.

4.4 Consolidation Cycle 2 – Standard Risk APL

4.4.1 Consolidation Therapy Delivery Map Cycle 2 – Standard Risk APL

Consolidation Cycle 2 starts on Day 57 of Cycle1 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.

_____ Patient COG ID number _____ DOB

Consolidation Cycle 2 lasts 8 weeks. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m²/dose, twice daily	1 - 14 and 29 - 42	**Total Dose:** 25 mg/m²/day divided twice daily. Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV over 2 hours*	0.15 mg/**kg**/day	1 - 5, 8 - 12, 15 - 19, 22 - 26	*May be extended to 4 hours see Section 4.4.3 for additional details
Triple Intrathecal Therapy (ITT) Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age / MTX / HC / ARAC 1-1.99 yrs: 8 mg / 15 mg / 30 mg 2-2.99 yrs: 10 mg / 25 mg / 50 mg ≥ 3 yrs: 12 mg / 35 mg / 70 mg	15 and 43	Only patients with documented CNS disease or CNS bleed will require intrathecal treatments (see Sections 3.3.4 and 4.4.3 for details).

Ht _____**cm** **Wt** _____**kg** **BSA** _____**m²**

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations

Date Due	Date Given	Day	ATRA _____mg _____mg	ATO _____mg	ITT _____mg (MTX) _____mg (HC) _____mg (ARAC)	Studies
			Enter calculated dose above and actual dose administered below			
		1	_____mg _____mg	_____mg	***Only patients with CNS disease or CNS bleed will require intrathecal treatments*** *(see Sections 3.3.4 and 4.4.3 for details)*	a – g
		2	_____mg _____mg	_____mg		
		3	_____mg _____mg	_____mg		
		4	_____mg _____mg	_____mg		
		5	_____mg _____mg	_____mg		
		6	_____mg _____mg			
		7	_____mg _____mg			
		8	_____mg _____mg	_____mg		c, d, e, f
		9	_____mg _____mg	_____mg		
		10	_____mg _____mg	_____mg		
		11	_____mg _____mg	_____mg		
		12	_____mg _____mg	_____mg		
		13	_____mg _____mg			
		14	_____mg _____mg			
		15		_____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)	c, d, e, f
		16		_____mg		
		17		_____mg		
		18		_____mg		
		19		_____mg		
		---	---	---		
		22		_____mg		c, d, e, f
		23		_____mg		
		24		_____mg		
		25		_____mg		
		26		_____mg		
		27				
		28				
		29	_____mg _____mg			a, c, e
		---	↓			
		42	_____mg _____mg			
		43			_____mg (MTX) _____mg (HC) _____mg (ARAC)	h, i*, j*
		44				
		---	---	---		
		56				
		57	*A bone marrow evaluation is performed for clinical RQ-PCR of PML-RARα on Day 43. If negative continue to Consolidation Cycle 3 (Section 4.6) on Day 57 of this cycle. If positive, repeat 1-2 weeks later. If repeat test is negative continue to Consolidation Cycle 3 (see Section 4.6) on Day 57 of this cycle. If repeat test is confirmed positive continue to MRD Positive Consolidation Cycle (see Section 4.5) on Day 57 of this cycle.*		

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.4.2 Required Observations in Consolidation Cycle 2 – Standard Risk APL

a. Physical Exam with VS: Every 4 weeks
b. Ht, Wt, BSA
c. CBC, differential, platelets: Weekly while receiving ATO and on Day 29.
d. Electrolytes including Ca^{++}, Mg^{++}, K^{+} and creatinine: Weekly while receiving ATO
e. AST, ALT, Total Bilirubin (and Direct Bilirubin if Total Bilirubin is >2 mg/dL): Weekly while receiving ATO and on Day 29.
f. ECG for QTc monitoring: Weekly while receiving ATO
g. Cholesterol, triglycerides
h. BMA for clinical RQ-PCR of PML-RARα: Obtain on Day 43 of Consolidation Cycle 2. This testing is separate from research samples submitted for the optional MRD study; this **mandatory** clinical testing is not free of charge and the cost is not covered by the study, but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing; a list of approved labs is available on the protocol-specific web page of the COG website. If the initial test is positive, contact the study chair and a repeat sample must be sent 1-2 weeks later. This testing is not paid for by the study, but it is recommended that this confirmation sample be sent to either Hematologics, Inc, Seattle, WA, USA or the Molecular Haematology Lab, Royal Prince Alfred Hospital, NSW, Australia due to their experience with these samples.
i. FLT3 (optional)*: bone marrow on Day 43 of Consolidation Cycle 2. See Section 15.1 for details.
j. Research MRD (optional)*: bone marrow and peripheral blood on Day 43 of Consolidation Cycle 2. See Section 15.2 for details. Results of this research testing will not be returned to the sites.

*Only obtain in patients who have consented to participation in this component of the trial.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.4.3 Consolidation Cycle 2 Treatment Details – Standard Risk APL

Consolidation Cycle 2 lasts 56 days.

Tretinoin (ATRA): PO divided BID
Days: 1 - 14 and 29 - 42
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily. Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients).

Arsenic Trioxide (ATO): IV over 2 hours (may lengthen infusion to 4 hours if active vasomotor symptoms occur)
Days: 1 - 5, 8 - 12, 15 - 19 and 22 - 26
Dose: 0.15 mg/**kg**/day (no maximum dose)

NOTE: Some patients may require infusion in a clinic setting (i.e. unable to arrange home infusion) and holidays may result in intermittent clinic closure. Therefore it is permissible for patients to miss doses of ATO on those days at the discretion of the treating physician. It is suggested that patients not miss more than 2 doses in a 4 week period (10% of doses). If more than 2 doses are missed in a 4 week period due to holidays, then make-up doses (following Day 26) may be administered at the discretion of the treating physician.

Indications for intrathecal therapy
Intrathecal Triple Therapy (ITT): Only for patients with documented history of CNS bleed or CNS positive disease.

Days: 15 and 43
Dose: Age based dosing as follows

	Triple Intrathecal Therapy (ITT)		
Age	Methotrexate	Hydrocortisone	Cytarabine
1 - 1.99 years	8 mg	15 mg	30 mg
2 - 2.99 years	10 mg	25 mg	50 mg
≥ 3 years	12 mg	35 mg	70 mg

Disease Evaluation:
A clinical bone marrow evaluation is performed for RQ-PCR of PML-RARα on Day 43. This testing is separate from research samples submitted for the optional MRD study; this mandatory clinical testing is not free of charge (cost is not covered by the study), but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing. A list of approved labs is available on the protocol-specific web page of the COG website. If initial clinical RQ-PCR testing is negative continue to Consolidation Cycle 3 (Section 4.6) on Day 57 of this cycle or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later. If the initial clinical RQ-PCR test is positive, contact the study chair and a repeat sample must be sent 1-2 weeks later. This testing is not paid for by the study, but it is recommended that this confirmation sample be sent to either Hematologics, Inc, Seattle, WA, USA or the Molecular Haematology Lab, Royal Prince Alfred Hospital, NSW, Australia due to their experience with these samples. If repeat test is negative continue to Consolidation Cycle 3 (see Section 4.6) on Day 57 of this cycle. If repeat test is confirmed positive continue to MRD Positive Consolidation (Section 4.5) on Day 57 of this cycle.

MRD Positive Consolidation is only for those patients with RQ-PCR of PML-RARα confirmed positive after Consolidation Cycle 2.

If the RQ-PCR of PML-RARα is negative after Consolidation Cycle 2, proceed to Consolidation Cycle 3 (see Section 4.6)

4.5 MRD Positive Consolidation – Standard Risk APL

4.5.1 MRD Positive Consolidation Therapy Delivery Map – Standard Risk APL

MRD Positive Consolidation is only for those patients with RQ-PCR of PML-RARα confirmed positive after Consolidation Cycle 2. Start on Day 57 of Cycle 2 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.

_____
Patient COG ID number

_____
DOB

This course lasts 28 days. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
High Dose Cytarabine (HD ARAC)	IV over 1-3 hours every 12 hours	1000 mg/m^2/dose, twice daily if BSA < 0.6m^2, 33.3 mg/**kg**/dose, twice daily	1 - 4	Total dose: 2000 mg/m^2/day, divided twice daily **or** 66.6 mg/kg/day, divided twice daily if BSA < 0.6 m^2. Use eye drops as described in Section 4.5.3.
MitoXANtrone (MITOX)	IV daily over 15-30 minutes	12 mg/m^2/dose If BSA < 0.6 m^2, 0.4 mg/**kg**/dose daily	3 – 6	On Days 3 and 4, administer 8 hours after the 5th and 7th cytarabine infusions are completed. See Section 4.5.3 for details.
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 14	**Total Dose:** 25 mg/m^2/day divided twice daily. Administer with food. Refer to Appendix II for dosing table.

Ht _____cm **Wt _____kg** **BSA _____m^2**
Actual body weight (not ideal or adjusted weight) should be used for all dose calculations

Date Due	Date Given	Day	HD ARAC _____mg _____mg	MITOX _____mg	ATRA _____mg _____mg	Studies
			Enter calculated dose above and actual dose administered below			
		1	_____mg _____mg		_____mg _____mg	a – g
		2	_____mg _____mg		_____mg _____mg	
		3	_____mg _____mg	_____mg	_____mg _____mg	
		4	_____mg _____mg	_____mg	_____mg _____mg	
		5		_____mg	_____mg _____mg	
		6		_____mg	_____mg _____mg	
		7			_____mg _____mg	
		8			_____mg _____mg	c, d, e
		9			_____mg _____mg	
		10			_____mg _____mg	
		11			_____mg _____mg	
		12			_____mg _____mg	
		13			_____mg _____mg	
		14			_____mg _____mg	
		15				c, d, e
		16				
		17				
		18				
		19				
		20				
		21				
		22				c, d, e
		23				
		24				
		25				
		26				
		27				
		28				
		29	*A bone marrow evaluation will be done for clinical RQ-PCR of PML-RARα. If negative, continue to Consolidation Cycle 3 (see Section 4.6). If positive in 2 successive specimens, patient will go off protocol therapy.*			a, c, h

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.5.2 Required Observations in MRD Positive Consolidation – Standard Risk APL

a. Physical Exam with VS: every 4 weeks b. Ht, Wt, BSA c. CBC, differential, platelets: Weekly d. Electrolytes and creatinine: Weekly e. AST, ALT, Total Bilirubin (and prior to Mitoxantrone a Direct Bilirubin if Total Bilirubin is >3.3 mg/dL): Weekly f. Cholesterol, triglycerides g. Echocardiogram or MUGA h. BMA for **mandatory** clinical RQ-PCR of PML-RARα: Obtain on Day 29. If sample is positive, repeat 1 - 2 weeks later. This testing is not paid for by the study. It is recommended that this testing be sent to either Hematologics, Inc, Seattle, WA, USA or the Molecular Haematology Lab, Royal Prince Alfred Hospital, NSW, Australia due to their experience with these samples.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.5.3 MRD Positive Consolidation Treatment Details – Standard Risk APL

MRD Positive Consolidation consists of a combination of high dose cytarabine, mitoxantrone and twice daily ATRA. This cycle lasts for 28 days. It is strongly recommended that the patients remain inpatient for the duration of this cycle of Consolidation and until count recovery.

Antifungal prophylaxis should be strongly considered (dependent on institutional practice) during this cycle due to an expected prolonged period of neutropenia. However, treating physicians should be aware that azole antifungal medications may increase ATRA toxicity due to inhibition of cytochrome P - 450 metabolism of ATRA. Thus patients should be monitored closely for adverse events such as, pseudotumor cerebri or renal dysfunction, during periods of concomitant use. For prophylactic antifungal use, initiation of an azole antifungal could be delayed until after completion of ATRA on Day 14 of this cycle or an alternate non-azole antifungal should be considered.

High Dose Cytarabine: IV over 1 - 3 hours every 12 hours
Days: 1 - 4 (8 total doses)
Dose: 1,000 mg/m^2/dose every 12 hours. If BSA < 0.6 m^2, 33.3 mg/**kg**/dose.

NOTE: Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose and continuing for 24 hours after the final dose. If patient does not tolerate steroid eye drops, may administer artificial tears on an every 2 - 4 hour schedule.

MitoXANtrone: IV daily over 15 - 30 minutes
Days: 3 - 6
Dose: 12 mg/m^2/dose once daily. If BSA < 0.6 m^2 0.4 mg/**kg**/dose.
Administer through the tubing of a rapidly infusing solution of D_5W or 0.9% NaCl. Avoid extravasation; the use of a central line is suggested. On Days 3 and 4, mitoxantrone should be given 8 hours after the 5th and 7th high dose cytarabine infusions are complete.

Tretinoin (ATRA): PO divided BID
Days: 1 - 14
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients).

A bone marrow evaluation will be done for clinical RQ-PCR of PML-RARα on Day 29. This testing is not paid for by the study, but it is recommended that this testing be sent to either Hematologics, Inc, Seattle, WA, USA or the Molecular Haematology Lab, Royal Prince Alfred Hosptial, NSW, Australia due to their experience with these samples. If negative, continue to Consolidation Cycle 3 (see Section 4.6) on Day 29 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later. If positive, repeat 1 - 2 weeks later and if second test is positive then patient will go off protocol therapy.

4.6 Consolidation Cycle 3 – Standard Risk APL

4.6.1 Consolidation Therapy Delivery Map Cycle 3 – Standard Risk APL

Start Consolidation Cycle 3 only if RQ-PCR of PML-RARα is negative. *Cycle 3 starts on Day 57 of Cycle 2 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.* ***OR*** *Consolidation Cycle 3 starts on Day 29 of MRD Positive Consolidation cycle if needed or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.*

_____ Patient COG ID number _____ DOB

Consolidation Cycle 3 lasts 8 weeks. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 14 and 29 - 42	**Total Dose:** 25 mg/m^2/day divided twice daily. Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV over 2 hours*	0.15 mg/**kg**/day	1 - 5, 8 - 12, 15 - 19, 22 - 26	*May be extended to 4 hours see Section 4.6.3 for additional details
Triple Intrathecal Therapy (ITT) Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age / MTX / HC / ARAC 1-1.99 yrs: 8 mg / 15 mg / 30 mg 2-2.99 yrs: 10 mg / 25 mg / 50 mg ≥3 yrs: 12 mg / 35 mg / 70 mg	15 and 43	Only patients with documented CNS disease or CNS bleed will require intrathecal treatments (see Sections 3.3.4 and 4.6.3 for details).

Ht _____cm **Wt _____kg** **BSA _____m^2**

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations

Date Due	Date Given	Day	ATRA _____mg _____mg	ATO _____mg	ITT _____mg (MTX) _____mg (HC) _____mg (ARAC)	Studies
			Enter calculated dose above and actual dose administered below			
		1	_____mg _____mg	_____mg	***Only patients with CNS disease or CNS bleed will require intrathecal treatments*** *(see Sections 3.3.4 and 4.6.3 for details)*	a – g, h*
		2	_____mg _____mg	_____mg		
		3	_____mg _____mg	_____mg		
		4	_____mg _____mg	_____mg		
		5	_____mg _____mg	_____mg		
		6	_____mg _____mg			
		7	_____mg _____mg			
		8	_____mg _____mg	_____mg		c, d. e, f
		9	_____mg _____mg	_____mg		
		10	_____mg _____mg	_____mg		
		11	_____mg _____mg	_____mg		
		12	_____mg _____mg	_____mg		
		13	_____mg _____mg			
		14	_____mg _____mg			
		15		_____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)	c, d, e, f
		16		_____mg		
		17		_____mg		
		18		_____mg		
		19		_____mg		
		---	---	---		
		22		_____mg		c, d, e, f
		23		_____mg		
		24		_____mg		
		25		_____mg		
		26		_____mg		
		---	---	---		
		29	_____mg _____mg ↓			a, c, e

		42	_____mg _____mg			
		43			_____mg (MTX) _____mg (HC) _____mg (ARAC)	
		---	---	---		
		56				
		57	*Proceed to Consolidation Cycle 4 (see Section 4.7) on Day 57 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.*			

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.6.2 Required Observations in Consolidation Cycle 3 – Standard Risk APL

a. Physical Exam with VS: every 4 weeks
b. Ht, Wt, BSA
c. CBC, differential, platelets: Weekly while receiving ATO and on Day 29.
d. Electrolytes including Ca^{++}, Mg^{++}, K^{+} and creatinine: Weekly while receiving ATO
e. AST, ALT, Total Bilirubin (and Direct Bilirubin if Total Bilirubin is >2 mg/dL): Weekly while receiving ATO and on Day 29.
f. ECG for QTc monitoring: Weekly while receiving ATO
g. Cholesterol, triglycerides
h. Neurocognitive Testing (optional)*: CogState and BRIEF on Day 1 of Consolidation Cycle 3 (+/-2 weeks). See Section 16 for details.

*Only obtain in patients who have consented to participation in this component of the trial.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.6.3 Consolidation Cycle 3 Treatment Details – Standard Risk APL

Consolidation Cycle 3 lasts 56 days.

Tretinoin (ATRA): PO divided BID
Days: 1 - 14 and 29 - 42
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients).

Arsenic Trioxide (ATO): IV over 2 hours (may lengthen infusion to 4 hours if active vasomotor symptoms occur)
Days: 1 - 5, 8 - 12, 15 - 19 and 22 - 26
Dose: 0.15 mg/**kg**/day (no maximum dose)

NOTE: Some patients may require infusion in a clinic setting (i.e. unable to arrange home infusion) and holidays may result in intermittent clinic closure. Therefore it is permissible for patients to miss doses of ATO on those days at the discretion of the treating physician. It is suggested that patients not miss more than 2 doses in a 4 week period (10% of doses). If more than 2 doses are missed in a 4 week period due to holidays, then make-up doses (following Day 26) may be administered at the discretion of the treating physician.

Indications for intrathecal therapy

Intrathecal Triple Therapy (ITT): Only for patients with documented history of CNS bleed or CNS positive disease.

Days: 15 and 43
Dose: Age based dosing as follows

	Triple Intrathecal Therapy (ITT)		
Age	Methotrexate	Hydrocortisone	Cytarabine
1 - 1.99 years	8 mg	15 mg	30 mg
2 - 2.99 years	10 mg	25 mg	50 mg
≥ 3years	12 mg	35 mg	70 mg

Proceed to Consolidation Cycle 4 on Day 57 or when blood counts recover (ANC ≥1,000/µL and platelet count ≥ 100,000/µL), whichever occurs later. See Section 4.7 for details.

4.7 Consolidation Cycle 4 – Standard Risk APL

4.7.1 Consolidation Therapy Delivery Map Cycle 4 – Standard Risk APL *Consolidation Cycle 4 starts on Day 57 of Cycle 3 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.*	_____ Patient COG ID number _____ DOB

Consolidation Cycle 4 lasts 4 weeks. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 14	**Total Dose:** 25 mg/m^2/day divided twice daily Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV over 2 hours*	0.15 mg/**kg**/day	1 - 5, 8 - 12, 15 - 19, 22 - 26	*May be extended to 4 hours see Section 4.7.3 for additional details

Ht _____cm Wt _____kg BSA _____m^2

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations.

Date Due	Date Given	Day	ATRA _____mg _____mg	ATO _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below			
		1	_____mg _____mg	_____mg	a – g	
		2	_____mg _____mg	_____mg		
		3	_____mg _____mg	_____mg		
		4	_____mg _____mg	_____mg		
		5	_____mg _____mg	_____mg		
		6	_____mg _____mg			
		7	_____mg _____mg			
		8	_____mg _____mg	_____mg	c, d, e, f	
		9	_____mg _____mg	_____mg		
		10	_____mg _____mg	_____mg		
		11	_____mg _____mg	_____mg		
		12	_____mg _____mg	_____mg		
		13	_____mg _____mg			
		14	_____mg _____mg			
		15		_____mg	c, d, e, f	
		16		_____mg		
		17		_____mg		
		18		_____mg		
		19		_____mg		
		---	---	---		
		22		_____mg	c, d, e, f	
		23		_____mg		
		24		_____mg		
		25		_____mg		
		26		_____mg		
		27	---	---		
		28			a, c, h, i, j*,k*	

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.7.2 Required Observations in Consolidation Cycle 4 – Standard Risk APL

a. Physical Exam with VS: Days 1 and 28
b. Ht, Wt, BSA
c. CBC, differential, platelets: Weekly
d. Electrolytes including Ca^{++}, Mg^{++}, K^{+} and creatinine: Weekly while receiving ATO
e. AST, ALT, Total Bilirubin (and Direct Bilirubin if Total Bilirubin is >2 mg/dL): Weekly while receiving ATO
f. ECG for QTc monitoring: Weekly while receiving ATO
g. Cholesterol, triglycerides
h. Echocardiogram or MUGA: at the end of protocol therapy
i. BMA for clinical RQ-PCR of PML-RARα: at the end of protocol therapy. This clinical testing is separate from research samples submitted for the optional MRD study; this **mandatory** clinical testing is not free of charge and the cost is not covered by the study, but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing; a list of approved labs is available on the protocol-specific web page of the COG website.
j. Research MRD (optional)*: bone marrow and peripheral blood at the end of protocol therapy. See Section 15.2 for details.
k. Neurocognitive Testing (optional)*: CogState, BRIEF and the psychologist administered battery at the end of protocol therapy (up to 3 months after the end of protocol therapy). See Section 16 for details.

