ARRANON® (nelarabine) Injection

For treatment of patients with T-cell acute lymphoblastic leukemia or T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

FDA Advisory Committee Briefing Document

Oncologic Drugs Advisory Committee

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Abbreviations

AE	Adverse event
ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil counts
ara-G	9-β-D-arabinofuranosylguanine
ara-GTP	9-β-D-arabinofuranosylguanine triphosphate
AUC	Area under the concentration-time curve
BMT	Bone marrow transplant
CALGB	Cancer and Leukemia Group B
CCG	Children's Cancer Group
CI	Confidence interval
CLcr	Creatinine clearance
Cmax	Maximum concentration
CNS	Central nervous system
COG	Children's Oncology Group
CR	Complete response
CR*	Complete response without hematologic recovery
CTEP	Cancer Therapy Evaluation Program
DCTD	Division of Cancer Therapy and Diagnosis
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
LBL	Lymphoblastic lymphoma
MedDRA	Medical dictionary for regulatory activities
MSC	Mental status changes
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
ODAC	Oncologic Drugs Advisory Committee
OS	Overall survival
PD	Pharmacodynamics
PK	Pharmacokinetics
PNP	Purine nucleoside phosphorylase
PNS	Peripheral nervous system
POG	Pediatric Oncology Group
SWOG	Southwest Oncology Group
T-ALL	T-cell acute lymphoblastic leukemia
T-LBL	T-cell lymphoblastic lymphoma
US	United States of America

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ARRANON

1. EXECUTIVE SUMMARY

1.1. INTRODUCTION AND PRODUCT DEVELOPMENT RATIONALE

T-cell acute lymphoblastic leukemia (T-ALL) is a subset of ALL with distinct biologic and clinical features. T-cell lymphoblastic lymphoma (T-LBL), formerly classified as an aggressive non-Hodgkin's lymphoma (NHL), is now considered to represent the same disease entity (precursor T-cell neoplasm) as T-ALL. In pediatric ALL, the T-immunophenotype has been identified as an independent predictor of treatment failure and is frequently associated with other high-risk factors in the relapsed setting.

Current intensive, multi-agent, risk adapted therapy administered in the front-line setting for patients with T-ALL/T-LBL is reasonably effective with long-term overall survival rates of 70%-75% for pediatric T-ALL and 50% for adult T-ALL patients. However, those patients whose disease persists despite such intensive front-line therapy have treatment resistant disease and are rarely cured. Even more challenging are those patients who have received multiple prior induction regimens and whose disease has continued to relapse, or has proven refractory. These patients have a poor prognosis, and no standard of care. New treatments are needed for these patients with multiply relapsed or refractory T-ALL/T-LBL.

ARRANON (nelarabine, 506U78) is a prodrug of 9-β-D-arabinofuranosylguanine (ara-G), a deoxyguanosine analogue that recapitulates pharmacologically the T-lymphopenia observed in patients with a genetic deficiency in purine nucleoside phosphorylase (PNP). Clinically meaningful activity has been observed in patients who have received ARRANON beginning with the first clinical trial in 1994.

ARRANON received Fast Track designation by the US Food and Drug Administration (FDA) for the treatment of patients with T-cell malignancies (ALL and LBL) on October 19, 2003. This designation is granted to products in development that demonstrate a potential to address an unmet medical need for a serious or life-threatening condition. ARRANON received Orphan Drug Designation on August 10, 2004. This designation is granted to products under development for a rare (i.e., affects fewer than 200,000 people in the US) disease or condition. Approximately 1600 patients are newly diagnosed with T-ALL/T-LBL each year in the US. An estimated 500 patients per year in the US have relapsed or refractory T-ALL/T-LBL with approximately 200 of these patients being children and 300 being adults.

The clinical assessment of ARRANON in the extremely limited population of adults and children with relapsed or refractory T-ALL/T-LBL benefited from collaborative efforts between GlaxoSmithKline (GSK) and the Cancer Therapy and Evaluation Program (CTEP) of the National Cancer Institute (NCI). This collaboration proved essential in efficiently evaluating ARRANON in this uncommon disease with the patient population who exhibited medical need and were most likely to receive clinical benefit. In addition, GSK, NCI, and the cooperative groups conducted independent assessments of the clinical trials data according to the practices of each entity and have arrived at similar conclusions

regarding patient benefit and risk for ARRANON. Fourteen clinical trials have been conducted with nelarabine since 1994. Three of these trials are still ongoing, along with a Special Exceptions Program. Plans for a Phase III randomized trial in a front-line setting are proceeding.

1.2. PIVOTAL TRIALS

The ARRANON application was submitted under Section 505(b) of the Federal Food Drug and Cosmetic Act on April 29, 2005. The following two multi-center trials conducted under the NCI IND serve as the basis of the submission (i.e., pivotal trials):

- Study COG P9673 conducted by Children's Oncology Group (COG), entitled: A Phase II Study of 506U78 in Patients with Refractory T-Cell Malignancies
- Study CALGB 19801 an inter-group trial coordinated by Cancer and Leukemia Group B (CALGB), entitled: A Phase II Study of nelarabine (506U78) in Patients with Refractory or Relapsed T-Lineage Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL).

Both studies enrolled patients with relapsed or refractory T-ALL/T-LBL. A total of 151 patients were treated on COG P9673 during this five year study, representing the largest clinical trial experience to date for children with relapsed or refractory T-ALL/T-LBL. Eighty-four of these patients received the proposed pediatric dose, 39 of whom had already received two or more prior induction regimens. In the CALGB 19801 inter-group trial, a total of 39 adult patients were treated during this four year study. Twenty-eight of these patients had previously received two or more prior induction regimens.

The proposed dose of ARRANON for pediatric patients is 650 mg/m^2/dose daily for five consecutive days of a 21 day cycle. The proposed dose of ARRANON for adults is 1500 mg/m^2/dose on days 1, 3, and 5 of a 21 day cycle.

These multi-center trials enrolled a targeted patient population for whom there is no standard of therapy in this treatment setting, precluding a randomized comparison to a proven treatment. To assess clinical benefit, these studies utilized uniformly applied and accepted outcome measures for response. Finally, these cooperative group studies have a broad geographic distribution and encompass a comprehensive range of investigative sites, which provides greater confidence that the clinical results obtained will appropriately reflect ARRANON's anticipated benefit and risk when it becomes approved for use.

1.2.1. Pivotal Trial Results

The development program for ARRANON was discussed with the FDA at various milestones throughout the clinical development of the product. Based on these discussions, endpoints of complete response (CR) and CR* (CR-star = complete response without full hematologic recovery) were pursued, and the protocols for the pivotal trials were amended to collect hematologic recovery data to assess engraftment following

transplant. In addition, cross-study analyses were performed to assess possible predictive factors for neurologic adverse events.

The population that provides efficacy data to support the proposed indication is patients who received two or more prior induction attempts. Results from the two pivotal trials show that subjects who received two or more prior induction regimens (i.e., multiply relapsed or refractory) before enrolling in the pivotal studies achieved CR plus CR* response rates of 21% and 23% following single agent ARRANON in the adult and pediatric studies, respectively (Table 1). The majority of responses were CRs, with CR rates of 18% in the adult study and 13% in the pediatric study. Responses (CR plus CR*) were considered durable in these patients with aggressive disease (adults: 4.0 to 195.4+ weeks, pediatric: 3.3 to 42.1 weeks), and generally long enough to allow for arrangement of a stem cell transplant procedure, a frequent goal in this treatment setting. Durations of CRs were 15.1 to 195.4+ weeks in adults, and 4.7 to 36.4 weeks in pediatric patients. Patients had a median survival of 20.6 weeks for adults and 13.1 weeks for children following ARRANON. One-year survival in these studies was 29% in adults and 14% in children with multiply relapsed or refractory disease.

The response rates provided in this document were determined independently by GSK based on data provided by COG and CALGB. These response rates determined by GSK are somewhat lower than published results [Berg, 2005; DeAngelo, 2002] for these studies due to a more conservative approach for analysis, for example GSK utilized an all treated subjects analysis.