*Only obtain in patients who have consented to participation in this component of the trial.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.7.3 Consolidation Cycle 4 Treatment Details – Standard Risk APL

Consolidation Cycle 4 lasts 28 days.

Tretinoin (ATRA): PO divided BID
Days: 1 - 14
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients).

Arsenic Trioxide (ATO): IV over 2 hours (may lengthen infusion to 4 hours if active vasomotor symptoms occur)
Days: 1 - 5, 8 - 12, 15 - 19 and 22 - 26
Dose: 0.15 mg/**kg**/day (no maximum dose)

NOTE: Some patients may require infusion in a clinic setting (i.e. unable to arrange home infusion) and holidays may result in intermittent clinic closure. Therefore it is permissible for patients to miss doses of ATO on those days at the discretion of the treating physician. It is suggested that patients not miss more than 2 doses in a 4 week period (10% of doses). If more than 2 doses are missed in a 4 week period due to holidays, then make-up doses (following Day 26) may be administered at the discretion of the treating physician.

A bone marrow evaluation is performed for clinical RQ-PCR of PML-RARα on Day 28. This testing is separate from research samples submitted for the optional MRD study; this mandatory clinical testing is not free of charge (cost is not covered by the study), but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing; a list of approved labs is available on the protocol-specific web page of the COG website.

4.8 Induction – High Risk APL

4.8.1a Induction Therapy Delivery Map – High Risk APL

High Risk APL is defined as WBC ≥ 10,000/μL at diagnosis.

_____ Patient COG ID number _____ DOB

This course lasts 28 days (beyond Day 28 up to 70 days if not in hCR/hCRi) See Section 4.8.3 for treatment details. This TDM is on 3 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 28 minimum. Continue up to Day 70 if not in hCR/hCRi.	**Total Dose:** 25 mg/m^2/day divided twice daily Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV daily over 2 hours*	0.15 mg/**kg**/day	1 - 28 minimum. Continue up to Day 70 if not in hCR/hCRi.	*May lengthen infusion to 4 hours if active vasomotor symptoms occur.
IDArubicin (IDA)	IV bolus over 15 minutes	12 mg/m^2/dose (**NOTE:** if BSA < 0.6 m^2, 0.4 mg/**kg**/dose)	1, 3, 5, 7	
Dexamethasone (DEX)	PO/IV	2.5 mg/m^2/dose, twice daily	1 - 14	**Total Dose:** 5 mg/m^2/day divided twice daily
Triple Intrathecal Therapy (ITT) Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age / MTX / HC / ARAC 1-1.99 yrs / 8 mg / 15 mg / 30 mg 2-2.99 yrs / 10 mg / 25 mg / 50 mg ≥3 yrs / 12 mg / 35 mg / 70 mg	**If CNS Disease:** Twice weekly until CSF cleared plus 2 additional twice weekly treatments (minimum of 4 and maximum of 6 treatments). **If CNS Bleed:** Day 29 only	Only patients with CNS disease or CNS bleed will require intrathecal treatments (see Sections 3.3.4 and 4.8.3 for details).
Leucovorin (LCV)	PO/IV	10 mg/m^2/dose	**CNS Disease ONLY:** Leucovorin should be given 24 hours after IT methotrexate.	

Ht _____cm **Wt _____kg** **BSA _____m^2**

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations

Date Due	Date Given	Day	ATRA ___mg ___mg	ATO ___mg	IDA ___mg	DEX ___mg	ITT ___mg (MTX) ___mg (HC) ___mg (ARAC)	LCV ___mg	Studies
			Enter calculated dose above and actual dose administered below						
		1	___mg ___mg	___mg	___mg	___mg	***Only for patients with CNS disease (not CNS Bleed)*** *give ITT twice weekly as directed (see Section 4.8.3 for details).* ***Caution:*** *Most patients will not need intrathecal treatment. Lumbar puncture is recommended only for patients with neurologic symptoms consistent with CNS disease and should not be performed until coagulopathy resolves.*		a-r*, s*, t*
		2	___mg ___mg	___mg		___mg			f, h, l
		3	___mg ___mg	___mg	___mg	___mg			f, h, l
		4	___mg ___mg	___mg		___mg			f, h, l
		5	___mg ___mg	___mg	___mg	___mg			f, h, l
		6	___mg ___mg	___mg		___mg			f, h, l
		7	___mg ___mg	___mg	___mg	___mg			f, h, l
		8	___mg ___mg	___mg		___mg	Date CNS disease diagnosed: _____		b, f, h, j, l, m, t*
		9	___mg ___mg	___mg		___mg	Date Given: _____		
		10	___mg ___mg	___mg		___mg	___mg (MTX) ___mg (HC) ___mg (ARAC)		
		11	___mg ___mg	___mg		___mg		___mg	
		12	___mg ___mg	___mg		___mg	Date Given: _____		
		13	___mg ___mg	___mg		___mg	___mg (MTX) ___mg (HC) ___mg (ARAC)		
		14	___mg ___mg	___mg		___mg		___mg	
		15	___mg ___mg	___mg					b, f, h, j, l, m, t*
		16	___mg ___mg	___mg			Date Given: _____		
		17	___mg ___mg	___mg			___mg (MTX) ___mg (HC) ___mg (ARAC)		
		18	___mg ___mg	___mg				___mg	
		19	___mg ___mg	___mg			Date Given: _____		
		20	___mg ___mg	___mg			___mg (MTX) ___mg (HC) ___mg (ARAC)		
		21	___mg ___mg	___mg				___mg	
		22	___mg ___mg	___mg					b, f, h, j, m
		23	___mg ___mg	___mg			Date Given: _____		
		24	___mg ___mg	___mg			___mg (MTX) ___mg (HC) ___mg (ARAC)		
		25	___mg ___mg	___mg				___mg	
		26	___mg ___mg	___mg			Date Given: _____		
		27	___mg ___mg	___mg			___mg (MTX) ___mg (HC) ___mg (ARAC)		
		28	___mg ___mg	___mg				___mg	
		29	*A bone marrow evaluation is performed on Day 29. If hCR/hCRi is achieved, proceed to Consolidation (see Section 4.9). If hCR/hCRi is not achieved on Day 29, continue with Induction (see Page 2 of this TDM). A bone marrow evaluation is done every 2 weeks until hCR/hCRi is achieved. When hCR/hCRi is achieved, proceed to Consolidation (see Section 4.9).* ___mg ___mg	___mg			***Day 29: Only for Patients with CNS Bleed (not CNS Disease):*** ___mg (MTX) ___mg (HC) ___mg (ARAC)		b, c, f, h, j, l, m, o, s*, t*

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Induction – High Risk

4.8.1b Induction Therapy Delivery Map Continued– High Risk APL

High Risk APL is defined as WBC ≥ 10,000/μL at diagnosis.

_____ Patient COG ID number _____ DOB

This course lasts 28 days (beyond Day 28 up to 70 days if not in hCR/hCRi) See Section 4.8.3 for treatment details. This TDM is on 3 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 28 minimum. Continue up to Day 70 if not in hCR/hCRi.	**Total Dose:** 25 mg/m^2/day divided twice daily Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV daily over 2 hours*	0.15 mg/**kg**/day	1 - 28 minimum. Continue up to Day 70 if not in hCR/hCRi.	*May lengthen infusion to 4 hours if active vasomotor symptoms occur.
IDArubicin (IDA)	IV bolus over 15 minutes	12 mg/m^2/dose **NOTE:** if BSA < 0.6 m^2, 0.4 mg/**kg**/dose	1, 3, 5, 7	
Dexamethasone (DEX)	PO/IV	2.5 mg/m^2/dose, twice daily	1 - 14	Total Dose: 5 mg/m^2/day divided twice daily
Triple Intrathecal Therapy (ITT) Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age / MTX / HC / ARAC 1-1.99 yrs / 8 mg / 15 mg / 30 mg 2-2.99 yrs / 10 mg / 25 mg / 50 mg ≥3 yrs / 12 mg / 35 mg / 70 mg	**If CNS Disease:** Twice weekly until CSF cleared plus 2 additional twice weekly treatments (minimum of 4 and maximum of 6 treatments). **If CNS Bleed:** Day 29 only	Only patients with CNS disease or CNS bleed will require intrathecal treatments (see Section 3.3.4 and 4.8.3 for details).
Leucovorin (LCV)	PO/IV	10 mg/m^2/dose	**CNS Disease ONLY:** Leucovorin should be given 24 hours after IT methotrexate.	

Ht _____cm Wt _____kg BSA _____m^2

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations

Date Due	Date Given	Day	ATRA _____mg _____mg	ATO _____mg	ITT _____mg (MTX) _____mg (HC) _____mg (ARAC)	LCV _____mg	Studies
			Enter calculated dose above and actual dose administered below				
		30	_____mg _____mg	_____mg	***Only for patients with CNS disease (not CNS Bleed)*** *give ITT twice weekly as directed (see Section 4.8.3 for details).* ***Caution:*** *Most patients will not need intrathecal treatment. Lumbar puncture is recommended only for patients with neurologic symptoms consistent with CNS disease and should not be performed until coagulopathy resolves.* **NOTE: A MAXIMUM OF 6 TREATMENTS OF INTRATHECAL THERAPY SHOULD BE ADMINISTERED DURING INDUCTION** **ALL DOSES WILL BE RECORDED ON PAGE 1 OF THIS TDM.**		
		31	_____mg _____mg	_____mg			
		32	_____mg _____mg	_____mg			
		33	_____mg _____mg	_____mg			
		34	_____mg _____mg	_____mg			
		35	_____mg _____mg	_____mg			
		36	_____mg _____mg	_____mg			b, f, h, j, m
		37	_____mg _____mg	_____mg			
		38	_____mg _____mg	_____mg			
		39	_____mg _____mg	_____mg			
		40	_____mg _____mg	_____mg			
		41	_____mg _____mg	_____mg			j
		42	_____mg _____mg	_____mg			
		43	_____mg _____mg	_____mg			b, f, h, j, m, o
		44	_____mg _____mg	_____mg			
		45	_____mg _____mg	_____mg			
		46	_____mg _____mg	_____mg			
		47	_____mg _____mg	_____mg			
		48	_____mg _____mg	_____mg			
		49	_____mg _____mg	_____mg			
		50	_____mg _____mg	_____mg			b, f, h, j, m
		51	_____mg _____mg	_____mg			
		52	_____mg _____mg	_____mg			
		53	_____mg _____mg	_____mg			
		54	_____mg _____mg	_____mg			
		55	_____mg _____mg	_____mg			
		56	_____mg _____mg	_____mg			
		57	_____mg _____mg	_____mg			b, c, f, h, j, m, o
		58	_____mg _____mg	_____mg			
		59	_____mg _____mg	_____mg			
		60	_____mg _____mg	_____mg			
		61	_____mg _____mg	_____mg			
		62	_____mg _____mg	_____mg			
		63	_____mg _____mg	_____mg			
		64	_____mg _____mg	_____mg			b, f, h, j m
		65	_____mg _____mg	_____mg			
		66	_____mg _____mg	_____mg			
		67	_____mg _____mg	_____mg			
		68	_____mg _____mg	_____mg			
		69	_____mg _____mg	_____mg			
		70	_____mg _____mg	_____mg			o
			A bone marrow evaluation is done every 2 weeks until hCR/hCRi is achieved. When hCR/hCRi is achieved, proceed to Consolidation (see Section 4.9). If hCR/hCRi is not achieved by Day 70, patient will go off protocol therapy.				

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Induction – High Risk

4.8.2 Required Observations in Induction – High Risk APL

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. Obtain other studies during Induction as indicated.

a. History
b. Physical Exam with VS: weekly
c. Ht, Wt, BSA: Days 1, 29 and 57
d. Performance status
e. Pregnancy test: Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.
f. CBC, differential, platelets: daily during Week 1, then at least once weekly
g. Urinalysis
h. Electrolytes including Ca^{++}, Mg^{++}, K^{+} and creatinine: daily during Week 1, then at least once weekly
i. Uric Acid
j. AST, ALT, Total Bilirubin (and Direct Bilirubin if Total Bilirubin is >2 mg/dL): Once weekly
k. Cholesterol triglycerides
l. PT, PTT, fibrinogen, D-Dimer: daily during Week 1, then on Days 8, 15 and 29 (more frequently if needed for active coagulopathy)
m. ECG for QTc monitoring: Weekly
n. Echocardiogram or MUGA
o. BMA for morphology: At diagnosis and Day 29 and every 2 weeks thereafter as needed until hCR/hCRi
p. BMA for flow cytometry, cytogenetics & FISH: At diagnosis
q. BMA for clinical RQ-PCR of PML-RARα: At diagnosis. This clinical testing is separate from research samples submitted for the optional MRD RQ-PCR study; this **mandatory** clinical testing is not free of charge and the cost is not covered by the study, but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing; a list of approved labs is available on the protocol-specific web page of the COG website.
r. FLT3 (optional)*: bone marrow (or peripheral blood if bone marrow is unavailable) at diagnosis. See Section 15.1 for details.
s. Research MRD (optional)*: bone marrow and peripheral blood at diagnosis and Day 29 of Induction. See Section 15.2 for details. Results of this research testing will not be returned to sites. This research testing does not take the place of the mandatory RQ-PCR clinical testing that must be done at the time of initial diagnosis (see observation "q" above).
t. Coagulopathy (optional)*: peripheral blood at diagnosis (if available), Day 1, Day 8, Day 15 and Day 29 of Induction. See Section 15.3 for details.

*Only obtain in patients who have consented to participation in this component of the trial.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.8.3 Induction Treatment Details – High Risk APL

ATRA should be started at the time of first suspicion of APL diagnosis and then idarubicin and ATO should be given on Day 1 of protocol therapy. If an institution does not have ATO available on Day 1 when idarubicin is given, it will not be a protocol violation to start protocol directed therapy with idarubicin and ATRA as long as the ATO is started within 48 hours of the first idarubicin dose.

Induction for high risk APL consists of daily ATO, twice daily ATRA, IDArubicin, and prophylaxis dosing of dexamethasone. Induction lasts at least 28 days (ATRA pre-treatment without ATO is not included in the 28 days). A bone marrow evaluation is performed on Day 29. Patients should remain on daily ATO/ATRA therapy while awaiting results of Day 29 bone marrow hCR/hCRi assessment.

If hCR/hCRi is achieved, patients should stop daily induction therapy and proceed to Consolidation. If hCR/hCRi is not achieved, patients continue with Induction up to a maximum of 70 days, and a bone marrow evaluation is done every 2 weeks until hCR/hCRi is achieved. This end Induction determination of hematologic complete response is not dependent on results of genetic testing (such as cytogenetics, FISH or RQ-PCR testing). Patients who appear not to have achieved hematological complete remission after Day 43 of Induction may benefit from consultation for a rapid pathology review beginning with the Day 57 marrow sample (See Section 13 for details).

Induction ends with the confirmation of an hCR/hCRi and after a minimum of 28 days of induction. Then patient proceeds to Consolidation Cycle 1 (see Section 4.9). Following completion of Induction, Consolidation starts a minimum of 14 days from the end of Induction or when blood counts have recovered (ANC ≥ 1,000/μL and platelets ≥ 100,000/μL), whichever occurs later.

Tretinoin (ATRA): PO divided BID
Days: 1 - 28 minimum. Continue beyond Day 28 if not in hCR/hCRi up to a maximum of 70 days (See Section 10.2 for response criteria and definition of hCR/hCRi)
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients). Guidance for administration of tretinoin by parents/caregivers can be found in Appendix III.
Note: If the patient received pre-treatment with ATRA prior to starting Day 1 of protocol directed therapy (see Section 3.2.3), these pre-treatment doses are NOT considered part of the required 28 days minimum of induction protocol therapy.

Arsenic Trioxide (ATO): IV daily over 2 hours (may lengthen infusion to 4 hours if active vasomotor symptoms occur)
Days: 1 - 28 minimum. Continue beyond day 28 if not in hCR/hCRi up to a maximum of 70 days (See Section 10.2 for response criteria and definition of hCR/hCRi)
Dose: 0.15 mg/**kg**/day (no maximum dose)

IDArubicin: IV bolus over 15 minutes
Days: 1, 3, 5, 7
Dose: 12 mg/m^2/dose, once a day
NOTE: if BSA < 0.6 m^2, 0.4 mg/**kg**/dose

Dexamethasone: PO/IV BID
Days: 1 - 14
Dose: 2.5 mg/m^2/dose twice daily. The total daily dose is 5 mg/m^2/day.
Note: This is prophylaxis dosing of dexamethasone. If the patient develops actual symptoms of differentiation syndrome, refer to Section 5.1 for recommendations on diagnosis and management of differentiation syndrome including treatment dosing of dexamethasone.

Indications for intrathecal therapy

CNS Bleed
Patients with documented CNS bleed will receive CNS prophylaxis to include triple intrathecal chemotherapy at Day 29 of Induction. See table below for age-based dosing.

CNS Disease
Patients with CNS disease (see Section 3.3.4 for definition) will receive twice weekly triple intrathecal chemotherapy (with a minimum interval of 48 hours between treatments) until the CSF is cleared plus two additional twice weekly treatments (minimum of 4 and maximum of 6 treatments). During Induction, patients with CNS disease will also receive a 10 mg/m^2 dose of leucovorin, 24 hours after each of the twice weekly triple intrathecal therapies.

Age-based dosing of triple intrathecal therapy:

	Triple Intrathecal Therapy (ITT)		
Age	Methotrexate	Hydrocortisone	Cytarabine
1 - 1.99 years	8 mg	15 mg	30 mg
2 - 2.99 years	10 mg	25 mg	50 mg
≥ 3 years	12 mg	35 mg	70 mg

See Section 5.0 for Dose Modifications based on Toxicities.

4.9 Consolidation Cycle 1 – High Risk APL

4.9.1 Consolidation Therapy Delivery Map Cycle 1 – High Risk APL

Consolidation Cycle 1 starts a minimum of 14 days after end of Induction therapy or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.

_____ Patient COG ID number

_____ DOB

Consolidation Cycle 1 lasts 8 weeks. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 14 and 29-42	**Total Dose:** 25 mg/m^2/day divided twice daily. Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV over 2 hours*	0.15 mg/**kg**/day	1 - 5, 8 - 12, 15 - 19, 22 - 26	*May be extended to 4 hours see Section 4.9.3 for additional details
Triple Intrathecal Therapy (ITT) Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age / MTX / HC / ARAC 1-1.99 yrs: 8 mg / 15 mg / 30 mg 2-2.99 yrs: 10 mg / 25 mg / 50 mg ≥3 yrs: 12 mg / 35 mg / 70 mg	15 and 43	Only patients with documented CNS disease or CNS bleed will require intrathecal treatments (see Sections 3.3.4 and 4.9.3 for details).

Ht _____cm **Wt _____kg** **BSA _____m^2**

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations

Date Due	Date Given	Day	ATRA _____mg _____mg	ATO _____mg	ITT _____mg (MTX) _____mg (HC) _____mg (ARAC)	Studies
			Enter calculated dose above and actual dose administered below			
		1	_____mg _____mg	_____mg	***Only patients with CNS disease or CNS bleed will require intrathecal treatments*** *(see Sections 3.3.4 and 4.9.3 for details)*	a – g, h*
		2	_____mg _____mg	_____mg		
		3	_____mg _____mg	_____mg		
		4	_____mg _____mg	_____mg		
		5	_____mg _____mg	_____mg		
		6	_____mg _____mg			
		7	_____mg _____mg			
		8	_____mg _____mg	_____mg		c, d, e, f
		9	_____mg _____mg	_____mg		
		10	_____mg _____mg	_____mg		
		11	_____mg _____mg	_____mg		
		12	_____mg _____mg	_____mg		
		13	_____mg _____mg			
		14	_____mg _____mg			
		15		_____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)	c, d, e, f
		16		_____mg		
		17		_____mg		
		18		_____mg		
		19		_____mg		
		---	---	---		
		22		_____mg		c, d, e, f
		23		_____mg		
		24		_____mg		
		25		_____mg		
		26		_____mg		
		---	---	---		
		29	_____mg _____mg			a, c, e
		---	↓			
		42	_____mg _____mg			
		43			_____mg (MTX) _____mg (HC) _____mg (ARAC)	
		---	---	---		
		56				
		57	*Proceed to Consolidation Cycle 2 (see Section 4.10) on Day 57 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later*			

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Consolidation – Cycle 1 - High Risk

4.9.2 Required Observations in Consolidation Cycle 1 – High Risk APL

a. Physical Exam with VS: Every 4 weeks
b. Ht, Wt, BSA
c. CBC, differential, platelets: Weekly while receiving ATO and on Day 29.
d. Electrolytes including Ca^{++}, Mg^{++}, K^{+} and Creatinine: Weekly while receiving ATO.
e. Total bilirubin (and direct bilirubin if total is > 2mg/dL), AST, ALT: Weekly while receiving ATO and on Day 29.
f. ECG for QTc monitoring: Weekly while receiving ATO.
g. Cholesterol, triglycerides
h. Neurocognitive Testing (optional)*: CogState and BRIEF on Day 1 of Consolidation Cycle 1 (+/- 2 weeks). See Section 16 for details.

*Only obtain in patients who have consented to participation in this component of the trial.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.9.3 Consolidation Cycle 1 Treatment Details – High Risk APL

Consolidation Cycle 1 lasts 56 days.

Tretinoin (ATRA): PO divided BID
Days: 1 - 14 and 29 - 42
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients).

Arsenic Trioxide (ATO): IV over 2 hours (may lengthen infusion to 4 hours if active vasomotor symptoms occur)
Days: 1 - 5, 8 - 12, 15 - 19 and 22 - 26
Dose: 0.15 mg/**kg**/day (no maximum dose)

NOTE: Some patients may require infusion in a clinic setting (i.e. unable to arrange home infusion) and holidays may result in intermittent clinic closure. Therefore it is permissible for patients to miss doses of ATO on those days at the discretion of the treating physician. It is suggested that patients not miss more than 2 doses in a 4 week period (10% of doses). If more than 2 doses are missed in a 4 week period due to holidays, then make-up doses (following Day 26) may be administered at the discretion of the treating physician.

Indications for intrathecal therapy

Intrathecal Triple Therapy (ITT): Only for patients with documented history of CNS bleed or CNS positive disease.

Days: 15 and 43
Dose: Age based dosing as follows:

	Triple Intrathecal Therapy (ITT)		
Age	Methotrexate	Hydrocortisone	Cytarabine
1 - 1.99 years	8 mg	15 mg	30 mg
2 - 2.99 years	10 mg	25 mg	50 mg
≥ 3 years	12 mg	35 mg	70 mg

Proceed to Consolidation Cycle 2 on Day 57 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later. See Section 4.10 for details.

4.10 Consolidation Cycle 2 – High Risk APL

4.10.1 Consolidation Therapy Delivery Map Cycle 2 – High Risk APL

Consolidation Cycle 2 starts on Day 57 of Cycle1 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.

_____ Patient COG ID number

_____ DOB

Consolidation Cycle 2 lasts 8 weeks. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m²/dose, twice daily	1 - 14 and 29 - 42	**Total Dose:** 25 mg/m²/day divided twice daily. Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV over 2 hours*	0.15 mg/**kg**/day	1 - 5, 8 - 12, 15 - 19, 22 - 26	*May be extended to 4 hours see Section 4.10.3 for additional details
Triple Intrathecal Therapy (ITT) Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age / MTX / HC / ARAC 1-1.99 yrs: 8 mg / 15 mg / 30 mg 2-2.99 yrs: 10 mg / 25 mg / 50 mg ≥ 3 yrs: 12 mg / 35 mg / 70 mg	15 and 43	Only patients with documented CNS disease or CNS bleed will require intrathecal treatments (see Sections 3.3.4 and 4.10.3 for details).

Ht _____cm **Wt _____kg** **BSA _____m²**

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations

Date Due	Date Given	Day	ATRA _____mg _____mg	ATO _____mg	ITT _____mg (MTX) _____mg (HC) _____mg (ARAC)	Studies
			Enter calculated dose above and actual dose administered below			
		1	_____mg _____mg	_____mg	***Only patients with CNS disease or CNS bleed will require intrathecal treatments*** *(see Sections 3.3.4 and 4.10.3 for details)*	a – g
		2	_____mg _____mg	_____mg		
		3	_____mg _____mg	_____mg		
		4	_____mg _____mg	_____mg		
		5	_____mg _____mg	_____mg		
		6	_____mg _____mg			
		7	_____mg _____mg			
		8	_____mg _____mg	_____mg		c, d, e, f
		9	_____mg _____mg	_____mg		
		10	_____mg _____mg	_____mg		
		11	_____mg _____mg	_____mg		
		12	_____mg _____mg	_____mg		
		13	_____mg _____mg			
		14	_____mg _____mg			
		15		_____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)	c, d, e, f
		16		_____mg		
		17		_____mg		
		18		_____mg		
		19		_____mg		
		---	---	---		
		22		_____mg		c, d, e, f
		23		_____mg		
		24		_____mg		
		25		_____mg		
		26		_____mg		
		27				
		28				
		29	_____mg _____mg			a, c, e
		---	↓			
		42	_____mg _____mg			
		43			_____mg (MTX) _____mg (HC) _____mg (ARAC)	h, i*, j*
		44				
		---	---	---		
		56				
		57	*A bone marrow evaluation is performed for clinical RQ-PCR of PML-RARα on Day 43. If negative continue to Consolidation Cycle 3 (Section 4.12) on Day 57 of this cycle. If positive, repeat 1-2 weeks later. If repeat test is negative continue to Consolidation Cycle 3 (see Section 4.12) on Day 57 of this cycle. If repeat test is confirmed positive continue to MRD Positive Consolidation Cycle (see Section 4.11) on Day 57 of this cycle.*		

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Consolidation – Cycle 2 – High Risk

4.10.2 Required Observations in Consolidation Cycle 2 – High Risk APL

a. Physical Exam with VS: Every 4 weeks
b. Ht, Wt, BSA
c. CBC, differential, platelets: Weekly while receiving ATO and on Day 29.
d. Electrolytes including Ca^{++}, Mg^{++}, K^{+} and creatinine: Weekly while receiving ATO
e. AST, ALT, Total Bilirubin (and Direct Bilirubin if Total Bilirubin is >2 mg/dL): Weekly while receiving ATO and on Day 29.
f. ECG for QTc monitoring: Weekly while receiving ATO
g. Cholesterol, triglycerides
h. BMA for clinical RQ-PCR of PML-RARα: Obtain on Day 43 of Consolidation Cycle 2. This clinical testing is separate from research samples submitted for the optional MRD RQ-PCR study; this **mandatory** clinical testing is not free of charge and the cost is not covered by the study, but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing; a list of approved labs is available on the protocol-specific web page of the COG website. If the initial test is positive, contact the study chair and a repeat sample must be sent 1-2 weeks later. This testing is not paid for by the study, but it is recommended that this confirmation sample be sent to either Hematologics, Inc, Seattle, WA, USA or the Molecular Haematology Lab, Royal Prince Alfred Hospital, NSW, Australia due to their experience with these samples.
i. FLT3 (optional)*: bone marrow on Day 43 of Consolidation Cycle 2. See Section 15.1 for details.
j. Research MRD (optional)*: bone marrow and peripheral blood on Day 43 of Consolidation Cycle 2. See Section 15.2 for details. Results of this research testing will not be returned to sites.

*Only obtain in patients who have consented to participation in this component of the trial.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.10.3 Consolidation Cycle 2 Treatment Details – High Risk APL

Consolidation Cycle 2 lasts 56 days.

Tretinoin (ATRA): PO divided BID
Days: 1 - 14 and 29 - 42
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients).

Arsenic Trioxide (ATO): IV over 2 hours (may lengthen infusion to 4 hours if active vasomotor symptoms occur)
Days: 1 - 5, 8 - 12, 15 - 19 and 22 - 26
Dose: 0.15 mg/**kg**/day (no maximum dose)

NOTE: Some patients may require infusion in a clinic setting (i.e. unable to arrange home infusion) and holidays may result in intermittent clinic closure. Therefore it is permissible for patients to miss doses of ATO on those days at the discretion of the treating physician. It is suggested that patients not miss more than 2 doses in a 4 week period (10% of doses). If more than 2 doses are missed in a 4 week period due to holidays, then make-up doses (following Day 26) may be administered at the discretion of the treating physician.

Indications for intrathecal therapy
Intrathecal Triple Therapy (ITT): Only for patients with documented history of CNS bleed or CNS positive disease.

Days: 15 and 43
Dose: Age based dosing as follows

	Triple Intrathecal Therapy (ITT)		
Age	Methotrexate	Hydrocortisone	Cytarabine
1 - 1.99 years	8 mg	15 mg	30 mg
2 - 2.99 years	10 mg	25 mg	50 mg
≥ 3 years	12 mg	35 mg	70 mg

A bone marrow evaluation is performed for clinical RQ-PCR of PML-RARα on Day 43. This testing is separate from research samples submitted for the optional MRD study; this mandatory clinical testing is not free of charge (cost is not covered by the study), but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing; a list of approved labs is available on the protocol-specific web page of the COG website. If the initial RQ-PCR is negative continue to Consolidation Cycle 3 (Section 4.12) on Day 57 of this cycle or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later. If the initial RQ-PCR test is positive, contact the study chair and a repeat sample must be sent 1-2 weeks later. This testing is not paid for by the study, but it is recommended that this confirmation sample be sent to either Hematologics, Inc, Seattle, WA, USA or the Molecular Haematology Lab, Royal Prince Alfred Hospital, NSW, Australia due to their experience with these samples. If repeat test is negative continue to Consolidation Cycle 3 (see Section 4.12) on Day 57 of this cycle. If repeat test is confirmed positive continue to MRD Positive Consolidation (Section 4.11) on Day 57 of this cycle.

MRD Positive Consolidation – High Risk

MRD Positive Consolidation is only for those patients with RQ-PCR of PML-RARα confirmed positive after Consolidation Cycle 2.

If the RQ-PCR of PML-RARα is negative after Consolidation Cycle 2, proceed to Consolidation Cycle 3 (see Section 4.12)

4.11 MRD Positive Consolidation – High Risk APL

4.11.1 MRD Positive Consolidation Therapy Delivery Map – High Risk APL

MRD Positive Consolidation is only for those patients with RQ-PCR confirmed positive after Consolidation Cycle 2. Start on Day 57 of Cycle 2 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.

_____
Patient COG ID number

_____
DOB

This course lasts 28 days. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
High Dose Cytarabine (HD ARAC)	IV over 1-3 hours every 12 hours	1000 mg/m^2/dose, twice daily if BSA < 0.6m^2, 33.3 mg/**kg**/dose, twice daily	1 - 4	Total dose: 2000 mg/m^2/day, divided twice daily **or** 66.6 mg/kg/day, divided twice daily if BSA < 0.6 m^2. Use eye drops as described in Section 4.11.3.
MitoXANtrone (MITOX)	IV daily over 15-30 minutes	12 mg/m^2/dose If BSA < 0.6 m^2, 0.4 mg/**kg**/dose daily	3 – 6	On Days 3 and 4, administer 8 hours after the 5th and 7th cytarabine infusions are completed. See Section 4.11.3 for details.
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 14	**Total Dose:** 25 mg/m^2/day divided twice daily. Administer with food. Refer to Appendix II for dosing table.

Ht _____cm **Wt _____kg** **BSA _____m^2**
Actual body weight (not ideal or adjusted weight) should be used for all dose calculations

Date Due	Date Given	Day	HD ARAC _____mg _____mg	MITOX _____mg	ATRA _____mg _____mg	Studies
			Enter calculated dose above and actual dose administered below			
		1	_____mg _____mg		_____mg _____mg	a – g
		2	_____mg _____mg		_____mg _____mg	
		3	_____mg _____mg	_____mg	_____mg _____mg	
		4	_____mg _____mg	_____mg	_____mg _____mg	
		5		_____mg	_____mg _____mg	
		6		_____mg	_____mg _____mg	
		7			_____mg _____mg	
		8			_____mg _____mg	c, d, e
		9			_____mg _____mg	
		10			_____mg _____mg	
		11			_____mg _____mg	
		12			_____mg _____mg	
		13			_____mg _____mg	
		14			_____mg _____mg	
		15				c, d, e
		16				
		17				
		18				
		19				
		20				
		21				
		22				c, d, e
		23				
		24				
		25				
		26				
		27				
		28				
		29	*A bone marrow evaluation will be done for RQ-PCR of PML-RARα. If negative, continue to Consolidation Cycle 3 (see Section 4.12). If positive in 2 successive specimens, patient will go off protocol therapy.*			a, h

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

MRD Positive Consolidation – High Risk

4.11.2 Required Observations in MRD Positive Consolidation – High Risk APL

a. Physical Exam with VS: every 4 weeks b. Ht, Wt, BSA c. CBC, differential, platelets: Weekly d. Electrolytes and creatinine: Weekly e. AST, ALT, Total Bilirubin (and prior to Mitoxantrone a Direct Bilirubin if Total Bilirubin is >3.3 mg/dL): Weekly f. Cholesterol, triglycerides g. Echocardiogram or MUGA h. BMA for clinical RQ-PCR of PML-RARα: Obtain on Day 29, if positive, repeat 1 - 2 weeks later. This **mandatory** testing is not paid for by the study. It is recommended that this testing be sent to either Hematologics, Inc, Seattle, WA, USA or the Molecular Haematology Lab, Royal Prince Alfred Hospital, NSW, Australia due to their experience with these samples.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.11.3 MRD Positive Consolidation Treatment Details – High Risk APL

MRD Positive Consolidation consists of a combination of high dose cytarabine, mitoxantrone and twice daily ATRA. This cycle lasts for 28 days. It is strongly recommended that the patients remain inpatient for the duration of this cycle of Consolidation and until count recovery.

Antifungal prophylaxis should be strongly considered (dependent on institutional practice) during this cycle due to an expected prolonged period of neutropenia. However, treating physicians should be aware that azole antifungal medications may increase ATRA toxicity due to inhibition of cytochrome P - 450 metabolism of ATRA. Thus patients should be monitored closely for adverse events such as, pseudotumor cerebri or renal dysfunction, during periods of concomitant use. For prophylactic antifungal use, initiation of an azole antifungal could be delayed until after completion of ATRA on Day 14 of this cycle or an alternate non-azole antifungal should be considered.

High Dose Cytarabine: IV over 1 - 3 hours every 12 hours
Days: 1 - 4 (8 total doses)
Dose: 1,000 mg/m^2/dose every 12 hours. If BSA < 0.6 m^2, 33.3 mg/**kg**/dose.

NOTE: Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose and continuing for 24 hours after the final dose. If patient does not tolerate steroid eye drops, may administer artificial tears on an every 2 - 4 hour schedule.

MitoXANtrone: IV daily over 15 - 30 minutes
Days: 3 - 6
Dose: 12 mg/m^2/dose once daily. If BSA < 0.6 m^2 0.4 mg/**kg**/dose.
Administer through the tubing of a rapidly infusing solution of D_5W or 0.9% NaCl. Avoid extravasation; the use of a central line is suggested. On Days 3 and 4, mitoxantrone should be given 8 hours after the 5th and 7th high dose cytarabine infusions are complete.

Tretinoin (ATRA): PO divided BID
Days: 1 - 14
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients).

A bone marrow evaluation will be done for clinical RQ-PCR of PML-RARα on Day 29. This testing is not paid for by the study, but it is recommended that this testing be sent to either Hematologics, Inc, Seattle, WA, USA or the Molecular Haematology Lab, Royal Prince Alfred Hosptial, NSW, Australia due to their experience with these samples. If negative, continue to Consolidation Cycle 3 (see Section 4.12) on Day 29 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later. If positive, repeat 1 - 2 weeks later and if second test is positive then patient will go off protocol therapy.

4.12 Consolidation Cycle 3 – High Risk APL

4.12.1 Consolidation Therapy Delivery Map Cycle 3 – High Risk APL

Start Consolidation Cycle 3 only if RQ-PCR of PML-RARα is negative. *Cycle 3 starts on Day 57 of Cycle 2 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.* ***OR*** *Consolidation Cycle 3 starts on Day 29 of MRD Positive Consolidation cycle if needed or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.*

_____ Patient COG ID number _____ DOB

Consolidation Cycle 3 lasts 8 weeks. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 14 and 29 - 42	**Total Dose:** 25 mg/m^2/day divided twice daily. Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV over 2 hours*	0.15 mg/**kg**/day	1 - 5, 8 - 12, 15 - 19, 22 - 26	*May be extended to 4 hours see Section 4.12.3 for additional details
Triple Intrathecal Therapy (ITT) Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age: 1-1.99 yrs: 8 mg MTX, 15 mg HC, 30 mg ARAC; 2-2.99 yrs: 10 mg MTX, 25 mg HC, 50 mg ARAC; ≥3 yrs: 12 mg MTX, 35 mg HC, 70 mg ARAC	15 and 43	Only patients with documented CNS disease or CNS bleed will require intrathecal treatments (see Sections 3.3.4 and 4.12.3 for details).

Ht _____cm **Wt _____kg** **BSA _____m^2**

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations

Date Due	Date Given	Day	ATRA _____mg _____mg	ATO _____mg	ITT _____mg (MTX) _____mg (HC) _____mg (ARAC)	Studies
			Enter calculated dose above and actual dose administered below			
		1	_____mg _____mg	_____mg	***Only patients with CNS disease or CNS bleed will require intrathecal treatments*** *(see Sections 3.3.4 and 4.12.3 for details)*	a – g, h*
		2	_____mg _____mg	_____mg		
		3	_____mg _____mg	_____mg		
		4	_____mg _____mg	_____mg		
		5	_____mg _____mg	_____mg		
		6	_____mg _____mg			
		7	_____mg _____mg			
		8	_____mg _____mg	_____mg		c, d. e, f
		9	_____mg _____mg	_____mg		
		10	_____mg _____mg	_____mg		
		11	_____mg _____mg	_____mg		
		12	_____mg _____mg	_____mg		
		13	_____mg _____mg			
		14	_____mg _____mg			
		15		_____mg	_____mg (MTX) _____mg (HC) _____mg (ARAC)	c, d, e, f
		16		_____mg		
		17		_____mg		
		18		_____mg		
		19		_____mg		
		---	---	---		
		22		_____mg		c, d, e, f
		23		_____mg		
		24		_____mg		
		25		_____mg		
		26		_____mg		
		---	---	---		
		29	_____mg _____mg ↓			a, c, e

		42	_____mg _____mg			
		43			_____mg (MTX) _____mg (HC) _____mg (ARAC)	
		---	---	---		
		56				
		57	*Proceed to Consolidation Cycle 4 (see Section 4.13) on Day 57 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.*			

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Consolidation – Cycle 3 – High Risk

4.12.2 Required Observations in Consolidation Cycle 3 – High Risk APL

a. Physical Exam with VS: every 4 weeks
b. Ht, Wt, BSA
c. CBC, differential, platelets: Weekly while receiving ATO and on Day 29.
d. Electrolytes including Ca^{++}, Mg^{++}, K^{+} and creatinine: Weekly while receiving ATO
e. AST, ALT, Total Bilirubin (and Direct Bilirubin if Total Bilirubin is >2 mg/dL): Weekly while receiving ATO and on Day 29.
f. ECG for QTc monitoring: Weekly while receiving ATO
g. Cholesterol, triglycerides
h. Neurocognitive Testing (optional)*: CogState and BRIEF on Day 1 of Consolidation Cycle 3 (+/-2 weeks). See Section 16 for details.

*Only obtain in patients who have consented to participation in this component of the trial.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

Consolidation – Cycle 3 – High Risk

4.12.3 Consolidation Cycle 3 Treatment Details – High Risk APL

Consolidation Cycle 3 lasts 56 days.

Tretinoin (ATRA): PO divided BID
Days: 1 - 14 and 29 - 42
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients).

Arsenic Trioxide (ATO): IV over 2 hours (may lengthen infusion to 4 hours if active vasomotor symptoms occur)
Days: 1 - 5, 8 - 12, 15 - 19 and 22 - 26
Dose: 0.15 mg/**kg**/day (no maximum dose)

NOTE: Some patients may require infusion in a clinic setting (i.e. unable to arrange home infusion) and holidays may result in intermittent clinic closure. Therefore it is permissible for patients to miss doses of ATO on those days at the discretion of the treating physician. It is suggested that patients not miss more than 2 doses in a 4 week period (10% of doses). If more than 2 doses are missed in a 4 week period due to holidays, then make-up doses (following Day 26) may be administered at the discretion of the treating physician.

Indications for intrathecal therapy

Intrathecal Triple Therapy (ITT): Only for patients with documented history of CNS bleed or CNS positive disease.