Table 1 Key Efficacy Results following ARRANON at the Proposed Dose Regimens in Patients with Two or More Prior Induction Attempts

	CALGB 19801 Adult Patients N=28	COG P9673 Pediatric Patients N=39
CR + CR*	21 %	23%
Duration of (CR + CR*)	4.0 to 195.4+ weeks	3.3 to 42.1 weeks
CR	18%	13%
Duration of CR	15.1 to 195.4+ weeks	4.7 to 36.4 weeks
Median Overall Survival	20.6 weeks	13.1 weeks
1-year Survival	29%	14%

The safety profile of ARRANON was acceptable at the proposed doses. Hematologic toxicity was the most common grade 3 or 4 adverse event, similar to that of other nucleoside analogs. Grade 3 and 4 nervous system disorders were observed in 10% and 3%, respectively, of patients in the adult studies (CALGB 19801 and PGAA2003) and 14% and 8%, respectively, of patients in the pediatric study (COG P9673), utilizing the standard Medical Dictionary for Regulatory Activities (MedDRA). Patients who received ARRANON on these trials were monitored by physical examination for neurologic adverse events. Dosing of ARRANON was discontinued when neurologic events persisted or reached grade 2 or greater. These same guidelines for ARRANON dosing are suggested post-approval.

An exploratory analysis across seven clinical trials of ARRANON identified potential pre-disposing factors for the occurrence of neurologic adverse events. Namely, higher ARRANON dose (specifically the prescribed cycle dose) and increased patient age were associated with higher risk for the occurrence of a neurologic adverse event. Similarly, CNS disease at baseline was associated with increased risk of experiencing a grade 3 or 4 neurologic adverse event.

A total of 588 patients have received ARRANON on GSK (n=268) or NCI (n=320) sponsored clinical trials. In addition, more than 392 patients have received ARRANON through Special Exceptions Protocols worldwide. The continued investigational requests for ARRANON through this mechanism demonstrates the assessment among physicians who treat these patients that ARRANON provides clinical benefit and has an acceptable benefit to risk ratio for these patients with multiply relapsed or refractory disease.

Patients with multiply relapsed or refractory T-ALL/T-LBL represent a focused and heavily pretreated patient population with a poor prognosis, and no proven treatment options. ARRANON provides clinically meaningful patient benefit and an acceptable benefit to risk ratio for use in the treatment of patients with multiply relapsed or refractory T-ALL/T-LBL.

1.3. ADDITIONAL SUPPORTIVE AND FUTURE STUDIES

Beginning with the first clinical trial of ARRANON (Study PGAA1001) clinically meaningful response rates have been observed. In Study PGAA1001, CR rates of 33% and 29% were observed in pediatric and adult patients, respectively, who had relapsed or refractory T-ALL/T-LBL. In the Special Exceptions Program, one center that enrolled multiple patients published results in 16 subjects with relapsed or refractory T-ALL [Goekbuget, 2003]. Nine (56%) subjects achieved a CR, one additional subject achieved an unconfirmed CR.

A Phase II study, PGAA2003, conducted in adult patients with chronic lymphocytic leukemia, contributed an additional 67 patients to the integrated safety database for the recommended adult dose. In addition, four Phase I studies enrolled patients with relapsed or refractory hematologic malignancies, contributing to the characterization of safety and activity of ARRANON. In total, 459 patients were enrolled across these seven studies. Seven additional Phase II studies and a Special Exceptions Program have also been conducted. Overall, more than 980 patients have participated in ARRANON trials as of data cutoff for this submission on October 18, 2004.

Based on a conclusion that an acceptable benefit to risk ratio exists for this compound, GSK is continuing its collaboration with NCI and the cooperative groups on the clinical development of ARRANON. For its only phase III study of front-line therapy in patients with T-ALL, the COG has chosen to evaluate the addition of ARRANON to a multi-agent regimen as part of a randomized, multi-center trial (AALL0434) to be conducted in this population over the next several years.

1.4. RISK AND CLINICAL BENEFIT IN THIS PATIENT POPULATION

Throughout development, ARRANON has consistently demonstrated activity as a single agent in adult and pediatric patients with relapsed or refractory T-cell hematologic malignancies, including patients refractory to multi-agent therapy and following multiple relapses.

The CR and CR* rates and durations indicate ARRANON will allow a meaningful proportion of patients with multiply relapsed and refractory T-ALL/T-LBL to proceed to stem cell transplant. While it is difficult to find a suitable comparator T-cell population in the medical literature, survival observed at one year following single agent ARRANON is comparable to multi-agent therapy for this patient population with poor prognosis.

Clinical benefit of ARRANON has been demonstrated in patients with no accepted standard multiple prior induction attempts by:

- Clinically meaningful rates of remission in heavily pretreated patients
  -- CR plus CR* rates of 21% and 23% in adults and children, respectively
  -- CR rates of 18% and 13% in adults and children, respectively
- Clinically meaningful rates of remission in heavily pretreated patients with disease refractory to prior multi-agent therapy
  -- CR plus CR* rates of 24% and 27% in adults and children, respectively
  -- CR rates of 18% in both adults and children
- Duration of response in majority of cases sufficient to get to transplant
  -- CR plus CR* duration: adults (4.0 to 195.4+ weeks), children (3.3 to 42.1 weeks)
  -- CR duration: adults (15.1 to 195.4+ weeks), children (4.7 to 36.4 weeks)
- Documented successful transplantation following nelarabine treatment
- One year survival estimates of 29% in the adult study population and 14% in the pediatric study population
- Similar or better efficacy results in patients with disease that had relapsed or was refractory to one prior induction regimen
- Similar or better response rates observed in supportive studies

Like other antimetabolites used in the treatment of leukemias and lymphomas, administration of ARRANON is associated with neurologic adverse events. As clinical experience has been gained in the use of ARRANON, the safety profile has improved. The safety profile of this cytotoxic agent is acceptable for the indicated patient population when patients are carefully observed for the onset of neurologic events and when ARRANON is administered according to the recommended regimens for children and adults. Clear labeling, including a Boxed Warning, to advise close monitoring of patients for the onset of neurologic adverse events, is proposed. Patients with relapsed or refractory T-ALL/T-LBL represent a patient population with a poor prognosis and an absence of accepted standard therapies. Treatment of this uncommon patient population is managed by health-care professionals who are accustomed to monitoring cancer

patients for possible dose limiting toxicities, including neurotoxicities associated with cytotoxic agents.

In conclusion, the efficacy demonstrated by ARRANON during independent, NCI sponsored Phase II trials provides evidence of effectiveness. ARRANON's safety profile is sufficiently well characterized to conclude a favorable risk to benefit profile exists to make this product available for use in this population of gravely ill patients with no suitable alternatives. GSK thus seeks approval for ARRANON for treatment of patients with T-cell acute lymphoblastic leukemia or T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

This briefing document summarizes the clinical efficacy and safety observed in patients who have received ARRANON with an emphasis on the pivotal trials.

2. DISEASE OVERVIEW

Acute lymphoblastic leukemia (ALL) is an aggressive disease that progresses rapidly in the absence of effective therapy. The T-immunophenotype occurs in approximately 15-20% of pediatric and 25% of adult patients with ALL. Each year, an estimated 2400 children and 1200 adults are diagnosed with ALL in the US.[National Cancer Institute, 2003] The T-immunophenotype occurs in 20-25% of cases.[Frankel, 2001] Therefore, approximately 720 patients are newly diagnosed with T-ALL each year in the US, two-thirds of whom are children. Based on long-term survival rates, approximately 250 patients, roughly half of whom are children, have persistent T-ALL (i.e., relapsed or refractory disease) in any given year.

Lymphoblastic lymphoma (LBL) represents approximately 30% of childhood and 3% of adult non-Hodgkin's lymphoma (NHL). LBL is often considered the lymphomatous variant of ALL in which extramedullary disease predominates in the presence of lesser involvement (<25% marrow blasts) of the bone marrow compared with ALL. The treatment of LBL utilizes the same drugs as those administered for ALL, frequently with the same protracted multi-stage treatment regimens. The outcome of frontline treatment for LBL is similar to that for ALL. An estimated 53,400 patients are diagnosed with NHL each year,[National Cancer Institute, 2003] of whom, approximately 900 have T-LBL. It is estimated that 300 patients have persistent T-LBL (i.e., relapsed or refractory disease) in any given year.