Days: 15 and 43
Dose: Age based dosing as follows

	Triple Intrathecal Therapy (ITT)		
Age	Methotrexate	Hydrocortisone	Cytarabine
1 - 1.99 years	8 mg	15 mg	30 mg
2 - 2.99 years	10 mg	25 mg	50 mg
≥ 3years	12 mg	35 mg	70 mg

Proceed to Consolidation Cycle 4 on Day 57 or when blood counts recover (ANC ≥1,000/µL and platelet count ≥ 100,000/µL), whichever occurs later. See Section 4.13 for details.

4.13 Consolidation Cycle 4 – High Risk APL

4.13.1 Consolidation Therapy Delivery Map Cycle 4 – High Risk APL *Consolidation Cycle 4 starts on Day 57 of Cycle 3 or when blood counts recover (ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL), whichever occurs later.*	_____ Patient COG ID number _____ DOB

Consolidation Cycle 4 lasts 4 weeks. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Tretinoin (ATRA)	PO	12.5 mg/m^2/dose, twice daily	1 - 14	**Total Dose:** 25 mg/m^2/day divided twice daily Administer with food. Refer to Appendix II for dosing table
Arsenic Trioxide (ATO)	IV over 2 hours*	0.15 mg/**kg**/day	1 - 5, 8 - 12, 15 - 19, 22 - 26	*May be extended to 4 hours see Section 4.13.3 for additional details

Ht _____cm Wt _____kg BSA _____m^2

Actual body weight (not ideal or adjusted weight) should be used for all dose calculations.

Date Due	Date Given	Day	ATRA _____mg _____mg	ATO _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below			
		1	_____mg _____mg	_____mg	a – g	
		2	_____mg _____mg	_____mg		
		3	_____mg _____mg	_____mg		
		4	_____mg _____mg	_____mg		
		5	_____mg _____mg	_____mg		
		6	_____mg _____mg			
		7	_____mg _____mg			
		8	_____mg _____mg	_____mg	c, d, e, f	
		9	_____mg _____mg	_____mg		
		10	_____mg _____mg	_____mg		
		11	_____mg _____mg	_____mg		
		12	_____mg _____mg	_____mg		
		13	_____mg _____mg			
		14	_____mg _____mg			
		15		_____mg	c, d, e, f	
		16		_____mg		
		17		_____mg		
		18		_____mg		
		19		_____mg		
		---	---	---		
		22		_____mg	c, d, e, f	
		23		_____mg		
		24		_____mg		
		25		_____mg		
		26		_____mg		
		27	---	---		
		28			a, c, h, i, j*, k*	

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Consolidation – Cycle 4 – High Risk

4.13.2 Required Observations in Consolidation Cycle 4 – High Risk APL

a. Physical Exam with VS: Day 1 and 28
b. Ht, Wt, BSA
c. CBC, differential, platelets: Weekly
d. Electrolytes including Ca^{++}, Mg^{++}, K^{+} and creatinine: Weekly while receiving ATO
e. AST, ALT, Total Bilirubin (and Direct Bilirubin if Total Bilirubin is >2 mg/dL): Weekly while receiving ATO
f. ECG for QTc monitoring: Weekly while receiving ATO
g. Cholesterol, triglycerides
h. Echocardiogram or MUGA: at the end of protocol therapy
i. BMA for clinical RQ-PCR of PML-RARα: at the end of protocol therapy. This testing is separate from research samples submitted for the optional MRD RQ-PCR study; this **mandatory** clinical testing is not free of charge (cost is not covered by the study), but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing; a list of approved labs is available on the protocol-specific web page of the COG website.
j. Research MRD (Optional)*: bone marrow and peripheral blood at the end of protocol therapy. See Section 15.2 for details.
k. Neurocognitive Testing (Optional)*: CogState, BRIEF and the psychologist administered battery at the end of protocol therapy (up to 3 months after the end of protocol therapy). See Section 16 for details.

*Only obtain in patients who have consented to participation in this component of the trial.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

Comments

4.13.3 Consolidation Cycle 4 Treatment Details – High Risk APL

Consolidation Cycle 4 lasts 28 days.

Tretinoin (ATRA): PO divided BID
Days: 1 - 14
Dose: 12.5 mg/m^2/dose, twice daily. The total dose is 25 mg/m^2/day divided twice daily.
Administer with food. Refer to Appendix II for dosing table (includes dose recommendations for very young patients).

Arsenic Trioxide (ATO): IV over 2 hours (may lengthen infusion to 4 hours if active vasomotor symptoms occur)
Days: 1 - 5, 8 - 12, 15 - 19 and 22 - 26
Dose: 0.15 mg/**kg**/day (no maximum dose)

NOTE: Some patients may require infusion in a clinic setting (i.e. unable to arrange home infusion) and holidays may result in intermittent clinic closure. Therefore it is permissible for patients to miss doses of ATO on those days at the discretion of the treating physician. It is suggested that patients not miss more than 2 doses in a 4 week period (10% of doses). If more than 2 doses are missed in a 4 week period due to holidays, then make-up doses (following Day 26) may be administered at the discretion of the treating physician.

A bone marrow evaluation is performed for RQ-PCR of PML-RARα on Day 28. This testing is separate from research samples submitted for the optional MRD study; this mandatory clinical testing is not free of charge (cost is not covered by the study), but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing; a list of approved labs is available on the protocol-specific web page of the COG website.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 APL Differentiation Syndrome

The APL differentiation syndrome (described below) is a life-threatening complication of APL generally seen during Induction therapy after starting tretinoin and arsenic trioxide and prior to the patient achieving remission. Patients with high risk APL will receive dexamethasone at prophylaxis dosing to help prevent this syndrome. Also patients with standard risk APL who have their WBC count rise to > 10,000/µL without symptoms of APL differentiation syndrome should begin prophylactic dosing of dexamethasone. If a patient develops symptoms of APL differentiation syndrome, follow guidelines for treatment dosing of dexamethasone (see below).

APL differentiation syndrome: a spectrum of clinical manifestations of a cardiorespiratory distress syndrome that include at least **three** of the following: respiratory distress, hypoxemia, fever, erythematous rash, pulmonary infiltrates, pleural or pericardial effusions, weight gain, peripheral edema, acute renal failure, congestive heart failure and hypotension. Patients with this syndrome may develop progressive cardiopulmonary failure.

If this syndrome is suspected:

- Promptly start treatment dose dexamethasone 5.8 mg/m^2/dose IV BID (max 10 mg/dose BID) for a minimum of 3 days and continue until resolution of symptoms, at which point dexamethasone should be continued at a prophylactic dose through Day 14.
- Hold tretinoin and arsenic trioxide. Once the symptoms and the patient's clinical condition improve, restart both medications at 50% of the previous dose (for tretinoin 6.25 mg/kg/dose twice daily (12.5 mg/m^2/day), for arsenic trioxide, 0.075 mg/**kg**/day) during the first 7 days. After 7 days, increase back to the full dose as prescribed in the protocol. Do not make-up missed doses during the cycle. If patients experience recurrent symptoms of APL differentiation syndrome, follow the same dose reduction directions above again and ensure the patient is on dexamethasone at treatment doses.
  NOTE: In patients with high risk APL, Induction doses of IDArubicin should not be held or dose adjusted due to APL differentiation syndrome unless the clinician feels that cardiac function is impaired to a degree that would make idarubicin dosing contraindicated. If IDArubicin doses are held for this reason, the doses should be restarted when tolerable (do not skip idarubicin doses).
- Furosemide may be used as clinically indicated to treat fluid overload.
- Notify the study chair of any patient with persistent signs/symptoms of the APL differentiation syndrome that requires holding tretinoin and arsenic trioxide for more than 3 days.

5.2 Tretinoin Dose Modifications (Including Modifications for Pseudotumor Cerebri)

Commonly observed toxicities with tretinoin include hepatotoxicity (increased AST and ALT), neurologic changes including headache or pseudotumor cerebri (see below), dermatology/skin changes and others including chelitis, epistaxis, fatigue, musculoskeletal pain, and conjunctivitis. If a patient experiences a Grade ≥ 3 toxicity that is felt to be related to tretinoin, then tretinoin will be held until the toxicity has resolved to the Grade 1 level.

At that time restart tretinoin at 25% dose reduction (19 mg/m^2/day divided twice daily). Dosing of tretinoin should be as close as possible to 19 mg/m^2/day divided twice daily, i.e., round to the nearest 10 mg (round < 5 mg down and ≥ 5 mg up). If necessary, the AM dose may differ from the PM dose to deliver a total daily dose as close as possible to 19 mg/m^2/day divided twice daily. Recurrent episodes of Grade ≥ 3 toxicity will result in discontinuation of the tretinoin until the toxicity resolves to Grade ≤ 1; tretinoin will then be resumed with an additional 25% reduction (50% total dose reduction) in the tretinoin dose (12.5 mg/m^2/day divided twice daily). Dosing of tretinoin should be as close as possible to 12.5 mg/m^2/day divided twice daily; i.e., round to the nearest 10 mg (round < 5 mg down and ≥ 5 mg up). If necessary, the AM dose may differ from the PM dose to deliver a total daily dose closest to 12.5 mg/m^2/day divided twice daily. Patients experiencing Grade ≥ 3 toxicity attributable to tretinoin while on 12.5 mg/m^2/day of tretinoin should have tretinoin held until the toxicity resolves to Grade ≤ 1. tretinoin will then be resumed at the same 50% dose reduction (12.5 mg/m^2/day divided twice daily) while continuing to monitor for toxicity and holding doses as needed for Grade ≥ 3 toxicity. Please notify the study chair about patients experiencing Grade ≥ 3 toxicity while on 50% dose reduction.

If patients whose doses are reduced by 25% (19 mg/m^2/day divided twice daily) or 50% (12.5 mg/m^2/day divided twice daily) tolerate the lower dose for 7 days without recurrence of the toxicity that led to dose adjustment, a dose escalation may be attempted. If the patient had been decreased to 50% dosing (12.5 mg/m^2/day divided twice daily) and tolerates an escalation to 75% dosing (19 mg/m^2/day divided twice daily) for an additional 7 days, another escalation back to 100% dosing (25 mg/m^2/day divided twice daily) may be attempted.

The APL Differentiation Syndrome should be treated as outlined in Section 5.1.

5.2.1 Pseudotumor Cerebri

Pseudotumor cerebri (PTC) must be confirmed by proper history, exam and other clinically relevant studies. Symptoms/signs of PTC include headache, papilledema, visual field defects (ocular/visual), and absence of focal neurological symptoms, except for occasional cranial nerve (CN) VI palsy (neuropathy: cranial CN VI). Cerebrospinal fluid should be evaluated and should be negative for signs of infection. However, lumbar puncture should be avoided while active coagulopathy is present. An opening pressure should be obtained; a pressure > 200 mm water helps to establish the diagnosis of PTC. A CT or MRI of the brain (to evaluate for meningitis, intracranial bleed, intracranial thrombosis, etc.) should be performed and should be compatible with PTC. Neurological and ophthalmologic consultations should be obtained in order to assist in making the proper diagnosis. Carefully follow the visual field status of the patient. One should also strongly consider obtaining a MRI/MRV to exclude the possibility of a sagittal sinus thrombosis. Consider acetazolamide (Diamox) therapy and periodic lumbar puncture with therapeutic removal of cerebrospinal fluid as appropriate for age/size.

If PTC develops:

- Hold tretinoin until this toxicity improves to Grade 0 or 1 (“mild” headache).

- Restart tretinoin at 75% of the original dose (19 mg/m^2/day divided twice daily). If PTC reoccurs, hold tretinoin as above and then resume at 50% of original dose (12.5 mg/m^2/day divided twice daily).

If the patient tolerates reduced dosing for more than 7 days, dose re-escalation can be attempted. Dose escalation from 50% (12.5 mg/m^2/day divided twice daily) to 75% (19 mg/m^2/day divided twice daily) to 100% (25 mg/m^2/day divided twice daily) at 7 day intervals may be attempted if clinically appropriate.

5.3 Arsenic Trioxide Dose Modifications

Missed doses due to holidays or dose modifications do not need to be made up. However, if more than 2 doses are missed in a 4 week period due to holidays (not dose modifications), then make-up doses (following Day 26 of Consolidation Cycles 1 - 4) may be administered at the discretion of the treating physician.

5.3.1 Hepatotoxicity

At initial diagnosis, patients may have abnormal liver function tests due to their malignancy and no dose adjustment of arsenic trioxide is needed at initiation of therapy. Hepatotoxicity that occurs during arsenic trioxide treatment should prompt dose modifications as noted below.

If during arsenic trioxide administration, the patient has either:

- AST > 5 fold increase over the upper limit of normal (ULN)
- or direct bilirubin > 2 mg/dL

then hold arsenic trioxide until AST ≤ 3x ULN and direct bilirubin ≤ 0.5 mg/dL, after which resume arsenic trioxide treatment with a 50% dose reduction (0.075 mg/**kg**/day) during the first 7 days.

After 7 days of the reduced dose, and in the absence of worsening of the previous toxicity, arsenic trioxide should be resumed at full dose.

If a patient meets hepatotoxicity criteria for holding arsenic trioxide a second time, again hold arsenic trioxide until AST ≤ 3x ULN and direct bilirubin ≤ 0.5 mg/dL, then resume treatment with a 50% dose reduction (0.075 mg/**kg**/day) for all further doses of arsenic trioxide (no re-escalation of dose). If hepatotoxicity recurs while on 50% dosing, hold arsenic trioxide again until AST ≤ 3x ULN and direct bilirubin ≤ 0.5 mg/dL prior to restarting again at the 50% dose reduction (0.075 mg/**kg**/day). Please notify the study chair of cases in which hepatotoxicity occurs while on 50% dosing.

5.3.2 Hematological Toxicity

During Induction: No dose adjustment is required for anemia, decreased neutrophil count or decreased platelet count.

During Consolidation: If the patient has absolute neutrophil count < 1,000/uL or platelets < 50,000/uL lasting more than 5 weeks, then during the next cycle arsenic

trioxide should be dosed at 75% (0.11 mg/**kg**/day). If the patient again has absolute neutrophil count < 1,000/uL or platelets < 50,000/uL lasting more than 5 weeks, then during the next cycle arsenic trioxide should be dosed at 50% (0.075 mg/**kg**/day).

5.3.3 Nausea/Vomiting

Nausea/vomiting of any grade should be handled with symptomatic treatment with anti-emetics. If > 6 - 8 episodes occur daily, despite adequate trial of anti-emetics, then hold treatment until clinical improvement before resuming treatment at full dose. If treatment-refractory nausea/vomiting recurs, then hold treatment until improvement to Grade ≤ 1 and then resume treatment with a 50% dose reduction (0.075 mg/**kg**/dose). The dose may be escalated back to 100% (0.15 mg/**kg**/dose) at the next cycle.

When selecting anti-emetics, investigators should consider the potential for QTc prolongation when used in conjunction with arsenic trioxide.

5.3.4 Cardiac Toxicity

Guidelines for the management of prolongation of the corrected QT (QTc) interval are as follows:

Measure the QT interval (from the start of the Q wave to the end of the T wave) and the preceding RR interval. The QTc interval will be calculated using Bazett's formula: the QT interval (msec) divided by the square root of the RR interval (msec).

- QTc interval 450 - 500 msec: Continue arsenic. Serum K^+, Mg^{++}, and Ca^{++} should be monitored and repleted only if low.
- QTc interval 501 - 600 msec: Hold arsenic temporarily and replete serum K^+, Mg^{++}, and Ca^{++} with IV and/or oral supplements immediately. Serum K^+ and Mg^{++} should be repleted to minimum target levels of 4.0 and 1.8 mg/dL, respectively. Discontinue any medications that prolong the QT interval. Resume arsenic on same day if target levels are achieved; re-check serum electrolytes prior to the next dose.
- QTc interval > 600 msec: Hold arsenic. Aggressive IV K^+ and Mg^{++} repletion. If the QTc interval falls below 600 msec, outpatient management may be considered with additional oral supplements and an ECG should be repeated the following day and/or prior to further arsenic treatment. Serum K^+ and Mg^{++} should be repleted to minimum target levels of 4.0 and 1.8 mg/dL, respectively. Discontinue any medications that prolong the QT interval. Resume arsenic on same day if target levels are achieved; re-check serum electrolytes prior to the next dose. If the QTc interval does not fall below 600 msec with this level of repletion, the patient should undergo ECG monitoring by telemetry, preferably in the hospital, along with continued IV K^+ and Mg^{++}.
- Consider cardiology consultation if QTc is found to be prolonged.
- If syncope or rapid or irregular heartbeat develops, the patient should be hospitalized for monitoring and serum electrolytes should be assessed. Treatment with arsenic trioxide should be temporarily discontinued until

the QTc interval regresses to below 450 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease.

5.3.5 Neurologic Toxicity

Arsenic trioxide may cause neuropathy which most commonly involves painful peripheral neuropathy. This should be managed with medications appropriate for neuropathy (such as gabapentin or pregabalin) and pain medication (including narcotics as needed). Arsenic trioxide dosing should be modified for Grade ≥3 neuropathy by following the guidelines in Section 5.3.6 below.

5.3.6 Other Toxicities (Excludes hepatic, hematologic, nausea/vomiting, and cardiac toxicities which are described above)

If a patient has active vasomotor symptoms during the infusion (including dizziness, hypotension, tachycardia, or flushing) the infusion time may be extended to 4 hours.

If a patient experiences a Grade ≥ 3 toxicity that is felt to be related to arsenic trioxide, arsenic trioxide will be held until the toxicity has resolved to Grade ≤ 1. At that time restart arsenic trioxide at a 75% dose (0.11 mg/**kg**/day). Recurrent episodes of Grade ≥ 3 toxicity will result in holding of arsenic trioxide until the toxicity resolves to Grade ≤ 1; arsenic trioxide will then be resumed with an additional 25% reduction in the arsenic trioxide dose (0.075 mg/**kg**/day). Patients experiencing Grade ≥ 3 toxicity attributable to arsenic trioxide while on 0.075 mg/**kg**/day of arsenic trioxide should be discussed with the study chair.

5.4 IDArubicin and MitoXANtrone Dose Modifications

5.4.1 Hepatic Toxicity

IDArubicin

Dose Adjustments for IDArubicin		
Direct Bilirubin	**BSA ≥ 0.6m^2**	**BSA < 0.6m^2**
< 2.6 mg/dL	100% dosing (12 mg/m^2/dose)	100% dosing (0.4 mg/**kg**/dose)
2.6-5 mg/dL	50% dosing (6 mg/m^2/dose)	50% dosing (0.2 mg/**kg**/dose)
> 5 mg/dL	**Hold until direct bilirubin < 5 mg/dL**	**Hold until direct bilirubin < 5 mg/dL**

If held for direct bilirubin > 5 mg/dL, start (or restart) IDArubicin doses once the direct bilirubin falls below 5 mg/dL (give at 50% dose if the direct bilirubin is 2.6 - 5 mg/dL or give at full dose if direct bilirubin is < 2.6 mg/dL). Although the doses may be delayed, **all high risk patients should still receive a total of 4 IDArubicin doses** (each dose may be either full dose or reduced dose) spaced at least 48 hours apart during Induction. Please notify the study chair of patients who require delays in IDArubicin doses due to direct hyperbilirubinemia in Induction

MitoXANtrone

Dose Adjustments for MitoXANtrone		
Direct Bilirubin	**BSA ≥ 0.6m²**	**BSA < 0.6m²**
< 3.4 mg/dL	100% dosing (12 mg/m²/dose)	100% dosing (0.4 mg/**kg**/dose)
3.4-5 mg/dL	25% dosing (3 mg/m²/dose)	25% dosing (0.1 mg/**kg**/dose)
> 5 mg/dL	**Hold until direct bilirubin < 5 mg/dL**	**Hold until direct bilirubin < 5 mg/dL**

In severe liver dysfunction, the half-life of mitoXANtrone is prolonged and the AUC may be more than 3 fold that of patients with normal hepatic function. If the direct bilirubin is > 5 mg/dL, hold the mitoXANtrone dose. If the direct bilirubin is between 3.4 and 5 mg/dL, give 25% of the mitoXANtrone dose. Monitor the direct bilirubin closely and if it decreases to < 3.4 mg/dL, further doses of mitoXANtrone may be given at full dose.

5.4.2 Renal Toxicity

If creatinine clearance (CrCl) < 50 mL/minute, administer 75% of the IDArubicin dose (if BSA < 0.6 m², 0.3 mg/**kg**/dose, if BSA ≥ 0.6 m², 9 mg/m²/dose).

5.4.3 Left Ventricular Cardiac Function Toxicity

IDArubicin and mitoXANtrone will be withheld if there is significant evidence of cardiac disease by echocardiogram or MUGA (shortening fraction < 27%). Do not re-start these drugs if withheld for this reason.

5.5 Cytarabine Dose Modifications

5.5.1 Neurological Toxicity

Patients with Grade ≥ 3 neurotoxicity from high dose cytarabine should not receive further high dose cytarabine. The most common neurotoxicity is an acute cerebellar syndrome that may manifest itself as ataxia, nystagmus, or dysarthria. However, seizures and encephalopathy have also occurred following therapy with high dose cytarabine.

5.5.2 Renal Toxicity

Patients with nephrotoxicity secondary to antibiotics, or antifungals, may have prolonged excretion of cytarabine leading to more severe marrow and extramedullary toxicity. Patients with a serum creatinine > 2 mg/dL or > 2 x upper limit of normal for age should be hydrated orally or intravenously. Following hydration, the patient must have a creatinine clearance ≥ 60 mL/min/1.73m² as measured preferably by a nuclear GFR scan, timed urine collection for creatinine clearance, or calculated by the IDMS-traceable Schwartz equation for children[68] or the IDMS-traceable MDRD study equation for adults[69] (see equations below) before proceeding with HD cytarabine therapy (doses of 1 g/m²). If the CrCl is abnormal (< 60 mL/min/1.73m²) then high dose cytarabine should be reduced from twice daily to once daily dosing, at the same previously prescribed doses (i.e., 50% daily dose reduction if BSA < 0.6 m², 33.3 mg/**kg**/day, if BSA ≥ 0.6 m², 1,000 mg/m²/day). With this approach, previous research has shown the prevention

of subsequent neurotoxicity in recipients of high dose cytarabine in the face of renal insufficiency.[70]

For patients < 18 years old:
GFR (in mL/min/1.73 m^2) = (0.41 x Height in cm)/(serum creatinine in mg/dL)

Online calculator **for patients < 18 years old** available at:
http://nkdep.nih.gov/lab-evaluation/gfr-calculators/children-conventional-unit.asp

For patients ≥ 18 years old:
GFR (in mL/min/1.73 m^2) = 175 x (serum creatinine in mg/dL)$^{-1.154}$ x (Age in years)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

Online calculator **for patients ≥ 18 years old** available at:
http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-conventional-unit.asp

6.0 DRUG INFORMATION

See the consent document for toxicities. All other information is available on the COG website in the commercial agent monographs manual titled "Drug Information for Commercial Agents used by the Children's Oncology Group." On the COG website, this manual is provided under Standard Sections for Protocols
at: https://www.cogmembers.org/site/pages/default.aspx?page=Prot_reference_materials

Please see Appendix IV for drug interactions associated with the drugs used in this study.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

7.1 Clinical Evaluation of RQ-PCR

Patients on AAML1331 require bone marrow samples for RQ-PCR of PML-RARα testing for clinical reasons. These specimens must be sent to one of the approved labs for PML-RARα RQ-PCR testing and the cost is not covered by the study. It should be billed as a regular clinical lab through the institution/insurance/patient as appropriate. A list of approved labs is available on the protocol-specific web page of the COG website located at https://cogmembers.org/PROT/AAML1331/AAML1331ValidatedRQ-PCRLabsList.pdf

7.1.1 Time Points for Clinical Evaluation of RQ-PCR of PML-RARα

- At diagnosis prior to initiating therapy. (See Section 3.1.4.1)
- Day 43 of Consolidation Cycle 2
    - If the initial Day 43 clinical RQ-PCR test is positive, contact the study chair and a repeat sample must be sent 1-2 weeks later. It is recommended that this confirmation sample be sent to either Hematologics, Inc, Seattle, WA, USA or the Molecular Haematology Lab, Royal Prince Alfred Hospital, NSW, Australia due to their experience with these samples. (These are billed to the patient) If repeat test is negative continue to Consolidation Cycle 3. If repeat test is confirmed positive continue to MRD Positive Consolidation.
- Day 29 of MRD Positive Consolidation if applicable
- End of protocol therapy
- Relapse

7.1.2 Required Specimens

Site should always confirm with the selected RQ-PCR laboratory with regard to what quantity of specimen and tube is appropriate for testing at their lab.

In general specimens can be drawn as follows:

- 3 mL of bone marrow in a purple top.

7.2 End of Therapy & Follow-up

STUDIES TO BE OBTAINED	End of Therapy	Follow-Up	Relapse
History			X
Physical Exam with VS	X	Monthly to 12 months, q3 months to 36 months, q6 months to 48 months, then yearly to 10 years	X
Ht, Wt, BSA			X
Performance Status	X		X
CBC, differential, platelets	X	Monthly to 12 months, q3 months to 36 months, q6 months to 48 months then yearly to 10 years	X
Electrolytes (Ca^{++}, Mg^{++}, K^{+}), and Creatinine			X
Uric Acid			X
Echocardiogram or MUGA, and ECG	X	Yearly to 10 years	
BMA for morphology			X
BMA for flow cytometry, cytogenetics & FISH			X
BMA for clinical RQ-PCR of PML-RARα	X	Strongly recommended for all patients with high risk APL and those patients with standard	X

		risk APL who required the MRD positive Consolidation Cycle: q3 months until 3 years from diagnosis.	

See COG Late Effects Guidelines for recommended post treatment follow-up at: http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

7.3 Research Studies for which Patient Participation is Optional

Optional Study	Specimen	Diagnosis	Day 1	Day 8	Day 15	Day 29	Consolidation Cycle 1 Day 1	Consolidation Cycle 2 Day 43	Consolidation Cycle 3 Day 1	End of therapy	2 years post therapy	4 years post therapy	Relapse (either molecular or morphologic)
FLT3	Bone Marrow	X[1, 3]						X					X
MRD	Bone Marrow AND Peripheral Blood	X[1]				X		X		X			X
Coagulopathy	Peripheral Blood in Citrate tube AND Peripheral Blood in CTI tube	X[2]	X	X	X	X							
Neurocognitive Testing[4]	CogState						X		X	X	X	X	
	BRIEF						X		X	X	X	X	
	Psychologist administered battery									X	X	X	

[1] If bone marrow is not obtained at diagnosis, may submit peripheral blood only.
[2] Requested if available.
[3] Diagnostic specimens collected on Project Every Child (APEC14B1).
[4] See Section 16.4.1 for evaluation time point details.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Failure to achieve an hCR/hCRi by Day 70 of Induction.
b) Refractory CNS leukemia following 6 doses of intrathecal therapy.
c) Failure to achieve molecular remission following the MRD Positive Consolidation cycle (mitoxantrone/cytarabine/ATRA)
d) Relapse (hematologic, molecular or extramedullary) during Consolidation therapy.
e) Repeat eligibility studies (if required) prior to initiation of protocol therapy are outside the parameters required for eligibility (see Section 3.2).
f) Refusal of further protocol therapy by patient/parent/guardian.
g) Completion of planned therapy.
h) Unacceptable toxicity due to protocol therapy (see Section 5.0)
i) Physician determines it is in patient's best interest.
j) Development of a second malignancy.
k) Pregnancy

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken Off Study.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence).
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of the date the patient was enrolled on this study.
f) RQ-PCR determines patient to be PML-RARα negative at diagnosis or RQ-PCR inevaluable (including patients determined to have a variant RARA translocation such as PLZF-RARα, NPM1-RARα, NUMA-RARα).
g) RQ-PCR sample not collected prior to initiation of protocol therapy.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

This is a non-randomized study of pediatric patients with APL stratified by risk group based on presenting WBC. Patients with standard risk disease (WBC < 10,000/μL at diagnosis) and high risk disease (WBC ≥ 10,000/μL at diagnosis) will be assessed independently for outcome measures. The primary endpoint will be event-free survival (EFS). EFS is defined as the time from on study to failure to achieve hematological CR prior to start of Consolidation, persistence of molecular positive disease after MRD Positive Consolidation course (mitoxantrone/cytarabine/ATRA chemotherapy course following Consolidation Cycle 2), relapse (molecular, morphologic or extramedullary), or death.

Other outcome measures will include the hematological, molecular, and cytogenetic remission rates after each phase of therapy, early death rates, overall survival from on study, treatment related mortality, relapse risk, percentage of patients experiencing Grade 3 or higher toxicity or any grade of cardiac toxicity, time to count recovery, and duration of hospitalization.

When AAML1331 was developed and opened, outcome data from the most recent prior COG APL study AAML0631 was not mature. Thus, similar to AAML0631, the statistical plan of AAML1331 initially used the historical comparator AIDA 0493 (the most mature and best outcomes published for pediatric APL). During the course of AAML1331 accrual, AAML0631 outcome data became available and demonstrated that the addition of arsenic trioxide (ATO) consolidation therapy resulted in higher survival estimates compared to AIDA0493. Therefore the statistical plan of AAML1331 was amended to include a primary outcome comparison to AAML0631.

AAML0631 included 2 cycles of ATO consolidation and has excellent survival results. Thus, we would not expect AAML1331 to be significantly superior to AAML0631, but rather the goal of the study should be to show non-inferiority to AAML0631. This design is clinically appropriate because the AAML1331 treatment regimen represents a significant reduction in cytotoxic chemotherapy treatments which should result in decreased toxicities (both in the short and long term). To demonstrate that AAML1331 therapy is non-inferior to AAML0631 would be a major step forward in reducing treatment morbidity and mortality.

Standard risk APL treatment on AAML0631 included 335 mg/m^2 of doxorubicin equivalents whereas AAML1331 includes no anthracycline for standard risk APL patients. Historical data suggests that patients with >300 mg/m^2 of anthracycline have a cardiomyopathy odds ratio of 27 compared to patients not exposed to anthracycline.[71] A large cohort of children treated with anthracycline and with long term follow-up has showed a clinical heart failure rate of 9.8% at 20 years when the cumulative anthracycline dose was >300 mg/m^2. Among patients who developed clinical heart failure (and did not die from their malignancy) the rate of death due to their heart failure was approximately 40%.[72] Therefore we believe it is appropriate to consider powering our analysis of standard risk APL outcomes on AAML1331 in a comparison that allows a very modest decrease in EFS from the 97% observed on AAML0631.

Our non-inferiority (NI) margin of 10% for the standard risk APL comparison is designed to allow sufficient power (80%) to demonstrate non-inferiority for an observed EFS of 95%. This allows a modest decrease of 2% from the 97% EFS observed on AAML0631 to account for the benefit of elimination of anthracycline chemotherapy (also knowing that most APL relapses are successfully treated with further therapy and autologous transplant consolidation). We also feel that the NI margin for the high risk group is clinically relevant given the degree of uncertainty in the AAML0631 survival estimates. The high risk group includes a NI margin of 14.5%, but the AAML0631 24 month EFS estimate has a similarly large confidence interval of +/-13%.

9.2 Patient Accrual and Expected Duration of Trial

The Children's Oncology Group recently completed a Phase III study of children with newly diagnosed APL (COG AAML0631). On AAML0631, the actual accrual rate was 31.5 patients per year (20 standard risk, 11.5 high risk). Allowing for up to 5% of patients

to be ineligible for study enrollment, enrollment of up to 158 patients will be required to assure that a total of 96 eligible patients with standard risk APL and 54 eligible patients with high risk APL are enrolled. It is estimated that accrual goals will be met in 5 years for both standard and high risk APL.

9.3 Statistical Analysis Methods

9.3.1 Analysis Plan

Primary Objective 1

EFS for patients with SR APL on this study will be compared against a fixed EFS of 97% at 24 months, which was observed for patients with SR APL treated on AAML0631.

The non-inferiority null hypothesis is that the 2-year EFS for SR patients on this study is not non-inferior to 97% with a non-inferiority (NI) margin of 10%. The alternative hypothesis is that the 2-year EFS for SR patients is non-inferior to 97% with a NI margin of 10%. The Kaplan-Meier method will be used to estimate 2-year EFS along with 90% log-minus-log transformed confidence limits for SR patients. If the lower confidence limit for the 2 year EFS exceeds 97% - 10% = 87%, non-inferiority will be concluded. The final analysis of EFS will occur after a minimum of 2-years following the enrollment of the last eligible SR patient.

Primary Objective 2

EFS for patients with HR APL on this study will be compared against a fixed EFS of 83% at 24 months, which was observed for patients with HR APL treated on AAML0631. The non-inferiority null hypothesis is that the 2-year EFS for HR patients on this study is not non-inferior to 83% with a NI margin of 14.5%. The alternative hypothesis is that the 2-year EFS for HR patients is non-inferior to 83% with a NI margin of 14.5%. The Kaplan-Meier method will be used to estimate 2-year EFS along with 90% log-minus-log transformed confidence limits for SR patients. If the lower confidence limit for the 3-year EFS exceeds 83% - 14.5% = 68.5%, non-inferiority will be concluded. The final analysis of EFS will occur after a minimum of 2 years following the enrollment of the last eligible HR patient.

9.3.2 Power Calculations

Primary Objective 1

A study of 96 evaluable SR patients using a one-sided type I error rate of 0.05 and 10% NI margin will have 80%, 91% and 97% power to reject the null hypothesis that the 2-year EFS is not non-inferior to 97% for a 2-year EFS of 95%, 96% and 97% respectively. Power calculations were performed using PASS 14.

Primary Objective 2

A study of 54 evaluable HR patients using a one-sided type I error rate of 0.05 and 14.5% NI margin will have 80% power to reject the null hypothesis that the 2-year EFS is not non-inferior to 83% for a 2-year EFS of 83%. Power calculations were performed using PASS 14.

9.3.3 Interim Monitoring

Interim analysis of the incidence of adverse events mainly due to arsenic trioxide will be performed for each cycle of therapy. If excessive toxicity is observed, then

treatment modification or study termination will be considered.

Futility monitoring – Standard Risk patients
The SR arm will be monitored for futility when approximately 50% of the expected number of EFS events have been observed (at least 4 of the 71 total events). The interim analysis is anticipated to occur after 80% of the patients are enrolled. We will calculate the conditional probability that the 90% log-minus-log transformed confidence limits for 2-year EFS exceeds 87%. For those who have not experienced an EFS event by the time of analysis, EFS time will be simulated under the alternative hypothesis using cure models consistent with 2-year EFS of 96%. If the conditional probability of rejecting the null hypothesis is less than 5%, the treatment arm will be identified for possible closure of accrual.

Simulations of the operating characteristics of this futility monitoring plan were performed 500 times assuming that EFS for SR patients enrolled up to the time of the interim monitoring would follow a cure model, S(t), consistent with a 2-year EFS of 87%. That is, $S(t) = [S_{0631}(t)]^{3.41}$, where
$S_{0631}(t) = 0.906 + 0.094 \exp(-0.0238*t)$, t measured in months, is the cure model corresponding to the AAML0631 EFS results for SR patients. For those who have not experienced an EFS event by the time of analysis (including those who have not enrolled yet), EFS was simulated 500 times using a cure model, S(t), consistent with a 2-year EFS of 97%. That is, $S(t) = [S_{0631}(t)]^{0.746}$. 60.4% of the time the conditional probability of rejecting the null hypothesis was less than 5%.

Simulations of the impact of this futility monitoring plan on overall power were performed 500 times assuming that EFS for SR patients enrolled up to the time of the interim monitoring would follow a cure model, S(t), consistent with a 2-year EFS of 97%. That is, $S(t) = [S_{AIDA}(t)]^{0.746}$, where
$S_{0631}(t) = 0.906 + 0.094 \exp(-0.0238*t)$, t measured in months, is the cure model corresponding to the AAML0631 EFS results for SR patients. For those who have not experienced an EFS event by the time of analysis (including those who have not enrolled yet), EFS was simulated 500 times using the same cure model S(t). The overall power accounting for stopping due to futility monitoring is 95%.

Futility monitoring – High Risk patients
The HR arm will be monitored for futility when approximately 50% of the expected number of EFS events have been observed (at least 6 of the 12 total events). The interim analysis is anticipated to occur after 80% of the patients are enrolled. We will calculate the conditional probability that the 90% log-minus-log transformed confidence limits for 2-year EFS exceeds 68.5%. For those who have not experienced an EFS event by the time of analysis, EFS time will be simulated under the alternative hypothesis using cure models consistent with 2-year EFS of 82%. If the conditional probability of rejecting the null hypothesis is less than 5%, the treatment arm will be identified for possible closure of accrual.

Simulations of the operating characteristics of this futility monitoring plan were performed 500 times assuming that EFS for HR patients enrolled up to the time of the interim monitoring would follow a cure model, S(t), consistent with a 3-year EFS of 71%. That is, $S(t) = [S_{0631}(t)]^{1.73}$, where

$S_{0631}(t) = 0.7973 + 0.2027 \exp(-0.0976*t)$, t measured in months, is the cure model corresponding to the AAML0631 EFS results for HR patients. For those who have not experienced an EFS event by the time of analysis (including those who have not enrolled yet), EFS was simulated 500 times using a cure model, S(t), consistent with a 2-year EFS of 82%. That is, $S(t) = [S_{0631}(t)]^1$. 58.4% of the time the conditional probability of rejecting the null hypothesis was less than 5%.

Simulations of the impact of this futility monitoring plan on overall power were performed 500 times assuming that EFS for HR patients enrolled up to the time of the interim monitoring would follow a cure model, S(t), consistent with a 2-year EFS of 82%. That is, $S(t) = [S_{0631}(t)]^1$, where
$S_{0631}(t) = 0.7973 + 0.2027 \exp(-0.0976*t)$, t measured in months, is the cure model corresponding to the AIDA 0493 EFS results for HR patients. For those who have not experienced an EFS event by the time of analysis (including those who have not enrolled yet), EFS was simulated 500 times using this cure model S(t). The overall power accounting for stopping due to futility monitoring is 78%.

9.4 Correlative Biology Studies

9.4.1 Study design for Study Objective 1.2.1 (FLT3 Mutations)

A Fisher's exact test will be used to compare the Induction death rate for patients with FLT3 mutations to patients with wild type FLT3. Assuming 140 patients have FLT3 results available and a FLT3 mutation prevalence of 40% (based on prior pediatric APL data), this study will have 80% power with two-sided 0.05 type I error to detect differences of 19.5% and 15.5% in Induction death rates for Induction death rates of 30% and 20%, respectively, for FLT3 mutant patients.[42] The mutational analysis will be performed on diagnostic samples with an expected sample size of 140 and average accrual of 2.3 patients/month.

9.4.2 Study design for Study Objective 1.2.2 (Bone Marrow and Peripheral Blood MRD Testing)

For patients in remission at the end of Induction, the log-rank test will be used to test for differences in disease free survival (DFS) for those with end of Induction RQ-PCR of < 1 normalized copy number (NCN) compared with those with end of Induction RQ-PCR ≥ 1 NCN. Assuming 90% of patients are in remission at the end of Induction and 65% of these have specimens available to be analyzed by PCR, there will be at least 85 patients in remission at the end of Induction with PCR results. This corresponds to an average accrual rate of 1.4 patients/month. This study will have 80% power with two-sided 0.05 type I error to detect a difference of 32% in 5-year DFS (90% vs. 58%, 5.2 hazard ratio).

9.4.3 Study design for Study Objective 1.2.3 (Early Death and Coagulopathy Complications)

Adverse event reporting will be used to estimate the rate of serious early coagulopathy events (Grade 3 or higher hemorrhage or thrombosis from diagnosis through end of Induction). We will calculate the ISTH DIC score as has been previously described[49] and compare the sensitivity and specificity (to accurately predict patients who will experience a serious early coagulopathy event) of ISTH with that of thrombomodulin using McNemar's test for paired data. Based on a

target accrual of 150 patients for AAML1331, if all patients participate in this biology study with submission of specimens and the clinical data required to calculate ITSH, then the average accrual rate will be 2.5 patients/month. Estimating that serious early coagulopathy events occur in 20% of the patients (based on the rate seen in AAML0631), then there will be 30 AAML1331 patients with these events. AAML1331 will have 81% power to detect a difference in sensitivities of 22% (68% vs. 90%) using a 1 sided test with 0.05 significance level assuming 23% proportion discordant. There will also be at least 90% power to detect a difference in specificities of 20% (66% vs. 86%) using a 1 sided test with 0.05 significance level. To improve the predictive ability of the ISTH DIC score, we will use a stepwise combination of biomarkers (elevation in thrombomodulin levels, thrombin generation, fibrinolytic parameters and microparticles). Receiver operating characteristic (ROC) curve will be used to assess the accuracy in prediction of bleeding events during Induction and the areas under the ROC curve (AUC) will be compared.

9.4.4 Study design for Study Objective 1.2.4 (Neurocognitive Outcomes)

The primary objective of this study is to use CogState testing to evaluate change in neurocognitive function from end of Induction to 2 years off therapy. The three secondary objectives include first, use of parent-reporting on the BRIEF questionnaire to assess change in neurocognitive function from end of Induction to 2 years off therapy, and for the other secondary aims, use of a psychologist administered battery to assess change in neurocognitive function from end of therapy to 4 years off therapy.