Outcomes in newly diagnosed pediatric and adult T-ALL/T-LBL patients have improved dramatically in the past few decades with risk-adapted intensive front-line therapy. As a result, current treatment has achieved complete remission (CR) rates of >95% in children and 60-80% in adults, together with long-term overall survival rates of 70%-75% in pediatric T-ALL and 50% in adult T-ALL patients. Newly diagnosed ALL patients are typically treated with induction regimen based on vincristine, prednisone, and anthracycline with or without asparaginase. Therapy may also include intensification and consolidation phases, with exposure to additional agents, for as many as three years time.

2.1. FIRST RELAPSE

Despite the success often seen with intensive front-line therapy for patients with ALL, relapsed and refractory disease do occur in a substantial number of patients. Children with ALL whose disease relapses in the bone marrow while on-therapy or within 6 months of completion of initial therapy exhibit a 10% to 20% likelihood of long-term survival, while those whose disease relapses at over one year from completion of therapy have a 30% to 40% probability of long-term survival. Children with T-ALL who experience relapse have a particularly poor prognosis with currently available therapy. In adults, the median duration of remission for patients achieving a CR is only 15 months. Adult patients with ALL whose disease relapses and are treated with best available therapy are reported to have a median survival of about 6 months.

Therapy for relapsed and refractory patients is not standardized, rather is individualized, taking into account such features as the response to prior therapy, the duration of that

response, and total anthracycline dose received. In order to induce remission in patients with this aggressive disease, multi-agent and dose intense treatments may be used. Such therapy is also associated with more severe toxicity, including therapy related death rates often in the 10-20% range [Bernstein 1997, Thomas 1999].

No consensus for therapy of patients with relapsed or refractory disease has emerged, although a successful stem cell transplant is generally viewed as the best hope for cure for these patients. Typically, these patients receive reinduction chemotherapy, followed by an allogeneic transplant procedure when a suitable donor has been identified. Patients in remission at the time of transplant are known to have better outcomes.

2.2. SECOND RELAPSE

There are only limited data available on patients who have relapsed or refractory disease following two or more prior induction attempts. No randomized trials have been performed in either pediatric or adult patients with relapsed or refractory T-ALL/T-LBL.

Patients whose disease is in the second or greater relapsed/refractory setting are in desperate need of agents that can put their disease in remission and that can offer the hope of undergoing successful stem cell transplantation while in remission.

2.3. MEDICAL LITERATURE

No standard of therapy exists for the treatment of patients with relapsed or refractory T-ALL/T-LBL. In order to place the results of the open label, Phase II trials in perspective, short summaries of relevant published results are provided below.

2.3.1. Agents Approved in Last Two Decades

The only agent available in the US for single-agent therapy in relapsed or refractory childhood ALL is clofarabine which has received accelerated (not regular) approval. Clofarabine produced a CR in 12% (6/49) of patients with childhood ALL that was relapsed or refractory following ≥2 prior regimens. Durations of the 6 responses ranged from 43 to 160+ days. The rate of patients who achieved CR without platelet recovery (CRp) was reported as 20.4% for the multiply relapsed pediatric ALL population treated on clofarabine study CLO 212. Median survival for ALL patients on the clofarabine study was 11.7 weeks. Fifty five percent (37/67, 55%) of the pediatric ALL patients had drug related SAEs and three of the 67 pediatric ALL patients died due to clofarabine related events (acute vascular leak with cardiac arrest, respiratory failure/liver damage, and multiorgan failure with hand foot syndrome). The immunophenotype of responding patients was not described.

Teniposide is approved for the treatment of refractory childhood ALL in combination with other approved agents. The combination of teniposide and cytarabine produced CR in 3 of 9 patients who had failed prior induction with cytarabine-containing regimens. Teniposide was studied before many components of modern risk-adapted therapy were

incorporated into frontline treatment and the immunophenotype of treated patients was not described.

2.3.2. Older Approved Agents

Additional chemotherapy agents approved by the FDA for treatment of pediatric acute lymphoblastic leukemia include: vincristine, cytarabine, doxorubicin, daunorubicin, asparaginase, methotrexate, mercaptopurine, and cyclophosphamide.

The superiority of multi-agent therapy compared to single agent treatment in the frontline treatment childhood ALL was established in the 1950s. Therefore, most publications of single agent studies with approved drugs are quite dated. Examples of results with single-agent therapy in previously untreated patients using approved agents include CR rates of 20%-30% with methotrexate, mercaptopurine and cytarabine [Sallan, 2004]. Single agent cyclophosphamide produced a CR rate of 4% in a study that treated 49 pediatric and adult ALL patients who had received at least two prior cytotoxic agents. [Hoogstraten, 1962]. One large study with vincristine reported a CR rate of 57% in 103 relapsed pediatric ALL patients with median CR duration of only 9 weeks [Karon, 1966]. In adults in first or second relapse, high dose cytarabine demonstrated a 30% complete response rate with median duration of 3 months [Kantarjian, 1986].

Toxicity was clinically significant in the single agent studies with many currently approved agents. For example, in the largest daunorubicin study, which demonstrated a 30% CR rate in 102 previously treated pediatric ALL patients, the induction death rate of 32% suggested that the regimen used was unacceptably toxic [Jones, 1971]. In the largest pediatric idarubicin study which produced a CR rate of 44%, the treatment-related mortality was 9.5% [Tan, 1987]. In the adult cytarabine study cited above, the induction death rate was 8%.

2.3.3. Experimental Agents

Indicine N-oxide, α-interferon, methylprednisolone and trimetrexate were tested as single agents in refractory and relapsed pediatric ALL/T-ALL patients, the CR rates were 0-10% [Miser, 1992; Lauer, 1994; Pappo, 1990]. Among the newer studies published, no CRs were obtained following treatment with paclitaxel or troxacitabine [Colburn, 2003; Giles, 2002].

2.3.4. Multi-Agent Regimens

Multi-agent combination re-induction regimens have demonstrated high complete response rates in children with ALL who have relapsed after entering remission with frontline therapy. However, results in relapsed adults, children with multiple relapses and children and adults who were refractory to prior induction therapy are very limited and not as encouraging. Most studies in the relapsed/refractory setting were performed before the adoption of risk-adapted treatment, and thus high-risk patients (e.g., patients with T-immunophenotype) were likely to have received less intensive therapy in the

frontline. Many older studies did not characterize patients' prognostic factors (including immunophenotype), making direct comparison to nelarabine results difficult.

POG 9160 enrolled 82 pediatric patients with ALL and > 2 bone marrow relapses or patients who were refractory to prior induction. Treatment consisted of a four drug regimen that included cytarabine, idarubicin, etoposide and ifosfamide. Eleven percent of patients died within the first 28 days. The overall mortality from toxicity and complications was 17%. CR was achieved in 37% of all patients, and 30% (3/10) T-ALL patients. The duration of CR was not reported by immunophenotype. Among 13 patients with CR who received BMT, only one was alive at 600+ days. For the patients with CR who continued with chemotherapy, the mean duration of CR was 105 days. All patients died shortly after relapse [Bernstein, 1997].

In three CCG trials conducted from 1980-1992, 52 patients who were refractory to a re-induction regimen therapy after first relapse were re-treated with high-dose cytarabine and L-asparaginase. Nineteen percent of patients died within 28 day of therapy, and 12% of the deaths were treatment-related. The CR rate after re-induction was 30% in patients with M3 marrows (i.e., bone marrow blasts >25%) at enrollment. Duration of CR was short (median: 3 months, range: 0.7-19 months), and four patients died in CR due to treatment-related mortality. Only one patient was alive at 5+ years, and this patient received allogeneic BMT after having a partial response to the study regimen [Harris, 1998].

In short, cure rates in the front line setting have improved substantially over the decades, but the prognosis for patients with relapsed or refractory T-ALL/T-LBL remains poor, especially in the pediatric T-cell disease patients (COG, unpublished data). Stem cell transplantation in remission remains a goal for such patients but there are no standard approaches available, and available treatment is often marked by death rates of 10-20%. Agents unproven in the challenging T-cell population may be suitable for future investigations, but can not be seen as therapeutic options for these patients.