Actual CogState scores for each domain at each time point will be summarized and examined by descriptive statistics and scatter plots. Change in score for a domain from end of Induction will be calculated and similarly summarized by descriptive statistics. For the CogState scores, the mean change of score from end of Induction to a later time point will be estimated along with its 95% CI. One sample t-test on the change of score will be used to examine if there is significant decline in neurocognitive function from end of Induction to 2 years off therapy. Thus our analysis of CogState outcome data will be restricted to participants who have completed CogState testing following Induction (i.e., we will include data from patients who are 5 years of age or older by Day 1 of Consolidation Cycle 1). Outcomes for younger patients not completing the initial Induction assessment will be reported in a descriptive manner. Linear mixed models using scores from all time points as outcome will also be used to estimate the change in scores between time points with adjustment for within-patient correlation of the score by random effects for individual patients. If the change in score over time appears approximately linear in time, linear mixed models assuming time as a continuous covariate will be used to estimate the rate of decline over time and determine whether the rate of decline is significantly higher than zero.

Since each domain will be analyzed separately, the alpha level for each analysis is set to 0.01 for CogState and the psychologist administered battery and 0.017 for BRIEF according to Bonferroni adjustment to maintain an overall alpha of 0.05. For the primary objective utilizing CogState testing, assuming that there are 120 patients 5 - 18 years old who consent to participate in neurocognitive testing and receive all protocol therapy, there will be 80% power to detect the unit change

provided in the table below in the mean change score between end of Induction and 2 years off therapy using a one-sample t-test at two-sided alpha level for the SD of the change of score between two time points provided in the table below. For the secondary objectives, mean change score will be compared from end of Induction to 2 years off therapy for the BRIEF and from end of therapy to 4 years off therapy for the psychologist administered battery, BASC-2 Anxiety, Depression, and Social Skills scores, and the PedsQL Total and Physical Health scores.

Outcome	Unit Change	Change SD
CogState (each of five tasks)	4.3	13.6
BRIEF (each of three tasks)	4.3	14.5
Estimated IQ	6.7	20.4
CVLT Total Score	4.3	13.6
Processing Speed Index	6.5	20.4
CMS Stories and Faces Immediate Memory	1.3	4.1
ABAS-II General Adaptive Composite	6.5	20.4
BASC-2 (each of three scales)	8.2	26.0
PedsQL (each of two scales)	10.3	32.4

In AAML0631, 91.7% of participants were between the ages of 5 and 18 and the upper age of enrollment was 21 years of age. Therefore, we would anticipate 91.7% or 138 of the 150 subjects in the proposed sample to be 5 - 18 years old. Based on the accrual to date to this optional embedded study, we project that up to 120 patients 5 - 18 years old will participate in neurocognitive testing and receive all protocol therapy.

9.5 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	3	0	0	**3**
Asian	5	0	0	0	**5**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	11	9	0	0	**20**
White	57	38	21	14	**130**
More Than One Race	0	0	0	0	**0**
Total	**73**	**50**	**21**	**14**	**158**

This distribution was derived from AAML0631.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (i.e., v4.02 and all subsequent iterations prior to version 5.0).

10.2 Response Criteria for Patients with Acute Promyelocytic Leukemia

10.2.1 Hematologic Complete Remission (hCR and hCRi)

- In a bone marrow sample, hematologic complete remission (hCR) is defined as a differential count of at least 200 nucleated cells with less than 5% promyeloblasts/abnormal promyelocytes. There must be signs of recovering marrow with an absolute neutrophil count > 1,000/μL and platelets > 100,000/μL. Extramedullary disease must have resolved including clearance of the CNS (CSF negative for blasts) and resolution of chloromas.
- Hematologic complete remission with incomplete blood count recovery (hCRi): all the above criteria for hCR except for residual neutropenia (< 1,000/μL) or thrombocytopenia (< 100,000/μL).

Patients who appear not to have achieved hematological complete remission after Day 43 of Induction may benefit from consultation for a rapid pathology review (see Section 13).

10.2.2 Molecular Remission

- Molecular remission is the absence of PML-RARα fusion transcript by RQ-PCR (with an assay sensitivity of at least 10^{-4}) in a bone marrow specimen obtained after at least 14 weeks of Consolidation therapy. A positive test (detectable PML-RARα fusion transcripts) must be confirmed by a repeat test on a separate bone marrow specimen obtained at least 1 to 2 weeks later.

10.2.3 Treatment Failure/Events

- *Resistant Disease:* failure to achieve hCR/hCRi by Day 70 of Induction.

- *Molecular Resistant Disease:* persistence of PML-RARα fusion transcript by RQ-PCR in two consecutive marrow samples taken 1 - 2 weeks apart following the MRD Positive Consolidation cycle (mitoxantrone/cytarabine/ATRA).

- *Induction Death:* all deaths during Induction phase prior to achievement of hCR/hCRi.

10.2.4 Relapse

- *Hematologic Relapse:* reappearance of promyeloblasts/abnormal promyelocytes (> 5%) in the bone marrow with genetic confirmation of t(15;17) PML/RARα by cytogenetics, FISH or RQ-PCR in a patient who had previously achieved hCR/hCRi.

- *Molecular Relapse:* persistence of hematologic CR but reappearance of the PML-RARα transcript by PCR testing in two successive bone marrow samples in a patient who had previously achieved molecular remission.

- *Extramedullary Relapse:* reappearance or development of promyeloblasts/abnormal promyelocytes found in the CSF or on biopsy of any tissue with features suspicious for extramedullary disease. Genetic confirmation of PML-RARα with FISH or RT-PCR testing is required.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

11.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the *grade* (severity); 2) the *relationship to the study therapy* (attribution); and 3) the *prior experience* (expectedness) of the adverse event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

Determine the prior experience Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- ***the current known toxicities for each commercial agent as provided in the Drug Information for Commercial Agents Used by the Children's Oncology Group posted on the COG website; or***
- ***the drug package insert.***

Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

All secondary malignancies that occur following treatment need to be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

11.3 Reporting of Adverse Events for Commercial Agents – via CTEP-AERS

Expedited AE reporting must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via https://eapps-ctep.nci.nih.gov/ctepaers

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the front of this protocol immediately following the Study Committee roster.

- COG requires the CTEP-AERS report to be submitted within 7 calendar days of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Table B

Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

11.4 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting while on protocol therapy will include all toxicities reported via CTEP-AERS and all Grade 3 and higher non-hematological Adverse Events and all grades of the following cardiac adverse events: prolonged QTc interval, ventricular arrhythmia, and left ventricular systolic dysfunction. Routine reporting while in follow-up (off protocol therapy) will include all toxicities reported via CTEP-AERS and all grades of the following cardiac adverse events: prolonged QTc interval, ventricular arrhythmia, and left ventricular systolic dysfunction.

NOTE: Adverse events related to coagulopathy including hemorrhage/bleeding and thrombosis/clotting events are NOT considered hematologic toxicities for this study. Coagulopathy in APL is a targeted event in this study and therefore it is important to report all Grade 3 or higher hemorrhage/bleeding and thrombosis/clotting events included in the CTCAE catalog as follows:

- Hemorrhage (all sites)
- Bleeding (all sites)
- Disseminated Intravascular Coagulation
- Hematosalpinx
- Menorrhagia
- Epistaxis
- Purpura
- Hematoma
- Vascular Access Complication (if related to thrombosis)
- Ischemia cerebrovascular
- Superior Vena Cava syndrome
- Thromboembolic event
- Superficial Thrombophlebitis
- Portal Vein Thrombosis

12.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

13.0 PATHOLOGY GUIDELINES AND REQUIREMENTS

13.1 Review of Diagnostic CSF for CNS Disease Patients

For patients who are diagnosed with CNS disease based on blasts in the CSF, we strongly recommend that you contact the COG APL investigator James "Jim" Feusner, MD to discuss central review of the CSF slides. Dr. Feusner can be contacted at jfeusner@mail.cho.org and he will provide shipping information upon contact.

13.2 Review of End Induction Bone Marrow

Optional Pathology Consultation

In some cases the local pathologist may have difficulty or need a second opinion interpreting the marrow status at the end of Induction. If a consultation for a difficult case is desired then this would be arranged on a consultation basis only and a fee may be charged. If a consultation is desired, the institution may send pathology materials (stained and unstained slides from bone marrow and peripheral blood and pathology, bone marrow, flow cytometry reports including copies of blast gate and dot plots of markers) and pertinent cytogenetics data to the study pathologist. Please contact the study pathologist to request a consult and verify what is needed for the consultation prior to submitting pathology materials.
Copies of consult reports will be sent to contributing institution and study chair, in order to include them in study data files.

Materials sent for consultation must be shipped using the institution's courier account to:

AAML1331 Study Review Pathologist
Samir Kahwash, MD
Department of Pathology
Nationwide Children's Hospital
700 Children's Drive
Columbus, OH 43205
Phone: (614) 722-5450
Fax: (614) 722-2899
Email: Samir.Kahwash@nationwidechildrens.org

14.0 CYTOGENETIC ANALYSIS GUIDELINES AND REQUIREMENTS

14.1 Cytogenetic Analysis Overview

It is strongly recommended that all patients enrolled on AAML1331 have a cytogenetics/FISH PML-RARα study performed by a COG approved laboratory at the time of initial diagnosis and relapse.

The institutional CRA must inform the cytogenetics laboratory that the patient has been enrolled in a COG APL study and that the cytogenetics/FISH data must be **submitted within 2 weeks of enrollment** on the AAML1331 protocol. See Appendix V for cytogenetics procedures and for the Study Authorization Form for reflexive FISH testing.

14.2 Specimen Collection and Submission

It is strongly recommended that specimens for cytogenetic/FISH PML-RARα analysis be sent to a COG approved institutional cytogenetics laboratory. If a COG institution does not have a COG approved laboratory, the institution may send the samples for karyotyping/FISH studies to any COG approved cytogenetics laboratory on a fee-for-service basis. Prior arrangements for performing cytogenetics and/or FISH studies should be made with the laboratory. An authorization form for the reflexive FISH testing signed and dated (by the physician or designees just as with any order) and sent to the cytogenetics laboratory with the sample will simplify and enhance the ability to obtain FISH testing and results.

14.2.1 Specimen Collection

A minimum of 2 mL (optimal volume is 3 mL) of fresh whole bone marrow aspirated through a needle into a syringe containing sodium heparin (preservative-free is preferable) is recommended in all cases. A first or second draw, or a draw from a repositioned needle, is best to ensure a sufficient number of leukemic cells in the aspirate. The specimens should be kept at **room temperature** and transported to the institutional cytogenetics laboratory as quickly as possible (**always within 24 hours of collection**). If shipping is done by overnight courier to an approved laboratory, that laboratory should be contacted to obtain instructions on transport. Some laboratories request that specimens be transferred in a 15 mL conical tube filled with RPMI - 1640 and 15% heat inactivated fetal calf serum. Specimens should be kept at ambient temperature.

14.2.1.1 If bone marrow cannot be aspirated, a trephine biopsy should be submitted. Also if available, 1 - 2 unstained bone marrow aspirate slide(s) can be used for FISH with PML-RARα probes to confirm the diagnosis.

14.2.1.2 Peripheral blood (3 - 5 mL) collected in sodium heparin should be submitted as a back-up to the bone marrow when the marrow sample is suboptimal or unobtainable, if more than 20% circulating blasts are identified, or when a constitutional abnormality (e.g., trisomy 21) is a possibility.

Please note: Results of these studies should be submitted to the corresponding coordinator of the COG Myeloid Cytogenetics Committee for central review (see below).

14.2.2 Requirements for Data Submission

The following are required for each case: a completed COG Cytogenetics/FISH PML-RARα Reporting Form (found on the COG member website) and two original karyotypes (different cells), with corresponding full size metaphase spreads of each abnormal clone or two karyotypes of normal cells with corresponding full size metaphase spreads in the case of normal cytogenetic analysis. A normal karyotype in the leukemic cells of a patient with APL could be

due to a cryptic insertion/rearrangement that would be detected by FISH with PML-RARα probes. In such cases a sequential G-banded metaphase to FISH, or reverse DAPI on a metaphase should be performed to aid the localization of the probes. In very rare instances an evaluation of the case using a RARα break apart probe may be required. This information must be sent to the appropriate coordinating cytogeneticist **within 2 weeks of enrollment on the AAML1331 protocol** (see Appendix V) and within one month of disease relapse, if applicable. Reports must be sent electronically. Reporting Cytogenetics forms must be filled out for all cases, whether or not the cytogenetic analyses were successful. A separate form is required for each specimen (i.e., bone marrow and blood) analyzed. FISH form, using the PML-RARα probe, should also be completed and sent to the coordinating cytogeneticist with images documenting the abnormal or normal (in rare instances) FISH patterns. If the laboratory is not able to perform FISH, contact the COG cytogenetic coordinators for advice. Any discrepancies in interpretation between cytogenetics/FISH results from the laboratory and the coordinator will be discussed between the coordinators, with consult of additional cytogenetics committee members as necessary. The COG cytogenetics committee decision will be used for data analysis of trial results related to cytogenetic classification.

Cytogenetic Coordinators
Please send above materials by **e-mail** to the following COG Cytogenetics Laboratories:

WEST OF MISSISSIPPI RIVER
(INCLUDE MINNESOTA AND WISCONSIN), AUSTRALIA, NEW ZEALAND, WESTERN CANADA

SEND TO:
Betsy Hirsch, PhD
Director of Cytogenetics Laboratory
Department of Laboratory Medicine and Pathology
University of Minnesota
Mayo Mail Code 609
420 Delaware St. SE
Minneapolis, MN 55455
USA
Telephone: 612-273-4952/3171
Fax: 612-273-4689
E-mail: hirsc003@umn.edu

EAST OF MISSISSIPPI RIVER
(EXCLUDE MINNESOTA AND WISCONSIN), EUROPE, EAST CANADA

SEND TO:
Susana C. Raimondi, PhD, FACMG
Director of Cytogenetics Laboratory
Department of Pathology
(Room 4023A)
St. Jude Children's Research Hospital
262 Danny Thomas Place, Mail Stop 250
Memphis, Tennessee 38105-3678
USA
Telephone: 901-595-3537
Fax: 901-595-3100
E-mail: susana.raimondi@stjude.org

Recommendations for Case Analysis by Institutional, COG Approved Cytogenetics Laboratories. See Appendix V.

15.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

The exploratory studies detailed in this section are for research purposes only, and results will not be used to make clinical treatment decisions. Thus, results will not be obtained in real-time (but rather batched for retrospective review) and results will not be returned to the treating physician.

Please note, if there is an inadequate amount of bone marrow or blood for all optional studies, the studies should be prioritized in the following order:

1. Bone Marrow and Peripheral Blood Minimal Residual Disease Testing (see Section 15.2)
2. Early Death and Coagulopathy Complications in Pediatric APL (see Section 15.3)
3. Specimen Banking and FLT3 Mutations in Pediatric APL (see Section 15.1)

Additionally, if patient/parent/responsible party consents, any specimens left over on this study after required tests are performed will be banked for future research studies.

Optional Biology Specimens	Diagnosis	Induction	Consolidation Cycle 2	End of Therapy	Relapse
FLT3 Study (Section 15.1)	X		X (Day 43)		X
MRD Study (Section 15.2)	X	X (Day 29)	X	X	X
Coagulopathy Study (Section 15.3)	X	X (Days 1, 8, 15, 29)			

15.1 FLT3 Mutations in Pediatric APL

15.1.1 Specimens

From consenting patients, 1 mL to 3 mL of bone marrow specimen will be collected at the following time points:

- At diagnosis. If bone marrow is not obtained at diagnosis, may submit 3 to 10 mL of peripheral blood instead. When APEC14B1 opens to AML patients, this diagnostic specimen will be collected through enrollment on APEC14B1.
- Day 43 of Consolidation Cycle 2
- At the time of either a molecular or morphologic relapse, if applicable.

15.1.2 Preparation

Bone marrow (1 - 3mL) must be obtained in purple top tube (EDTA tube). If unable to obtain bone marrow, may send peripheral blood (3 - 10 mL) in purple top tubes (EDTA tube). Samples may be stored at room temperature if shipped on the day of collection. If stored for longer, please refrigerate. If the sample is stored for longer than 24 hours, please add equal volume of RPMI medium (1 mL RPMI for 1 mL of specimen).

Utilize AML Specimen Transmittal forms specific for AAML1331. Specimens should be placed inside a leak proof biohazard envelope with absorbent material and then a pressure resistance Tyvek envelope as per IATA regulations. Blood and

marrow should be shipped in a shipping container with an Exempt Human Specimen label.

15.1.3 Labeling

Label the tubes with COG patient ID number, patient name and date of birth, date and time of collection, time point (include treatment cycle and day of cycle), and source of material (i.e., bone marrow or blood).

15.1.4 Shipping

COG Leukemia Biospecimen Bank
Nationwide Children's Hospital
575 Children's Crossroads, Room WB2255
Columbus, OH 43215
Phone: (614)722-2866
Fax: (614)722-2887
Email: MGLab@nationwidechildrens.org

Call or email the Leukemia Bank only when shipping a sample to be delivered on Saturday.

Samples should be mailed by FEDERAL EXPRESS Priority Overnight. COG sites may use the COG Federal Express account number available at:
https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf

Samples should be sent as soon as possible and preferably less than 24 hours from sample collection; except samples collected on weekends or holidays should be shipped the first working day following collection.

15.1.5 Detection of FLT3 Mutations

FLT3 mutation testing will be performed in the laboratory of Dr. Soheil Meshinchi (Seattle, WA). Dr. Meshinchi has an NIH R01 grant to study the role of FLT3 mutations in myeloid disease.

Genomic DNA is used to amplify exon 14/15 and exon 20 of the FLT3 gene using duplex PCR with specifically designed primers. The amplified products will be subjected to EcoRV digestion, capillary electrophoresis and GenScan analysis for identification of FLT3-ITD as well as FLT3 activation loop mutations (FLT3-ALM)[73]. FLT3-ITD allelic ratio (ITD-AR) is determined as a ratio of mutant to normal product. Presence of FLT3-ALM and FLT3-ITD at various ITD-ARs will be correlated with clinical characteristics and outcome (on a retrospective research basis).

15.2 Bone Marrow and Peripheral Blood Minimal Residual Disease (MRD) Testing

Note: This optional research sample is different than the required RQ-PCR of PML-RARal research sa**clinical** reasons which should be sent to an approved CLIA certified lab at time points indicated in the protocol. See Section 7.1 for details.

15.2.1 Specimens

From consenting patients, 1 to 3 mL of bone marrow and 5 mL of peripheral blood will be obtained at the following timepoints to perform research evaluation of MRD. These samples are for research only and results will not be returned to the institution.

- At diagnosis (If bone marrow is not obtained at diagnosis, may submit peripheral blood only.)
- Induction Day 29
- Consolidation Cycle 2 Day 43 (and repeated 1-2 weeks later if positive)
- At the end of therapy
- At the time of either a molecular or morphologic relapse, if applicable

15.2.2 Preparation

Bone marrow (1 - 3mL) and peripheral blood (5 mL) must be obtained in purple top tubes (EDTA tubes). Samples may be stored at room temperature. Utilize AML Specimen Transmittal forms specific for AAML1331. Specimens should be placed inside a leak proof biohazard envelope with absorbent material and then a pressure resistance Tyvek envelope. Blood and marrow should be shipped in a shipping container with an Exempt Human Specimen label.

15.2.3 Labeling and Shipping

MRD specimens should be sent to the COG Leukemia Biospecimen Bank at Nationwide Children's Hospital. Please see Sections 15.1.3 and 15.1.4 for labeling and shipping information.

15.2.4 Research MRD Testing

The requested specimens for this biology study (including paired peripheral blood and bone marrow samples) are additional research-only specimens and results will not be reported back to the treating institution. This research testing will be batched (not performed in real-time) and performed at Hematologics, Inc. (Seattle, WA) or a similar qualified laboratory. RQ-PCR testing for the PML-RARα transcripts will be performed following EAC standards or per methods with similar or better reliability should new techniques be developed in the future.[74] The EAC standard testing includes use of 3 separate forward primers to cover the PML breakpoints along with a single reverse primer and probe for the RARα gene. NCN is calculated as copies PML-RARα divided by copies control gene ABL. Reportable NCN values will be within a range of 2.000 – 0.001. NCN values outside of this range will be reported as HIGH POSITIVE or LOW POSITIVE. For NCN < 0.0001 results will be reported as NEGATIVE within the quantitative range of this assay. If the specimen failed to amplify the ABL control gene with Ct values > 35 after repeat testing, RNA quality will be deemed inadequate. NB4 cell line cDNA will be used for positive control.

15.3 Early Death and Coagulopathy Complications in Pediatric APL

15.3.1 Specimens

Patients consenting to this biology study will have 5.4 mL of blood collected (2.7 mL into a citrate tube and 2.7 mL into a Corn Trypsin inhibitor tube) on Days 1, 8, 15 and 29 of Induction.

If any frozen citrated plasma sample is available from the day of presentation (diagnosis), it will also be analyzed for thrombomodulin levels and the CloFAL assay.

Corn Trypsin Inhibitor (CTI) tubes will be sent to each center by the central coordinating center (Children's Hospital of Michigan) upon study approval and will be replaced every 6 months (prior to the tube expiry) or if CTI tubes were used for a previous subject.

Blood will be drawn at each time point for measurement of thrombomodulin levels & for assessment of fibrinolysis by the CloFAL assay (2.7 mL citrate tube) and for thrombin generation and microparticle assay (2.7 mL Corn Trypsin inhibitor, CTI tube).

15.3.2 Preparation

Samples are to be drawn via atraumatic venipuncture. Please do not attach the CTI tube directly to the needle as it is not sterile. The tubes should be filled to ensure proper anticoagulant to blood ratio. All specimen processing should occur within 30 minutes after blood draw.

Citrate tube:

- Centrifuge at room temperature at 2500 xg for 15 minutes.
- Using a plastic disposable pipette, remove plasma, avoiding the buffy coat, and place into a plastic tube for the second spin.
- Centrifuge again using the same temperature and speed for another 15 minutes.
- Remove plasma using a clean plastic pipette, taking care to not disturb the cell button.
- Aliquot the plasma into at least 4 polypropylene tubes, 2 tubes with 500 µL and 2 tubes with 300 µL.
- Please clearly label with "Citrate tube" date of collection and type of sample (see Section 15.3.3).
- Please send any left over plasma in a separate tube (clearly label with "citrated plasma" and day of sample).
- Freeze samples at -80º C immediately after aliquoted into polypropylene tubes.

Corn Trypsin Inhibitor (CTI tube):

- Centrifuge at room temperature at 2400 xg for 20 minutes.
- Using a plastic disposable pipette, remove plasma, avoiding the buffy coat, and place into a plastic tube for the second spin.
- Centrifuge again at 2500 xg at room temp for another 20 minutes.

- Remove plasma using a clean plastic pipette, taking care to not disturb the cell button.
- Aliquot the plasma into at least 2 polypropylene tubes, with 1.0 mL in each tube.
- Please clearly label with "CTI tube" date of collection and type of sample (see Section 15.3.3).
- Please send any left over plasma in an additional separate polypropylene tube.
- Please clearly label with "CTI plasma" and day of sample.
- Freeze samples at -80º C immediately after aliquoted into polypropylene tubes.

15.3.3 Labeling

In addition to the study number, COG patient ID number and BPC number, clearly label "citrate" tube or "CTI" tube, date of collection and type of sample (diagnosis, Days 1, 8, 15 or 29).

15.3.4 Shipping

Samples should be sent to:

Children's Hospital of Michigan
3901 Beaubien St.
Detroit, MI 48201
Phone: (313) 993-8805
Fax: (313) 745-5237

Contact Person: Wendy Hollon
E-mail: whollo@med.wayne.edu
Phone: (313) 745-5529
Fax: (313) 745-5237
Lab PI: Madvhi Rajpurkar, MD

Samples should be sent frozen, on dry ice, using overnight delivery. Deliveries are accepted Tuesday – Friday. Please contact Wendy Hollon prior to shipping to obtain a FedEx account number and provide her the FedEx tracking number so that the samples can be tracked. Include a COG Generic Specimen Transmittal Form with each shipment.

Samples can be stored frozen at -80ºC and shipped once all 4 or 5 (if additional frozen citrated sample from day of presentation is available) samples are collected for each subject.

15.3.5 Coagulation Studies

All patients will have local coagulation studies (including platelet count, PT, PTT, D-Dimer and fibrinogen levels) checked regularly during the first week of therapy as part of standard care to help manage any coagulopathy complications. The results of this testing will be collected on the Coagulation CRF. The study PI will

assign a score as per the International Society on Thrombosis and Haemostasis (ISTH) disseminated intravascular coagulation (DIC) score criteria.[49]

16.0 NEUROCOGNITIVE OUTCOMES IN PEDIATRIC APL TREATMENT

16.1 Study Design

The purpose of this optional embedded study is to longitudinally monitor cognitive side effects from this treatment, as defined by the following endpoints:

- Primary outcome:
  - To evaluate the change in CogState scores over time, defined as a decline of 5 units in mean scores apparent at 2 years off therapy, as measured by the five tasks of the computerized CogState battery (i.e., processing speed, visual attention, visual learning, working memory, executive functioning).
- Secondary outcomes:
  - To evaluate change in parent-reported executive functioning over time, defined as a decline of 5 units in mean scores apparent at 2 years off therapy, as measured by the Behavioral Regulation, Working Memory and Metacognition Indices of the parent-completed BRIEF.
  - To evaluate change in intellectual, memory, verbal learning, and adaptive functioning over time, defined by declines on the Wechsler-derived estimated IQ and Processing Speed scores, CMS Faces and Stories memory scores, CVLT Total score, and ABAS-II General Adaptive Behavior Composite score at 4 years off-therapy.
  - To evaluate change in parent-reported psychosocial functioning and quality of life over time, defined by declines on the BASC-2 Anxiety, Depression, and Social Skills scores, and the PedsQL Total and Physical Health scores at 4 years off-therapy.

For this study, we have chosen to maximize our ability to examine neurocognitive functioning across a wide age range with minimal institutional and participant burden. Towards this aim, a combination of computerized and traditional neurocognitive measures, using two batteries that are already widely used within COG member institutions will be utilized. Specifically, we will use a brief computerized assessment system (CogState; see below) that targets the neurocognitive processes known to be most affected in leukemia survivors (i.e., attention, processing speed, and memory), and a widely used rating scale (the BRIEF, see below) to evaluate real world behaviors related to these processes.[75] In addition, participants will also complete a short neurocognitive battery that has been used in COG ALTE07C1. Specifically, participants will complete a one hour screening battery of traditional neurocognitive tests, administered by a psychologist, evaluating intellectual functioning, immediate and learning memory, processing speed, and working memory.

Both the CogState battery and the psychologist administered screening battery are being used in COG protocols. The proportion of patients who consent to the neurocognitive ancillary study embedded within COG AALL1131 is currently 71.5%. We anticipate a similar participation rate on this trial, particularly given that the neurocognitive tests used on psychologist administered battery provide a clinical screening service to the patients at no cost. The results from the screening battery can be used clinically to either establish a

need for further testing that is more likely to be covered by insurance, or shared with the child's school to help establish the need for any accommodations or other services.

The batteries have some overlap in content, but are very different in terms of their ability to detect small changes in cognitive functioning over time, and to highlight clinical meaningfulness of any demonstrated deficits. Computerized batteries allow for a larger number of responses compared with traditional measures. When tasks have a small number of items, they become susceptible to skewed distributions as well as floor and ceiling effects. With CogState, however, data from a large number of short trials is obtained, resulting in data on a true interval scale. Computerized batteries thus have the potential to be more sensitive to subtle changes in performance across time, making this an ideal tool for use in the current protocol. Finally, test-retest scores for CogState in a large sample of healthy individuals differed by approximately 2% on average, compared with between 7 - 19% for traditional measures. The absence of practice effects is of particular benefit to the current study, as it will allow us to evaluate participants across shorter intervals than are typically suggested when using traditional neurocognitive measures.

Although CogState has highly desirable psychometric properties that make it ideal for use in longitudinal studies with assessment intervals shorter than one year, traditional neuropsychological measures have well described associations with real-world functioning. Thus, in combination, the CogState and traditional task batteries will provide the ability to detect any changes in cognition over time, as well as to determine the clinical and functional significance of those changes.

CogState may be administered by bachelor's level clinical or research staff who have completed online training. These measures are already being used in 120 institutions within COG in association with an embedded, ancillary study to COG AALL1131. The test battery used in that trial is identical to the current study, and has been associated with a 96% data collection rate (aggregated across time points). The ALTE07C1 battery is currently open at 131 institutions and is associated with 90% data collection rate at time 1. Thus, there is a well-established infrastructure within COG for successfully collecting neurocognitive data in this manner.

In sum, data for this ancillary study will be obtained from two sources:

1. During treatment, data will be obtained from testing with the CogState computerized battery and the Behavior Rating Inventory of Executive Function (BRIEF) from participants aged 5 - 18 years who enroll on the ancillary neurocognitive study embedded within AAML1331.
2. At approximately the end of treatment, data will also be obtained from testing with a brief, psychologist administered battery of performance-based measures and parent questionnaires.

16.2 Eligibility Criteria for the AAML1331 Neurocognitive Study

- Enrolled on AAML1331
- ≤ 18 years at diagnosis
- English-, French- or Spanish-speaking
- No known history of neurodevelopmental disorder prior to diagnosis of APL (e.g., Down syndrome, Fragile X, William syndrome, mental retardation)

- No significant visual or motor impairment that would prevent computer use or recognition of visual test stimuli

Note: Children who are younger than age 5 years at diagnosis may enroll on the neurocognitive study, but will not be evaluated with the CogState battery until the next assessment point following their 5th birthday. Similarly, children who are younger than 30 months of age at diagnosis may enroll on the neurocognitive study but will not be evaluated with the psychologist administered battery until they reach 30 months of age.

16.3 Neurocognitive Study Consent

This correlative study is embedded within the larger therapeutic study. Consent for this study is incorporated into the consent for enrollment of eligible patients onto the parent study. Patients who enroll in AAML1331 and meet the eligibility requirements listed above may elect to enroll on this ancillary study as an option, not a requirement.

Note: Patients enrolling on this embedded study will complete assessments similar to those used on ALTE07C1 and thus patients on this study should not need to co-enroll on ALTE07C1.

16.4 Required Observations

The required observations for participants in the neurocognitive study are included in the therapy delivery maps (see Section 4.0). To reduce participant burden, all study assessments coincide with regularly scheduled clinic visits when possible.

16.4.1 Schedule of Observations

In previous literature describing neurocognitive effects in both pediatric cancer populations and in children who have been exposed to heavy metals, some changes may appear acutely (and later resolve), whereas other cognitive changes may take years to fully emerge. The assessment intervals are designed to be able to detect both acute neurocognitive changes as well as more subtle changes that would emerge over time, according to the schedule listed below.

Observation Number	Treatment Phase	CogState battery	BRIEF	Psychologist battery
1	Day 1 of Consolidation Cycle 1 (+/- 2 weeks)	✔	✔	
2	Day 1 of Consolidation Cycle 3 (+/- 2 weeks)	✔	✔	
3	End of therapy (+ 3 months)	✔	✔	✔
4	2 years Off-therapy (+/- 3 months)	✔	✔	✔
5	4 years Off-therapy (+/- 3 months)	✔	✔	✔

It is important to note that the CogState battery has not been validated in children less than 5 years of age, which means that we will be unable to capture data from computerized testing from children who are less than 5 year at diagnosis. In AAML0631, only 6 eligible participants (5%) were enrolled who were less than 5 years, so it is likely that we will have similarly few children enrolled on this trial in this age range. However, in an effort to capture information about cognitive changes in this vulnerable age group, we will attempt to collect computerized neurocognitive data (i.e., CogState) for children who are under age 5 at enrollment as soon as they turn 5 years of age. In addition, we will collect data from the performance-based measures for patients once they turn 30 months of age. Of note, the psychologist administered battery also includes standardized measurement of adaptive functioning, including developmental milestones for young patients, which may be particularly relevant in describing outcomes of interest for this age group.

16.4.2 Procedure

For each computerized assessment, participants will complete a 20 - 30 minute computerized cognitive evaluation, administered by a clinical research assistant, nurse, psychologist, or any other professional available in the pediatric oncology clinic who completes our online training in administration of CogState. While patients are completing the computerized assessment, their parent/guardian will be asked to complete a paper-and-pencil measure of executive functioning (the BRIEF, see below).[76] Completion of the BRIEF takes approximately 10 - 12 minutes.

Psychologist administered evaluations based on the ALTE07C1 battery will include abbreviated testing for intellectual functioning, memory, working memory, and verbal learning. Parents or caregivers will also be asked to complete questionnaire measures of the child's social, emotional, and behavioral functioning.

16.5 Measures

16.5.1 Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF is a widely used assessment of executive functioning for children aged 4 - 18 years.[76] The parent report version consists of 86 items, which map onto 2 broad areas: behavioral regulation and metacognition, as well as 2 validity scales. The Behavioral Regulation domain is further divided into 3 clinical subscales: Inhibit, Shift, and Emotional Control, whereas the Metacognition domain is divided into 5 clinical subscales: Initiate (i.e., beginning a task), Working Memory (i.e., holding information), Plan/Organize (i.e., anticipating future events and developing appropriate strategies), Organization of Materials (i.e., maintaining order in memory), and Monitor. Parents are asked to consider the frequency with which each item has been a problem over the last 6 months, responding on a 3 point Likert scale consisting of "never," "sometimes," and "often." Items were developed to be ecologically valid behavioral correlates to presumed neurocognitive difficulties with executive functioning; thus, this measure was selected to provide parent and patient reported outcomes of problems related to attention, memory, and executive function that occur in everyday life.

Psychometric properties of this measure are strong using normative samples (1,419 parents) weighted to match ethnic and gender proportions in the US population. Internal consistency is high (alpha range = 0.73 to 0.90) and test-retest reliability exceeds 0.80 for both measures over intervals from 2 to 4 weeks. Scores are linear transformations of raw scores into T scores (mean = 50, SD = 10); higher scores indicate greater difficulties.

16.5.2 CogState

CogState is a computerized testing software package that offers a range of semi-automated assessment modules for individuals aged 5 - 90 years.[75] The software can be installed on most computer systems and can be proctored by a research assistant after completing minimal training. For this study, we use 5 tasks, described in the table below, in the following domains: (1) visual learning; (2) processing speed; (3) visual attention; (4) executive function, and (5) working memory. These tasks were selected because they measure the neurocognitive functions identified in previous research as being susceptible to decline in children exposed to environmental heavy metals. The entire battery is estimated to take approximately 20 to 30 minutes. For CogState, reliability (intra-class correlation) is 0.77 with very good stability (i.e., low within-subjects standard deviations) and negligible practice effects when testing intervals are greater than one week.[77] For healthy individuals (n = 867), stability of performance is robust, particularly compared with that of traditional, paper and pencil neuropsychological measures. Specifically, test-retest scores in a large sample of healthy individuals differed by approximately 2% on average, compared with between 7 - 19% for traditional measures.[78]

The table below lists descriptions and other information about the CogState tasks.

Neurocognitive Function	Name of Task	Task Duration	Task Description	Interpretation
Visual learning	One-card learning	5 - 7 mins	Subject must indicate whether or not a card has been shown previously in the battery	Higher scores reflect better performance
Executive function	Groton Maze-Learning Task	6 - 10 mins	Subject must complete a hidden maze by following clues on the computer	Lower scores reflect better performance
Visual attention	Identification Task	3 - 4 mins	Subject must indicate whether or not a card is red	Lower scores reflect better performance
Processing speed	Detection Task	2 - 3 mins	Subject must quickly indicate when a card has flipped over on the screen	Lower scores reflect better performance
Working memory	One-back test	4 - 6 mins	Subject must indicate when a stimuli is the same as the one that preceded it (one-back); or is the same as the one two items previously (two-back test)	Higher scores reflect better performance

Demographic and symptom information:
CogState can be programmed to allow input of customized patient data at the time of testing. For this study, the CRA (or other individual administering the computerized testing) should enter each participant's COG identification number, gender, and age into the computer program. At the first evaluation, the CRA should also ask the parent or guardian accompanying the child to provide information about their highest level of education attained to estimate socioeconomic status (SES), given recent recommendations that this data be collected and included as a potential moderator of outcomes in studies of this kind. Finally, because prior longitudinal work suggests that children experiencing physical complaints at the time of testing perform more poorly on assessments both then and at subsequent evaluations, we also ask participants to report on their current experience of fatigue and nausea on a 4 point Likert scale anchored by (none/not at all and very much).

16.5.3 Psychologist administered battery

The screening battery of established neuropsychological measures as described in the ALTE07C1 protocol is being utilized. Specifically, that battery consists of an abbreviated intellectual test Block Design and Vocabulary subtests from the Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV[79]; ages 30 months through 5 years), the Wechsler Intelligence Scale for Children – Fifth Edition[80] (WISC-V; ages 6 years through 16 years), or the Wechsler Adult Intelligence Scale – Fourth Edition[81] (WAIS-IV; ages 17 and up). In addition, participants complete two measures of immediate visual memory (Children's Memory Scale[82] (CMS; ages 5 through 17 years) Dot Locations and Faces, a measure of immediate verbal memory (CMS Stories subtest), and a measure of verbal learning (California Verbal Learning Test – Children's Version[83] for 5 years through 17 years, or California Verbal Learning Test – Second Edition[84] for 17 and up). Finally, participants complete measures of working memory (WISC-V or WAIS-IV Digit Span subtest) and processing speed (WISC-V or WAIS-IV processing speed index tasks).

The measures vary by age group and should be completed in the order presented in Appendix VI.

Patient-Completed Measures

Wechsler Intelligence Scales (WPPSI-IV[79]; WISC-V[80]; WAIS-IV[81]). The Wechsler batteries measure intellectual functioning in children aged 2½ - 7 (WPPSI-IV), 6 - 16 (WISC-V), and 16+ (WAIS-IV). For this project, the Vocabulary and Block Design subtests from the version appropriate for each child's age will be used at baseline only to estimate IQ. Additionally, one working memory subtest (Digit Span) for participants age 6 years and up will be administered.

Children's Memory Scale (CMS[82]). The CMS is a test to assess verbal and visual memory in individuals 5 - 16 years of age.

Wechsler Memory Scale, 4th edition (WMS-IV[85]). The WMS-IV is a test to assess verbal and visual memory in individuals greater than 16 years of age.

California Verbal Learning Tests (CVLT-C[83]; CVLT-II[84]). The CVLT-C and CVLT-II involve verbally presenting a list learning task over the course of 5 trials. The test measures multiple aspects of how verbal learning occurs, or fails to occur, as well as the amount of verbal material learned. The CVLT-C is for individuals 5 - 16 years of age while the CVLT-II is for individuals older than 16 years of age.

Parent-Completed Measures

Behavior Assessment System for Children, 2nd edition (BASC-II[86]). The BASC-II describes the behaviors, thoughts, and emotions of children and adolescents. The parent rating scale will be utilized for individuals older than 2 years and less than 18 years of age. The questionnaire yields composite and scale scores in the domains of externalizing, internalizing, school, and other problems as well as adaptive skills and behavioral symptoms.

Behavior Rating Inventory of Executive Functioning (BRIEF; BRIEF-P[87]) is a parent-completed measure of behavioral executive functioning. There are two versions available: one for preschoolers (BRIEF-P) and one for older children and adolescents (BRIEF). For this study, items from the Metacognition subscales will be used. *The BRIEF will be administered at all time points as an additional outcome measure.*

Adaptive Behavior Assessment System, 2nd edition (ABAS-II[88]). The ABAS-II will be used for the assessment of adaptive skills in individuals older than 2 years and less than 18 years of age. Separate scale scores are available for 10 areas of adaptive skills.

Pediatric Quality of Life Inventory Version 4 (PedsQL 4.0). The PedsQL 4.0 is a modular approach to measuring health-related quality of life in healthy children and adolescents as well as in those with acute and chronic health conditions. The Generic Version consists of 23 items, with separate parent-report forms for ages 2 - 4, 5 - 7, 8 - 12, and 13 - 18. Patients who are > 18 years of age will complete a self-report form. The questionnaire yields domain scores for Physical, Emotional, Social, and School Functioning as well as summary scores for Total Quality of Life, Physical Health, and Psychosocial Health. Reliability and validity have been established for this measure. Questions regarding the PedsQL 4.0, including question regarding access, should be sent to Dr. Kristina Hardy at: AAML1331_neurocog@childrensoncologygroup.org

COG Language Preference Questionnaire. The 8 item COG Language Preference Questionnaire was developed to determine the primary language of study participants. Parents will complete this questionnaire for patients who are between 2 - 18 years of age. This questionnaire is available on the COG website at https://members.childrensoncologygroup.org/Prot/AAML1331/AAML1331COGLangPrefQuest.pdf.

16.6 Feedback to Participants

Real-time scoring is available for the CogState measure; thus, scores for each participant may be generated immediately. CogState is not designed to be a comprehensive measure

of neurocognitive functioning; however, problems identified by CogState may indicate that the patient may require a more complete neuropsychological evaluation. Consistent with the existing protocol developed for AALL1131, we plan to inform the health care providers of participants who have scored in the bottom 7% (i.e., 1.5 SD below the mean) relative to the standardization sample for CogState, or in the most extreme 7% of scores on the BRIEF, given that extreme scores on either of these measures may reflect significant difficulties that can interfere with learning. Score reports for the BRIEF and CogState are generated automatically by the scoring programs for each measure. When children receive scores at or more extreme than 1.5 SD from the mean, their health care team will be informed of the results in the form of a letter listing the scores of concern, provided by the correlative study research team. There will not be recommendations for dose modification based on the CogState score alone, as this battery has not been validated in this manner. The health care team can follow up with families to determine if further assessment is warranted based on whether or not families are observing difficulties in their child's functioning at home or in school, and make a referral as they would normally do when families report concerns of this kind.