3. OVERVIEW OF ARRANON

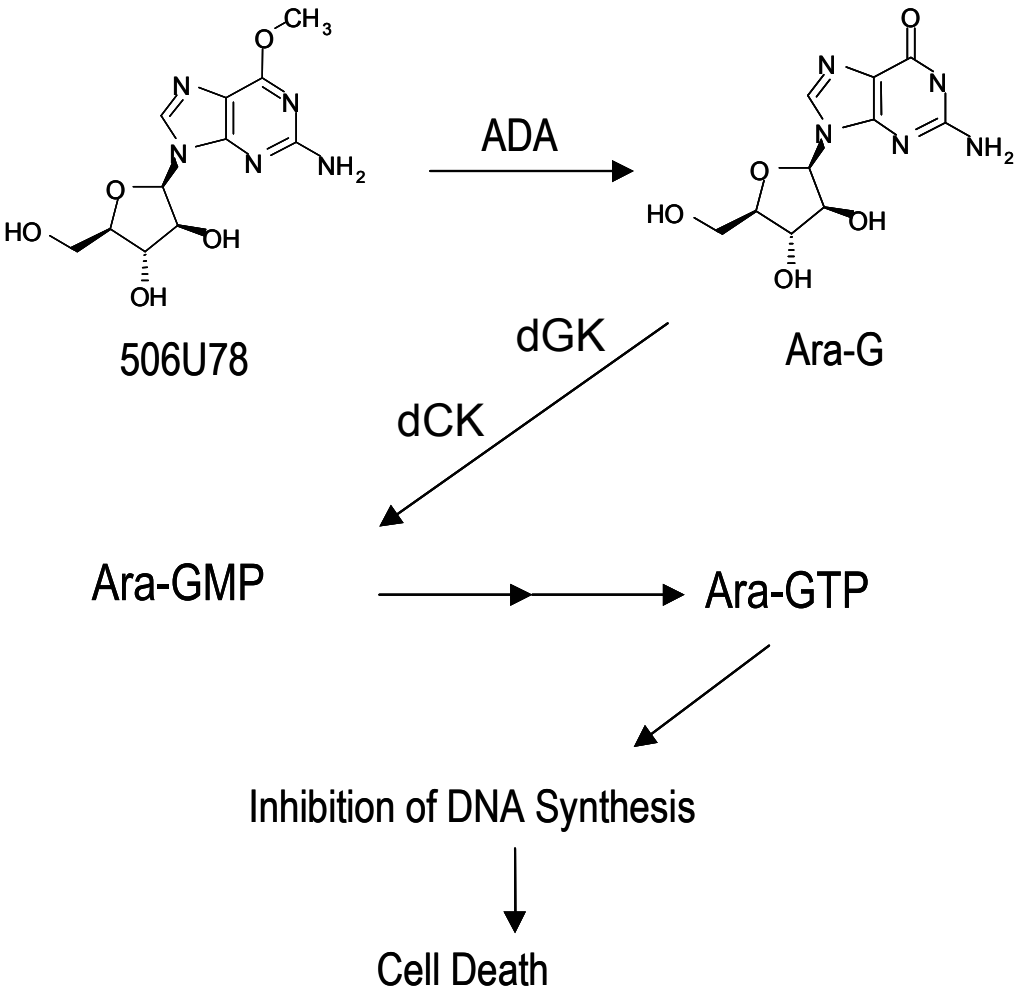
3.1. BACKGROUND INFORMATION

3.1.1. Summary of Pharmacologic Effects

Nelarabine is a water-soluble prodrug of the deoxyguanosine derivative ara-G. Nelarabine is demethylated by adenosine deaminase (ADA) to form ara-G (Figure 1). Ara-G is phosphorylated by cellular deoxycytidine kinase (dCK) and deoxyguanosine kinase (dGK) to ara-GMP, which on subsequent phosphorylation is converted to active ara-GTP. Ara-GTP accumulates *in vitro* to significantly higher levels and for longer duration in T-cells than in other cell types including B-cells. Accumulation of ara-GTP in leukemic blasts allows for preferential incorporation of ara-GTP into deoxyribonucleic acid (DNA) leading to inhibition of DNA synthesis which results in cell death. Other mechanisms such as inhibition of DNA polymerase α, β, δ, ε, and γ, in rank order, may contribute to the cytotoxic effects of nelarabine.

The *in vitro* T-cell cytotoxic potency and selectivity of nelarabine and ara-G were characterized in human hematopoietic cell lines. Studies conducted in human leukemic cell lines of T-cell, B-cell, and monocyte/macrophage lineages demonstrated that nelarabine and ara-G were cytotoxic to T-cells with high potency and selectivity. Generally, the IC_{50} values for cytotoxicity in B-cells with nelarabine and ara-G were at least 20-fold higher than for those of T-cells.

Figure 1. Mechanism of Action of Nelarabine (506U78)



3.1.2. Summary of Nonclinical Toxicology

The toxic potential of nelarabine was evaluated in the mouse, rabbit and monkey. The monkey was the most appropriate nonclinical species for this assessment as they were shown to have an ara-G pharmacokinetic profile comparable to that of humans and were more sensitive to the anticipated adverse effects of nelarabine administration (neurotoxicity and antiproliferative effects). Nelarabine was administered intravenously

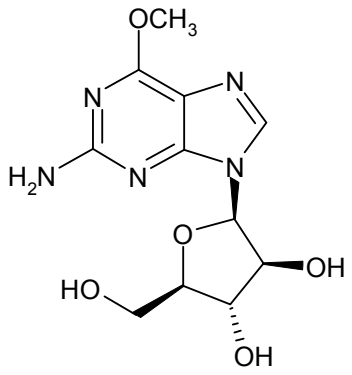
in definitive toxicity studies of 1 and 5 days duration in the mouse and 5 and 30 days duration in the monkey, as this is the route of administration in man. These studies were appropriately designed to support the administration of nelarabine on days 1, 3 and 5 of a 21-day cycle in adult humans or days 1 through 5 of a 21-day cycle in the pediatric population. As with other cytotoxic nucleoside analogues, nelarabine-induced adverse effects on the nervous system and the mitotically active cells, e.g., bone marrow, lymphoid organs, and intestinal tract, were observed. The incidence and severity of these findings were dose- and time-dependent. Clinical signs of neurotoxicity were dose-limiting in the monkeys and resulted in morbidity and mortality at high dose levels. The neurotoxic effects generally correlated with greater systemic exposure to ara-G. A dose of nelarabine at 120 mg/m^2/day for 30 days was well tolerated with only slight, reversible decreases in red and white blood cell counts and reduced thymus gland weights. Systemic exposure at this dose was approximately 30 to 40% of the therapeutic AUC achieved in clinical trials. However, unlike the clinical dose schedule, monkeys were treated for 30 consecutive days with no off-drug period. Like other drugs in the nucleoside analogue class, nelarabine was mutagenic in the mouse lymphoma assay and caused maternal and embryo-fetotoxicity, including treatment-related malformations when given to pregnant rabbits.

The nonclinical safety studies support the use of ARRANON for life-threatening (refractory or relapsed) T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma.

3.1.3. Pharmaceutics Overview

Nelarabine is an ampholyte (weak acid/weak base) with an aqueous solubility of 8-9 mg/mL (25°C) over the pH range of 4–10.

Structure



Drug Product Description

The drug product, ARRANON Injection, 5 mg/mL is a clear, colorless injection solution containing 5 mg of nelarabine per milliliter filled into a Type I, clear glass vial with a gray rubber stopper and aluminum seal.

3.2. CLINICAL DEVELOPMENT

3.2.1. Clinical Development History

A total of 588 patients have received ARRANON on GSK (n=268) or NCI (n=320) sponsored clinical trials as of the data cut-off on 18 October 2004. In addition, more than 392 patients have received ARRANON through Special Exceptions Protocols worldwide over this period. Five of the clinical trials were sponsored by GlaxoSmithKline, while nine were sponsored by the Division of Cancer Therapy and Diagnosis (DCTD) of the National Cancer Institute (NCI). The Special Exceptions Protocols were sponsored by DCTD, NCI and enrolled patients with relapsed or refractory T-ALL/T-LBL not likely to benefit from available therapy and not eligible for available clinical trials.