With regard to the psychologist administered battery, the first administration of traditional tests will be at the end of therapy and thus results will not impact individual patient treatment decisions or dose modification.

17.0 RADIATION THERAPY GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

Radiation therapy (RT) for patients on COG protocols can only be delivered at approved COG RT facilities.

17.1 General guidelines

Radiation therapy is not routinely used in the curative treatment of APL and is reserved in this study for emergent situations with threat to neurologic or other function. Treatment is at the discretion of the treating physician. **Submission of treatment data is not required.**

17.2 Eligibility

No patient is required to receive radiation therapy. Radiation therapy may be considered for patients who present with a chloroma that is producing or threatens to produce an irreversible neurologic deficit.

17.3 Timing

If the patient presents with a chloroma that is producing or threatens to produce an irreversible neurologic deficit (e.g., visual impairment or myelopathy), radiation therapy may be given at the beginning of Induction therapy. However, radiation therapy is not required in this circumstance.

17.4 Equipment

17.4.1 Modality

Standard photon conformal arrangements or electron beam RT may be sufficient for most cases. Treatment modality is at the discretion of the treating radiation oncologist.

17.4.2 Calibration

All therapy units used for this protocol shall have their calibrations verified by the IROC Houston QA Center (RPC).

17.5 Target Volume

17.5.1 Standard Tumor and Target Volume Definitions

International Commission of Radiation Units and Measurements (ICRU) reports 50, 62, and 78 (www.icru.com) define prescription methods and nomenclature that will be utilized for this study. Treatment planning will be based on the following definitions:

17.5.1.1 *Gross tumor volume (GTV)* is the volume occupied by disease visible on diagnostic or planning imaging. For this study the GTV is the initial, pre-chemotherapy chloroma visible on 3D imaging.

17.5.1.2 *Clinical target volume (CTV)* includes the GTV and sites with potential occult tumor involvement. In this protocol this will include only microscopic disease just beyond the GTV. CTV is defined as GTV plus a uniform 0.5 cm expansion.

17.5.1.3 *Planning target volume (PTV)* is defined as CTV plus an institutional margin for day-to-day set up variation related to patient immobilization and physiological motion of the CTV. A minimum margin of 0.5 cm is recommended for photon and electron plans (total of 1 cm from GTV).

17.6 Target Dose

17.6.1 Prescription Point

Dose should be prescribed to an isodose surface that encompasses the PTV and allows the dose uniformity requirements to be satisfied.

17.6.2 Dose Definition

The absorbed dose is specified as cGy-to-muscle.

17.6.3 Tissue Heterogeneity

Calculations must take into account tissue heterogeneity and should be performed with CT based treatment planning to generate dose distributions and treatment calculations from CT densities.

17.6.4 Dose and Fractionation

A dose of 1,800 cGy will be delivered to the PTV in 10 fractions of 180 cGy each delivered once daily.

17.6.5 Dose Uniformity

The dose variations in the target volume will be within ±10% of the prescription dose.

17.7 Normal Tissue Sparing

An effort should be made to limit the radiation dose to the lens of each eye to less than 600 cGy, if this can be done without compromising the dose to the target.

17.8 Quality Assurance Review

Submission of RT treatment data on this study is not required for review.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Requirements for AAML1331 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Data Submission / Data Reporting

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the

enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

APPENDIX II: TRETINOIN (ALL-TRANS RETINOIC ACID, ATRA) DOSING TABLE

Dose: 25 mg/m^2/day	
BSA (m^2)	**Dose**
≤ 0.59	10 mg every day
0.6 - 0.99	10 mg twice daily
1 - 1.39	20 mg every AM, 10 mg every PM
1.4 - 1.79	20 mg twice daily
1.8 - 2.19	30 mg every AM, 20 mg every PM
2.2 - 2.59	30 mg twice daily
2.6 - 2.99	40 mg every AM, 30 mg every PM
3 - 3.39	40 mg twice daily

For additional administration guidelines for administering tretinoin (ATRA) to patients unable to swallow whole capsules either due to young age or level of consciousness (including intubated patients) please see Appendix III. Further details about tretinoin (ATRA) can also be found in the commercial agent monographs manual titled "Drug Information for Commercial Agents used by the Children's Oncology Group." This manual is provided under Standard Sections for Protocols at: https://www.cogmembers.org/site/pages/default.aspx?page=Prot_reference_materials .

APPENDIX III: INFORMATION FOR PARENTS/CAREGIVERS FOR GIVING TRETINOIN (ATRA):

Tretinoin gel capsules should be swallowed whole when possible. There is minimal data on the absorption of tretinoin when it is given by other methods. In addition, tretinoin is sensitive to heat, light and air, so avoid exposure to those as much as possible. Alternative methods of delivery should only be used when it is not possible to swallow the gel capsules (i.e., intubated patients, neurologically impaired patients, very young patients).

Note: Gloves must be worn when handling tretinoin capsules unless the capsules are intact.

For children unable to swallow the capsules whole, the following options may be used:

1. Capsules can be chewed then swallowed if the child is able. A small hole can be poked in the capsules before the child chews them to make this easier.
2. Capsules can be softened in water and the softened capsule can be chewed/swallowed and/or mixed with pudding or a fatty food and swallowed.
3. Contents of the capsules can be squeezed out and mixed with a fatty food. If at all possible, have the child suck on the empty capsule in hopes of getting more of the intended dose.

If the contents are withdrawn from the capsules and mixed with food, give the dose as soon as possible (within ONE hour).

APPENDIX IV: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.

Arsenic Trioxide (ATO)

Drugs that may interact with arsenic trioxide

• Antibiotics
  ○ Azithromycin, ciprofloxacin, clarithromycin, erythromycin, levofloxacin, moxifloxacin, telithromycin
• Antidepressants and antipsychotics
  ○ Citalopram, clozapine, escitalopram, paliperidone, quetiapine, risperidone, thioridazine, trazodone
• Heart medications
  ○ Amiodarone, dronedenarone, dofetilide, flecainide, ibutilide, procainamide, propafenone, sotalol
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  ○ Chloroquine, chlorpromazine, foscarnet, granisetron, haloperidol, ivabradine, methadone, mifepristone, ondansetron, pentamidine, pimozide, saquinavir, voriconazole

Food and supplements that may interact with arsenic trioxide**
• Unknown

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Tretinoin (ATRA)

Drugs that may interact with tretinoin
• Anti-seizure medications such as carbamazepine, phenobarbital, phenytoin, primidone • Arthritis medications such as leflunomide, tofacitinib • Some oral contraceptives • Some antibiotics, like doxycycline, tetracycline, and tigecycline • Other medications such as aminolevulinic acid, amiodarone, clopidogrel, deferasirox, gemfibrozil, irbesartan, losartan, mifepristone, natalizumab, pioglitazone, rabeprazole, rifampin, ritonavir, rosiglitazone, tranexamic acid
Food and supplements that may interact with tretinoin**
• Echinacea • St. John's Wort • Vitamin A supplements or multivitamins that contain vitamin A

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Cytarabine (IV)

Drugs that may interact with cytarabine
• Clozapine, digoxin, flucytosine, leflunomide

Food and supplements that may interact with cytarabine**
• Echinacea

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Dexamethasone

Drugs that may interact with dexamethasone
• Antibiotics o Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics o Aripiprazole, buproprion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine • Antifungals o Caspofungin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tofacitinib • Anti-rejection medications o Cyclosporine, sirolimus, tacrolimus • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir • Anti-seizure medications o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, amlodipine, dronedenarone, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Some oral contraceptives or birth control medications • Many other drugs, including the following: o Aprepitant, artemether/lumefantine, aspirin, deferasirox, ibuprofen, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin

Food and supplements that may interact with dexamethasone**
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Idarubicin

Drugs that may interact with idarubicin
• Antibiotics and antifungals o Clarithromycin, erythromycin, itraconazole, ketoconazole, rifampin • Antivirals and antiretrovirals o Darunavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranavir

- Anti-rejection medications
  - Cyclosporine, tacrolimus
- Anti-seizure medications
  - Carbamazepine, phenobarbital, phenytoin
- Arthritis medications
  - Leflunomide, tofacitinib
- Some heart medications
  - Amiodarone, carvedilol, digoxin, dronedarone, nicardipine, propranolol, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Other medications such as atorvastatin, clozapine, ivacaftor, natalizumab, trazodone

Food and supplements that may interact with idarubicin**
• Echinacea • Grapefruit, grapefruit juice • St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Leucovorin

Drugs that may interact with leucovorin
○ Some antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone)

Food and supplements that may interact with leucovorin**
• Folic acid

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Mitoxantrone

Drugs that may interact with mitoxantrone
• Aripiprazole • Clozapine • Cyclosporine • Dofetilide • Leflunomide • Natalizumab • Pimozide • Tofacitinib

Food and supplements that may interact with mitoxantrone**
• Echinacea

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

APPENDIX V: PROCEDURES FOR CYTOGENETIC/FISH STUDIES

(A COPY OF THIS SECTION MUST BE SENT TO THE RECOMMENDED INSTITUTIONAL COG-APPROVED CYTOGENETICS LABORATORY)

CHROMOSOME ANALYSIS

- Bone marrow should be studied by cytogenetics methods in all cases of APL.

- A back-up blood specimen should be studied when the bone marrow aspirate or trephine biopsy is inadequate or unobtainable (in which case short-term unstimulated cultures are established to examine spontaneously dividing [presumably leukemic] cells) or when a constitutional chromosomal abnormality is a possibility (phytohemagglutinin-stimulated cultures should be established to examine presumably nonleukemic [constitutional] lymphocytes).

- If no bone marrow sample is available to send to the cytogenetics laboratory, 1 - 2 unstained bone marrow slides could be sent for FISH PML-RARα to confirm APL.

- Short-term (15 - 48 hours) unstimulated cultures are recommended for each bone marrow sample. Analysis of direct preparations is successful in some laboratories. Mitogen-stimulated cultures of bone marrow samples should not be initiated.

- All preparations must be G-banded. (Q- or R-banding will not be accepted as a stand-alone banding method.)

- Complete analysis of 20 G-banded metaphases is required for each case, except as noted below. Complete analysis is defined as follows: the chromosomes in each metaphase cell have been counted; each chromosome has been examined to determine whether the banding pattern is normal, and all abnormalities present in the cell have been defined. Analysis may be accomplished by examining metaphase spreads under the microscope or by imaging. Sometimes analysis of 20 metaphases is not possible because of poor in vitro growth or a very limited quantity of specimen. However, limited characterization of the abnormal clone can still be informative. Such informative cases will be considered acceptable. A minimum analysis of 20 metaphases is required for a normal case.

- Identification of clones will follow the criteria of the Second International Workshop on Chromosomes in Leukemia, as stated in the General Report (Cancer Genet. Cytogenet 2:93-96, 1980): at least two metaphases with identical structural abnormalities or extra chromosomes, or at least three metaphases with identical missing chromosomes will constitute a clone. Nonclonal abnormalities (excluding random loss) should also be recorded.

- Karyotypes are to be designated according to the guidelines described in ISCN 2013, An International System for Human Cytogenetic Nomenclature (2013), Shaffer, McGowan-Jordan, Schmid (eds); S. Karger, Basel, 2013.

FLUORESCENCE *IN SITU* HYBRIDIZATION (FISH)

- FISH using commercially available probes for PML-RARα is required for all APL cases. If a case has the t(15;17)(q22;q21) by G-banding, FISH testing will confirm the PML-RARα fusion. Also FISH with PML-RARα, preferentially on metaphases, will allow the evaluation of missing deleted 3' or 5' regions of the participating genes. In cases with a t(15;17) present or normal chromosomes, if FISH with PML-RARα is not informative, the RARα break apart probe should be used to improve the detection of cryptic insertions. The laboratory is expected to follow the standards and guidelines

for FISH put forth by the American College of Medical Genetics. If the laboratory is unable to perform FISH tests, contact cytogenetics coordinators for advice.

CYTOGENETIC STUDY/*FISH* SUBMISSION
Steps to obtain the FORMS by the COG institution's CRA

1. **www.childrensoncologygroup.org**
2. COG members
3. Protocols ►Protocol Reference Materials ►Generic Forms
4. Under COG ►Cytogenetics Reporting/FISH Forms

The COG Forms should be completed by the designated individual in the Cytogenetics Laboratory and signed by the Cytogenetics Director. It is required to scan the Forms and e-mail with the appropriate documentation to COG reviewers for the Myeloid Committee.

The case must be sent to the appropriate reviewer within 2 weeks of enrollment.

Cytogenetic Coordinators
Please send above materials by **e-mail** to the following COG Cytogenetics Laboratories:

WEST OF MISSISSIPPI RIVER
(INCLUDE MINNESOTA AND WISCONSIN), AUSTRALIA, NEW ZEALAND, WESTERN CANADA
SEND TO:
Betsy Hirsch, PhD
Director of Cytogenetics Laboratory
Department of Laboratory Medicine and Pathology
University of Minnesota
Mayo Mail Code 609
420 Delaware St. SE
Minneapolis, MN 55455
USA
Telephone: 612-273-4952/3171
Fax: 612-273-4689
E-mail: hirsc003@umn.edu

EAST OF MISSISSIPPI RIVER
(EXCLUDE MINNESOTA AND WISCONSIN), EUROPE, EAST CANADA
SEND TO:
Susana C. Raimondi, PhD
Director of Cytogenetics Laboratory
Department of Pathology (Room 4023A)
St. Jude Children's Research Hospital
262 Danny Thomas Place, Mail Stop 250
Memphis, Tennessee 38105-3678
USA
Telephone: 901-595-3537
Fax: 901-595-3100
E-mail: susana.raimondi@stjude.org

CYTOGENETICS REVIEW

The region's cytogenetics coordinator will review each case when it is submitted. She/he will determine whether each case is adequate in terms of the numbers of metaphase cells analyzed, quality of banding, and interpretation of the karyotypes. If the coordinator agrees with the submitting laboratory, the results of the study will be entered into the appropriate Rave. If the coordinator does not agree, she/he will send the case to another member of the COG Cytogenetics Review Committee for rapid review. If the case is determined as not adequate it will be registered as unknown cytogenetics.

(A SIGNED AND DATED COPY OF THIS AUTHORIZATION FORM FOR REFLEXIVE FISH TESTING MUST BE SENT TO THE CYTOGENETICS LABORATORY, TOGETHER WITH THE BONE MARROW SAMPLE)

AUTHORIZATION FORM FOR REFLEXIVE FISH TESTS
Patients enrolled in AAML1331 are required to have cytogenetic/FISH PML-RARα testing.

It is authorized to perform reflexive FISH testing to rule-out cryptic aberrations and/or to evaluate molecular deletions.

Patient Registration # _____

_____
Print Name of Attending Physician

_____
Print Name of Institution and City, State

Signature of attending physician or designee: _____

Date: _____

APPENDIX VI: ADMINISTRATION ORDER FOR PSYCHOLOGIST ADMINISTERED BATTERIES

The measures vary by age group and should be completed in the order presented below.

	Parent Report	Patient report
2 years 6 months through 3 Years 11 Months	1. COG Language Preference Questionnaire* 2. PedsQL 4.0 Generic Version 3. BASC-2 4. BRIEF-Preschool Version 5. ABAS-II	1. WPPSI-IV (Receptive Vocabulary, Block Design, Picture Memory)
4 years 0 months through 4 years 11 months	1. COG Language Preference Questionnaire* 2. PedsQL 4.0 Generic Version 3. BASC-2 4. BRIEF-Preschool Version 5. ABAS-II	1. WPPSI-IV (Vocabulary, Block Design, Picture Memory, Bug Search, and Cancellation)
5 years 0 months through 5 years 11 months	1. COG Language Preference Questionnaire* 2. PedsQL 4.0 Generic Version 3. BASC-2 4. BRIEF-Preschool Version 5. ABAS-II	1. CVLT-C 2. WPPSI-IV (Vocabulary, Block Design, Picture Memory) 3. CVLT-C Recall 4. CMS (Story Memory, Faces, and Dot Location) 5. WPPSI-IV (Bug Search and Cancellation) 6. CMS Recall (Story Memory, Faces, and Dot Location)
6 years 0 months through 16 years 11 months	1. COG Language Preference Questionnaire* 2. PedsQL 4.0 Generic Version 3. BASC-2 4. BRIEF 5. ABAS-II	1. CVLT-C 2. WISC-V (Vocabulary and Block Design) 3. CVLT-C Recall 4. CMS (Story Memory, Faces and Dot Location) 5. WISC – V (Symbol Search, Coding and Digit Span) 6. CMS Recall (Story Memory, Faces, and Dot Location)
17 years 0 months through 17 years 11 months	1. COG Language Preference Questionnaire* 2. PedsQL 4.0 Generic Version 3. BASC-2 4. BRIEF 5. ABAS-II	1. CVLT-II 2. WAIS-IV (Vocabulary and Block Design) 3. CVLT-II Recall 4. WMS-IV (Logical Memory I and Symbol Span) 5. WAIS-IV(Symbol Search, Coding, and Digit Span) 6. WMS-IV Recall (Logical Memory II and Spatial Addition)
18 years 0 months and Older	No Parent Report	1. PedsQL 4.0 Generic Version (self report) 2. BASC-2 (self report) 3. ABAS-II (self report) 4. BRIEF-A (self report) 5. CVLT-II 6. WAIS-IV (Vocabulary and Block Design) 7. CVLT-II Recall 8. WMS-IV (Logical Memory I and Symbol Span) 9. WAIS-IV (Symbol Search, Coding, and Digit Span) 10. WMS-IV Recall (Logical Memory II and Spatial Addition)

* COG Language Preference Questionnaire will only be completed at the first psychologist administered battery time point.

APPENDIX VII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY
(for children from 7 through 12 years of age)

A Treatment Study of Children with Newly Diagnosed Leukemia Called APL

1. We have been talking with you about your acute promyelocytic leukemia (APL). Leukemia is a type of cancer that grows in the bone marrow. Bone marrow is the spongy tissue inside the bones of your body that make blood cells. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have APL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the type of leukemia you have. This kind of leukemia is usually treated with anti-cancer medicines. Some of these anti-cancer medicines may cause heart problems later in life. This research study will use a new way to treat leukemia. We do not know if the new treatment will be better than the usual treatment. That is why we are doing this study.

3. Children who are part of this study will be treated with anti-cancer medicines. Doctors want to see if this new treatment will make more children with leukemia get better, with fewer heart problems later in life. These medicines have been used together to treat leukemia in adults. They also have been used together to treat a small group of children. We don't know if the new treatment will work well in children.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is a better chance at getting rid of the leukemia for as long as possible. We also hope that the study treatment will help keep more children from having heart problems later in life. However, we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are receiving treatment that does not work as well as usual treatment at getting rid of the cancer for as long as possible. Another risk may be more problems, or side effects, from the study treatment. Other things may happen to you that we don't yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect extra blood and bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. You can still take part in this study even if you don't allow us to collect the extra blood and bone marrow samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY
(for teens from 13 through 17 years of age)

A Treatment Study of Children with Newly Diagnosed Leukemia Called APL

1. We have been talking with you about your acute promyelocytic leukemia (APL). Leukemia is a type of cancer that grows in the bone marrow. Bone marrow is the spongy tissue inside the bones of your body that make blood cells. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have APL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the type of leukemia you have. Standard treatment for the kind of leukemia you have is chemotherapy (anti-cancer drugs). Some of the drugs used may cause bad effects that show up a long time after treatment is finished. These are called "late effects". A common late effect from standard treatment is heart problems. This research study will use a new way to treat leukemia. We do not know if the new treatment will be better than the usual treatment. That is why we are doing this study.

3. Children and teens who are part of this study will be treated with chemotherapy. Doctors want to see if this new treatment will make children with leukemia get better with fewer late effects. These medicines have been used to treat leukemia in adults and a small group of children. We don't know if the new treatment will work well in children.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is a better chance at getting rid of the leukemia for as long as possible. We also hope that fewer late effects and heart problems will occur. However, we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are receiving treatment that does not work as well as standard treatment at getting rid of the cancer for as long as possible. Another risk may be more problems, or side effects, from the study treatment. Other things may happen to you that we don't yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood and bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. The bone marrow samples will be taken when other standard tests are being performed, so there would be no extra procedures. Some blood is requested when you would not usually need to have a blood sample taken. You can still take part in this study even if you don't allow us to collect the extra blood and bone marrow samples for research.

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