Table 2 Clinical Trials of ARRANON (nelarabine, 506U78)

Study Title	Phase	Study Status	Study Design	Number of Patients (as of 18 Oct 2004)
PGAA1001: A Phase I Study of 2-Amino-9-β-D-Arabinofuranosyl-6-Methoxy-9H-Purine (Compound 506) in Children and Adults with Refractory Hematologic Malignancies	I	Completed	Dose Escalation, Single Agent	93
PGAA1002: A Phase I Study of 506U78 Administered as a Two Hour Infusion Daily for 3 Consecutive Days in Adult Patients and as a Two Hour Infusion Daily Over 5 Consecutive Days in Pediatric Patients with Refractory Hematologic Malignancies	I	Completed	Dose Escalation, Single Agent	27
PGAA1003: A Phase I Study of 506U78 Administered as a Two Hour Infusion on a Day 1, 3, and 5 Schedule in Patients with Refractory Hematologic Malignancies	I	Completed	Dose Escalation, Single Agent	48
PGAA1005: Pilot Study of the Pharmacodynamic Investigation of Treatment with GW506U Combined with Fludarabine in Refractory Leukemics	I	Completed	Dose Escalation, Combination	13
CALGB69803: A phase I study of Compound 506U78 (NSC# 686673) in patients with hematologic malignancies and renal or hepatic impairment	I	Closed	Open Label, Single Agent	10
COG P9673 (PGAA2001): A Phase II Study of Compound 506U78 in Patients with Refractory T-Cell Malignancies	II	Completed	Open Label, Single Agent, Stratify by Number of Prior Inductions & Sites of Disease	151
CALGB19801 (PGAA2002): A Phase II Study of 506U78 in Patients with Refractory Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma	II	Completed	Open Label, Single Agent	39
PGAA2003: A Multicenter Study to Assess the Efficacy of 506U78 in Patients with Chronic Lymphocytic Leukemia Who Have Previously Failed Fludarabine Therapy	II	Completed	Open Label, Single Agent	87

Table 2 Clinical Trials of ARRANON (nelarabine, 506U78) (continued)

Study Title	Phase	Study Status	Study Design	Number of Patients (as of 18 Oct 2004)
MDACC 86: A phase II study of 506U78 (NSC #686673) in patients with previously treated cutaneous T-cell lymphoma	II	Closed	Open Label, Single Agent	2
CALGB59901: A phase II study of 506U78 (NSC #686673, IND#52611) in patients with previously systemically untreated cutaneous T-cell lymphoma (CTCL) or with refractory or relapsed non-cutaneous peripheral T-cell lymphoma (PTCL)	II	Closed	Open Label, Single Agent	19
SWOG S0010: A phase II trial of 506U78 (IND 52611) in patients with relapsed or refractory non T-cell acute lymphoblastic leukemia (ALL)	II	Closed	Open Label, Single Agent	20
COG AALL00P2: The use of modified BFM +/- Compound 506U78 (NSC #686673) in an intensive chemotherapy regimen for the treatment of T-cell leukemia	II	Ongoing	Open Label, Multi-agent	30
MDACC 430: A phase II study of 506U78 (NSC #686673) for patients with relapsed or refractory indolent B-cell or peripheral T-cell lymphoma	II	Ongoing	Open Label, Single Agent	23
TRC9701: Compound 506U78 (NSC #686673) in patients with refractory T-cell ALL or T-cell lymphoblastic lymphoma	II	Ongoing	Open Label, Single Agent	26
Special Exceptions Protocols	II	Ongoing	Open Label, Single Agent	392

3.2.2. Ongoing and Future Clinical Trials

Besides the availability of Special Exceptions Protocols, there are three ongoing clinical trials as noted in Table 2, including a pilot study evaluating the addition of ARRANON to multi-agent back-bone therapy for the treatment of pediatric patients with newly diagnosed T-ALL (COG Study designated AALL00P2).

GSK is continuing its collaboration with NCI and the cooperative groups on the clinical development of ARRANON. For its only Phase III study of front-line therapy in patients with T-ALL, the COG has chosen to evaluate the addition of ARRANON to a multi-agent regimen as part of a randomized, multi-center trial (AALL0434) to be conducted in this population over the next several years. A schema for the draft protocol appears in Attachment 1.

3.3. CLINICAL PHARMACOLOGY

3.3.1. Clinical Pharmacokinetics

3.3.1.1. Nelarabine and Ara-G

After intravenous administration, the prodrug nelarabine was rapidly and extensively converted to ara-G by adenosine deaminase, which is present in peripheral blood as well as virtually all human tissues. Nelarabine Cmax values generally occurred at the end of the infusion. Nelarabine was rapidly cleared from plasma ($t_{½}$ <30 min). The overall estimates of nelarabine clearance (138 L/h/m^2 in adults and 125 L/h/m^2 in pediatric patients) were high, as were the estimates of volume of distribution at steady state (115 L/m^2 in adults and 89 L/m^2 in pediatric patients). Consistent with the pharmacokinetic parameter estimates, no accumulation of nelarabine was seen with daily or every other day administration.

Ara-G Cmax values generally occurred at the end of the infusion and were generally higher than nelarabine Cmax values. Ara-G was cleared from plasma at a slower rate than nelarabine (overall geometric mean $t_{½}$ value 3.2 hours in adults and 2.0 h in pediatric patients). The overall estimates of ara-G apparent clearance were 9.5 L/h/m^2 in adults and 10.8 L/h/m^2 in pediatric patients, and the estimates of apparent volume of distribution at steady state were 45 L/m^2 in adults and 32 L/m^2 in pediatric patients. Consistent with the pharmacokinetic parameter estimates, no accumulation of ara-G was seen with daily or every other day administration of ARRANON.

Dose proportionality was shown for ara-G in both pediatric and adult patients and for nelarabine in adult patients; the increase in nelarabine AUC with increasing dose appeared to be less than proportional in pediatric patients. This result may reflect the high interpatient variability and small number of patients in the analysis; plots of nelarabine AUC values against dose showed that the pediatric values were similar to the adult values at similar dose levels.

The principal route of nelarabine and ara-G elimination was metabolism. Geometric mean renal elimination of ARRANON and ara-G over 24 h was 5-10% and 20-30% of the administered nelarabine dose, respectively. Data suggest that no dose adjustment for renal impairment is needed at CLcr >50 mL/min. There are insufficient data upon which to base dosing recommendations for patients with reduced renal function (CLcr <50 mL/min). Other potential factors (age, race, gender, study, disease category) did not appear to influence nelarabine and ara-G plasma pharmacokinetics.

3.3.1.2. Intracellular ara-GTP

Intracellular ara-GTP concentrations were quantified in 51 patients with leukemic blast counts >10,000/µL and showed considerable interpatient variability. Intracellular ara-GTP was generally eliminated slowly (half-life could not be estimated in the majority of patients) and accumulated with repeated ARRANON administration. On a Day 1, 3, and 5 dosing schedule, Cmax and AUC(0-t) values on Day 3 were ~50% and ~30% higher, respectively, than Cmax and AUC(0-t) values on Day 1.

Dose-normalized intracellular ara-GTP AUC(0-t) and Cmax values were influenced by gender (2- to 3-fold higher in adult female patients than in adult male patients). Other potential factors (age, race, body surface area, baseline calculated creatinine clearance, disease category, study) did not appear to influence intracellular ara-GTP exposure.

3.3.1.3. Drug Interactions

In a combination study of nelarabine and fludarabine (Study PGAA1005), no effect on nelarabine, ara-G, or intracellular ara-GTP pharmacokinetics was observed after fludarabine administration on Day 3.

Nelarabine and ara-G were neither substrates nor inhibitors of P-glycoprotein, nor did they inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). In addition, protein binding in human plasma for nelarabine and ara-G was low (<25%) and independent of concentration. These findings suggest that the potential for drug interactions via these mechanisms is low.

3.3.2. Clinical Pharmacokinetics/Pharmacodynamics

3.3.2.1. Response

Data from a group of patients in Study PGAA1001 were examined to look for relationships between intracellular ara-GTP exposure in leukemic blasts and response (defined as complete or partial response) [Gandhi, 1998]. Intracellular ara-GTP Cmax values were higher in patients who responded (median 157 μM) than in patients who did not respond (median 44 μM).

A cross-study PK/PD analysis which combined the data from Study PGAA1001 with data from other studies was performed to look for relationships between plasma nelarabine or ara-G pharmacokinetic parameters or intracellular ara-GTP exposure and clinical response using logistic regression models. The data from the nelarabine-fludarabine combination study (Study PGAA1005) were excluded as they had the potential to confound the PK/PD relationship.

The exposure measures evaluated were Cmax and AUC(0-t) values for nelarabine, ara-G, and intracellular ara-GTP. Response was defined as complete response or partial response. Pharmacokinetic measures of exposure, demographics (age, gender, race, BSA), disease category, and study were included in the full model. Each exposure measure was evaluated separately. Stepwise analysis was used to identify the factors associated with clinical response; factors with $p<0.05$ were considered statistically significant.

Intracellular ara-GTP exposure was generally higher in patients who responded (median Cmax 169 μM; median AUC(0-t) 3067 μM.h) than in patients who did not respond (median Cmax 68.5 μM; median AUC(0-t) 1330 μM.h). No relationship was seen between nelarabine or ara-G plasma exposure and response.

3.3.2.2. Neurologic Events

A cross-study PK/PD analysis was performed on three Phase I studies (i.e., Studies PGAA1001, PGAA1002, PGAA1003) to look for relationships between plasma nelarabine, plasma ara-G, or intracellular ara-GTP exposure and several functional categories of neurologic events using logistic regression models. Results from this analysis can be found in Section 5.6.3.

3.4. DOSE RATIONALE

Two ARRANON dose regimens are recommended for administration:

- 650 mg/m^2 infused over one hour daily for five consecutive days in pediatric patients
- 1500 mg/m^2 infused over two hours on a Day 1, 3, and 5 schedule in adult patients

Repeated cycles of each regimen are recommended for administration every 21 days.

Dose and schedule selection was guided primarily by safety and tolerability using a maximum tolerated dose (MTD) approach. The dose-limiting toxicity of ARRANON observed across the Phase I program was Grade 3 and Grade 4 neurotoxicity affecting both the central and peripheral nervous systems.

Three schedules were evaluated in Phase I: Days 1-5; Days 1-3; and Days 1, 3, and 5. The Days 1-3 schedule was not studied in Phase II since both the MTD and the response rate were lower than those observed with the other schedules.

The dose recommended for further study in both adult and pediatric patients with the Days 1-5 schedule was 1200 mg/m^2/dose. The dose recommended for further study in adult patients with the Days 1, 3, and 5 schedule was 2200 mg/m^2/dose.

The Days 1-5 schedule was selected for Phase II evaluation in pediatric patients because it was the best characterized schedule for pediatric patients; in addition, body weight-normalized clearance appeared slightly higher in pediatric patients than in adult patients suggesting that daily dosing would provide better drug exposure. Phase II was initiated at 1200 mg/m^2/dose on Days 1-5 in pediatric patients. This dose was later reduced to 650 mg/m^2/dose during Phase II due to an unacceptable incidence of serious neurologic events observed at higher doses.

The Days 1, 3, and 5 schedule was selected for Phase II evaluation in adult patients based upon greater dose intensity and a more favorable adverse event profile relative to the Days 1-5 schedule. Phase II was initiated at 2200 mg/m^2/dose on Days 1, 3, and 5 in adult patients. This dose was reduced to 1500 mg/m^2/dose during Phase II due to an unacceptable incidence of serious neurologic events at the higher dose.

4. OVERVIEW OF EFFICACY

4.1. ASSESSING EFFICACY IN PATIENTS WITH RELAPSED OR REFRACTORY T-ALL/T-LBL

Patients in the proposed indication with multiply relapsed or refractory T-ALL/T-LBL are in desperate need of efficacious treatment. At the time of ARRANON treatment, they have already undergone modern front-line therapy that has been risk adapted (usually meaning increased intensity for patients with T-cell disease) designed to offer the best opportunity for cure. Upon failure (relapse or failure to respond), these patients were treated with individualized therapy based on their prior responses, and prior exposures, again designed to offer the best chance for cure. Patients whose disease is refractory after multiple best attempts at cure using multi-agent regimens are unlikely to respond to a single agent unless that agent is able to provide meaningful benefit.

As indicated above, the treatment setting of patients with relapsed or refractory T-ALL/T-LBL complicates the assessment of efficacy in clinical trials. The efficacy of ARRANON has been measured clinically using endpoints of complete response, duration of response, and survival. Completed clinical trials with ARRANON have enrolled patients with relapsed or refractory hematologic malignancies. The Phase II pivotal studies CALGB 19801 and COG P9673 included patients with relapsed or refractory, T-lineage disease who received multiple prior multi-agent inductions. As with most clinical trials of cytotoxic agents, these studies were open label, so results must be interpreted within the context of the treatment setting, utilizing both results of individual patients and results from other studies in similar patients as a guide to evaluate the benefit provided by a new agent. The results of individual patients are meaningful in this setting since the choice of therapy for patients with relapsed or refractory T-ALL/T-LBL is more individualized, based on factors such as the nature of the patient's response to prior agents, and ability to tolerate further intensive therapy.

Treatment of patients during the CALGB 19801 and COG P9673 protocols, similar to other modern protocols, allowed for subsequent cycles of therapy with ARRANON prior to full recovery of platelets, neutrophils, or hemoglobin. The traditional definition of complete remission requires an ANC > 1500/μL and platelets > 100,000/μL.

Patients with relapsed or refractory disease have been heavily pretreated, including prior transplant in some patients, and may have slower or incomplete recovery of hematologic parameters. Thus, not all patients would be able to achieve a full CR, even though they may have received clinical benefit. A separate endpoint of CR* (CR-star) has therefore also been included in the analyses.

- **CR*** is defined as patients who have had complete clearing of all malignant cells from bone marrow and all other sites of disease (i.e., no evidence of disease). These patients may have hypocellular bone marrow and/or peripheral hemograms that do not completely normalize.

Similar to retreatment with chemotherapy, patients are often considered candidates for stem cell transplant once they have no evidence of disease, with adequate, but not necessarily complete recovery of their peripheral hemogram.

A stem cell transplant is often considered for the treatment of patients with relapsed or refractory T-ALL/T-LBL since chemotherapy is typically not curative. However, complete remission must first be induced and a suitable donor must be available. Because of the aggressive nature of this disease, patients will receive a transplant as soon as possible after induction of remission. A confirmatory bone marrow biopsy at 3-4 weeks after the initial documentation of response is therefore not always available, especially in children.

Inherent to the transplant procedure are many variables specific to each patient's procedure including differences in preparatory regimens, type and source of donor cells, and the degree of match between donor and recipient. Studies of chemotherapeutic agents in this setting, therefore, often do not include transplant but rather focus on endpoints related to response, date of relapse, and date of death.

Patients with disease refractory to prior multi-agent therapy are unlikely to respond to a single agent. Patients who have relapsed following multi-agent therapy have few treatment options and have a poor long-term prognosis.

ARRANON has shown clinically meaningful activity across a range of doses tested in Phase I and II studies in patients with both relapsed and refractory disease. The primary evidence of efficacy for this submission comes from two independently conducted clinical trials: CALGB 19801 and COG P9673.

4.2. STUDY CALGB 19801: ADULTS

4.2.1. Study Population: Adults

Patients enrolled in the CALGB 19801 trial had relapsed or refractory T-ALL/T-LBL, having received one or more prior inductions. For purposes of analysis, patients were stratified into groups who had received one prior, or two or more prior induction regimens.

Dose reductions took place during the Phase II program which affected this trial. The adult dose was decreased from 2200 mg/m^2 to 1500 mg/m^2 on the day 1, 3, 5 schedule due to neurologic events observed in patients on another trial (i.e., Study PGAA2003). There was minimal impact on the CALGB 19801 trial, where three patients received a total of four cycles of the higher dose. For purposes of efficacy and demographic analyses, these patients were not treated any differently from the other patients enrolled. None of these three patients treated with 2200 mg/m^2 dose achieved a CR or CR*, however, one of them achieved bone marrow blast count $\leq$ 5%.

The demographic characteristics of the patients enrolled in Study CALGB 19801 (Table 3) were representative of adult patients with ALL/LBL as a whole.

Table 3 Demographic Characteristics (Adult Study CALGB 19801)

	1 Prior Induction (N=11)	≥ 2 Prior Inductions (N=28)	Total (N=39)
Age Group n (%)			
16-21	0	6 (21)	6 (15)
22-64	10 (91)	21 (75)	31 (79)
≥65	1 (9)	1 (4)	2 (5)
Age (yrs)			
Mean	37.5	34.0	35.0
Min – Max	23-66	16 -65	16 -66
Sex, n (%)			
Male	9 (82)	23 (82)	32 (82)
Female	2 (18)	5 (18)	7 (18)
Race, n (%)			
Caucasian	10 (91)	17 (61)	27 (69)
African American	0	9 (32)	9 (23)
Native American	1 (9)	0	1 (3)
Hispanic	0	1 (4)	1 (3)
Oriental	0	1 (4)	1 (3)
Extramedullary Disease at Baseline, n (%)			
Yes	6 (55)	20 (71)	26 (67)
No	5 (45)	7 (25)	12 (31)
Unknown	0	1 (4)	1 (3)
History of CNS Leukemia, n (%)			
No	11 (100)	24 (86)	35 (90)
One Occurrence	0	3 (11)	3 (8)
> One Occurrence	0	1 (4)	1 (3)
Status Follow Most Recent Prior Therapy, n (%)			
Relapsed	9 (82)	11 (39)	20 (51)
Refractory	2 (18)	17 (61)	19 (49)
Prior Bone Marrow Transplant	1 (9)	4 (14)	5 (13)

Eleven of the patients enrolled in CALGB 19801 had received one prior multi-agent induction regimen. Twenty-eight patients enrolled in CALGB 19801 were more heavily pretreated, having received up to five prior induction regimens (Table 4). Of these 28, the majority (61%) had 3 or more prior inductions.

Table 4 Summary of Number of Prior Inductions (Patients with >= 2 Prior Inductions in Adult Study CALGB 19801)

	≥ 2 Prior Inductions N = 28
Number of Prior Inductions	n(%)
2	11 (39)
3	7 (25)
4	8 (29)
5	2 (7)

4.2.2. Efficacy Results: Adults

Multiple Prior Inductions

The focus of this submission is for the use of ARRANON in the treatment of patients with multiply relapsed or refractory T-ALL/T-LBL. That is, patients who have received multiple prior inductions.

A CR plus CR* rate of 21% (95% CI: 8%, 41%) was observed in adult patients with multiply relapsed or refractory T-ALL/T-LBL (Table 5). A complete response (CR) rate of 18% (95% CI: 6%, 37%) was observed in adult patients with relapsed or refractory T-ALL/T-LBL who had received two or more prior inductions (Table 5). All of the CR's were confirmed with follow-up bone marrow biopsies or aspirates.

Frequently, the treatment goal in patients with relapsed or refractory T-ALL/T-LBL is to prepare the patient for stem cell transplant. In this setting, the response must be of sufficient duration to allow for donor identification and harvest of the donor marrow, or peripheral stem cells, and partial recovery of the recipient's hematologic parameters. A period of at least 4-8 weeks from the first evidence of remission induction is usually needed to accomplish these activities. The duration of CRs observed in adult patients with at least two prior inductions were from 15.1 to 195.4+ weeks. When time to response is added to duration of CR, the period of disease control is obtained. Thus, all patients with CRs on this study had their disease controlled for at least 17.9 weeks and CR* for 7.7 weeks, which in most cases would provide sufficient time to arrange a stem cell transplant.

The median survival for adult patients with ≥2 prior inductions was 20.6 weeks (95% CI: 10.4, 36.4). The 29% one year survival for adult patients who had received ≥2 prior inductions is notable (Table 5). Historical survival data for patients in this population are not found in the literature, but the results observed here are similar to those reported for patients treated with multi-agent regimens after failure of one prior induction. For example, Thomas et al. reported 24% one year survival in 57 T-ALL patients treated with various multi-agent regimens [Thomas, 1999].

Table 5 Key Efficacy Endpoints (All Treated Patients: Adult Study CALGB 19801)

	1 Prior Induction N = 11	≥ 2 Prior Inductions N = 28	Total N = 39
Best Response (Complete Remission with or without Hematologic Recovery) and Duration			
CR+CR* n (%)	3 (27%)	6 (21%)	9 (23%)
[95% CI]	[6%, 61%]	[8%, 41%]	[11%, 39%]
Duration of Best Response (CR/CR*) (minimum to maximum)	4.7 to 212 wks	4.0 to 195.4+ wks	4.0 to 212 wks
Complete Remission and Duration			
CR n (%)	2 (18%)	5 (18%)	7 (18%)
[95% CI]	[2%, 52%]	[6%, 37%]	[8%, 34%]
Duration of CR (minimum to maximum)	51 and 212 wks	15.1 to 195.4+ wks	15.1 to 212 wks
Complete Remission without Hematologic Recovery and Duration			
CR* n (%)	1 (9%)	1 (4%)	2 (5%)
Duration of CR* (minimum to maximum)	4.7 wks	4.0 wks	4.0 and 4.7 wks
Survival			
Median OS (weeks)	20.1 wks	20.6 wks	20.4 wks
[95% CI]	[12.0, 220]	[10.4, 36.4]	[12.9, 36.4]
Survival at 1 year	36%	29%	31%
[95% CI]	[8%, 65%]	[12%, 45%]	[16%, 45%]

'+' indicates patient was still in remission at date of last contact

One Prior Induction

Patients with one prior induction also demonstrated benefit from single agent ARRANON. A CR plus CR* rate of 27% (95% CI: 6%, 61%) was achieved in the adult patients with one prior multi-agent induction (Table 5). Duration of response was from 4.7 to 212 weeks.

The CR rate was 18% (95% CI: 2%, 52%) among these 11 adult patients with one prior induction (Table 5). Adult patients had durations of CR lasting 51 and 212 weeks.

Refractory - Failure of Most Recent Prior Induction

Patients whose response to most recent prior therapy was reported by the investigator to be less than a CR during the most recent prior induction period were evaluated for response to ARRANON. The definition of response to prior therapy was not standardized, but accepted as reported by the investigator. These patients represent a group that is considered refractory and would not necessarily be expected to respond or gain benefit from additional chemotherapy, especially single agent chemotherapy.

Table 6 Summary of Best Response to ARRANON in Patients with Refractory Disease (Adult Study CALGB 19801)

	1 Prior Induction N = 2	≥ 2 Prior Inductions N = 17
CR+CR* n (%) [95% CI]	0	4 (24%) [7%, 50%]
Achieved CR on ARRANON n (%) [95% CI]	0	3 (18%) [4%, 43%]
Achieved CR* on ARRANON n (%)	0	1 (6%)

Note: Refractory disease = lack of CR to most recent prior induction therapy.

Of the 28 adult patients in Study CALGB 19801 who received at least two prior induction regimens, 17 had failed to achieve a CR during the most recent prior induction phase. The CR plus CR* rate in adult patients with refractory disease and more than two prior induction regimens was 24% (95% CI: 7%, 50%). Three of the 17 (18%) refractory patients achieved a CR on ARRANON, and an additional patient achieved CR* (6%) (Table 6).

The ability of a single agent to induce a CR in patients whose disease is refractory to modern, multi-agent, induction therapy is indicative of clinical benefit.

4.3. STUDY COG P9673: PEDIATRIC PATIENTS

4.3.1. Study Population: Pediatric Patients

Pediatric patients enrolled in the COG P9673 trial had relapsed or refractory T-ALL/T-LBL, having received one or more prior inductions. Patients were stratified into groups who had received one prior, or two or more prior induction regimens for purposes of analysis. This stratification was consistent with the COG P9673 study design which was based on two strata, (i.e., Strata 01 and 02) defined below. Two additional pilot strata (i.e., Strata 03 and 04) were also included in the COG P9673 trial.

- Stratum 01: patients at first relapse (or refractory)
- Stratum 02: patients at second or greater relapse (or refractory)
- Stratum 03: patients at first or greater relapse (or refractory) with CNS and bone marrow disease
- Stratum 04: patients with first or greater relapse (or refractory) isolated extramedullary disease, excluding patients with isolated CNS disease.

Dose reductions took place during the Phase II program. The original dose in the COG P9673 trial (1200 mg/m^2 daily X5 days) was decreased to 900 mg/m^2 daily following a serious neurologic adverse event in the first patient enrolled. After 18 patients were treated at 900 mg/m^2, the dose was further reduced based on adverse events in this study and special exceptions protocols to 650 mg/m^2 daily X5 days. The primary analysis for

safety and efficacy took place on the patients enrolled in Strata 01 and 02 who received the recommended dose of 650 mg/m^2.

The demographic characteristics of the patients enrolled in Study COG P9673 were representative of the pediatric ALL/LBL patient population as a whole (Table 7).

Table 7 Demographic Characteristics (Pediatric Study COG P9673/650 mg/m^2)

	Stratum 01 (N=31)	Stratum 02 (N=39)
Age (yrs), n (%)		
2 mo – 2 yrs	0	2 (5)
3 – 12 yrs	18 (58)	21 (54)
13 – 16 yrs	9 (29)	10 (26)
17 – 21 yrs	4 (13)	6 (15)
Age (yrs)		
Mean	11.56	11.45
Min - Max	3.2-21.7	2.5-20.0
Sex, n (%)		
Male	27 (87)	25 (64)
Female	4 (13)	14 (36)
Race, n (%)		
Caucasian	19 (61)	25 (64)
African American	6 (19)	3 (8)
Hispanic	5 (16)	7 (18)
Asian	1 (3)	2 (5)
Other	0	2 (5)
Extramedullary Disease at Baseline, n (%)		
Yes	10 (32)	17 (44)
No	18 (58)	15 (38)
Unknown	3(10)	7 (18)
History of CNS Leukemia		
Yes	1 (3)	1 (3)
No	27 (87)	32 (82)
Unknown	3 (10)	6 (15)
Status Follow Most Recent Prior Therapy, n (%)		
Relapsed	20 (65)	17 (44)
Refractory	9 (29)	22 (56)
Uknown	2 (6)	0
Prior Bone Marrow Transplant	2 (6)	8 (21)

Patients enrolled in COG P9673 Stratum 02/650 mg/m^2 were considered the primary efficacy population for this submission. These patients are heavily pretreated, having received up to five prior induction regimens (Table 8).

Table 8 Summary of Number of Prior Inductions (Patients in Stratum 02 Who Received 650 mg/m^2: Pediatric Study COG P9673)

	≥ 2 Prior Inductions (Stratum 02) N = 39
Number of Prior Inductions	**n (%)**
2	27 (69)
3	7 (18)
4	2 (5)
5	2 (5)
Unknown (≥ 2)	1 (3)

4.3.2. Efficacy Results: Pediatric Patients

Multiple Prior Inductions

The focus of this submission is for the use of ARRANON in the treatment of patients with multiply relapsed or refractory T-ALL/T-LBL (i.e., patients who have received multiple prior inductions).

A CR plus CR* rate of 23% (95% CI: 11%, 39%) was observed in pediatric patients with relapsed or refractory T-ALL/T-LBL who had received two or more prior inductions. A CR rate of 13% (95% CI: 4%, 27%) was observed in pediatric patients with relapsed or refractory T-ALL/T-LBL who had received two or more prior inductions. The standard of care in pediatric patients frequently did not permit confirmation of responses prior to initiation of subsequent therapy.

Pediatric patients in Stratum 02 650 mg/m^2 dose group of Study COG P9673 remained in continuous CR for a period of 4.7 to 36.4 weeks. Three of the five patients who attained a CR received an allogeneic bone marrow transplant during their response period. Duration of CR was 6.1 and 9.3 weeks in the patients who did not receive a stem cell transplant. All treated patients with CR in Stratum 02 650 mg/m^2 dose group had a period of disease control of at least 10.1 weeks, which would provide sufficient time to arrange a bone marrow transplant - consistent with the results in adults.

Table 9 Key Efficacy Endpoints (Patients in Strata 01 and 02 Who Received 650 mg/m^2: Pediatric Study COG P9673)

	1 Prior Induction (Stratum 01) N = 31	≥ 2 Prior Inductions (Stratum 02) N = 39
Best Response (Complete Remission with or without Hematologic Recovery) and Duration		
CR+CR* n (%)	15 (48%)	9 (23%)
[95% CI]	[30%, 67%]	[11%, 39%]
Duration of Best Response (CR/CR*) (minimum to maximum)	0.9 to 260.0+ wks	3.3 to 42.1 wks
Complete Remission and Duration		
CR n (%)	13 (42%)	5 (13%)
[95% CI]	[25%, 61%]	[4%, 27%]
Duration of CR (minimum to maximum)	0.9 to 260.0+ wks	4.7 to 36.4 wks
Complete Remission without Hematologic Recovery		
CR* n (%)	2 (6%)	4 (10%)
Duration of CR (minimum to maximum)	33.1 and 200.1+ wks	3.3 to 42.1
Survival		
Median OS (weeks)	33.3 wks	13.1 wks
[95% CI]	[24.1, 93.6]	[8.7, 17.4]
Survival at 1 year (%)	33%	14%
[95% CI]	[16%, 50%]	[3%, 26%]

'+' indicates patients was still in remission at date of last contact

The median survival for pediatric patients in the Stratum 02 650 mg/m^2 dose group was 13.1 weeks (95% CI: 8.7, 17.4) (Table 9). One year survival rate for the Stratum 02 650 mg/m^2 dose group was 14%. It is difficult to find a matched comparison for this population. COG has analyzed survival in patients originally enrolled in one of two large ALL trials (i.e., CCG-1952 and CCG-1961) who subsequently had two isolated bone marrow relapses. Utilizing the date of second isolated bone marrow relapse as the starting date, the one-year survival rate across all patients with any immunophenotype was <10%. Of these, the one-year survival rate for patients with T-ALL was 0%, as all 13 patients with T-ALL died within eight months of the second relapse. Thus, although comparison of time to event data across studies is fraught with difficulties, the 14% one year survival in patients with multiply relapsed/refractory T-ALL/T-LBL is clinically meaningful and puts into perspective the benefit of ARRANON in this patient population with severe unmet medical need.

One Prior Induction

Patients with one prior induction also demonstrated benefit from single agent ARRANON.

A larger number of pediatric patients (n=31) with one prior induction (Stratum 01) were treated at the recommended dose than were adult patients (n=11) discussed above. In the

larger group of patients, the CR plus CR* rate was 48% (95% CI: 30%, 67%). One patient in this group had a documented duration lasting less than one week. While the investigator determined the CR to have occurred approximately 12 weeks prior, infrequent documentation of the status of extramedullary disease did not allow declaration of CR by GSK. Eight of the 15 patients had durations of CR or CR* lasting more than 130 weeks, seven of whom were still in remission at the time of database closure.

Individually, CR and CR* rates were 42% (95% CI: 25%, 61%), and 6%, respectively (Table 9). All patients with CR or CR* in Stratum 01 650 mg/m^2 dose group had a period of disease control lasting at least 7.9 weeks.

These results are impressive for a single agent administered to patients whose disease has relapsed following or was refractory to modern, intensive, multi-agent therapy.

Refractory - Failure of Most Recent Prior Induction

Patients whose response to most recent prior therapy was reported by the investigator to be less than a CR during the most recent prior induction period were evaluated for response to ARRANON. The definition of response to prior therapy was not standardized, but accepted as reported by the investigator. These patients represent a group that is considered refractory and would not necessarily be expected to respond or gain benefit from additional chemotherapy.

Table 10 Summary of Response to ARRANON in Patients with Refractory Disease (Pediatric Study COG P9673)

	1 Prior Induction N = 9	≥ 2 Prior Inductions N = 22
CR+CR* [95% CI]	5 (56%) [21%, 86%]	6 (27%) [11%, 50%]
Achieved CR on ARRANON [95% CI]	4 (44%) [14%, 79%]	4 (18%) [5%, 40%]
Achieved CR* on ARRANON	1 (11%)	2 (9%)

Note: Refractory disease = lack of CR to most recent prior induction therapy.

On the COG P9673 study, 22 of the 39 patients in Stratum 02 650 mg/m^2 dose group had disease that was refractory to their most recent induction, based on the investigator's own criteria. A CR plus CR* rate of 27% (95% CI: 11%, 50%) was observed with single agent ARRANON in patients with refractory disease after multiple prior induction attempts. CR was achieved in 18% (95% CI: 5%, 40%) of patients with refractory disease and multiple prior inductions (Table 10).

Within the Stratum 01 650 mg/m^2 dose group of 31 patients, a subset of nine refractory patients had disease that had failed to respond to the prior (front-line) induction. A total CR plus CR* rate of 56% (95% CI: 21%, 86%) was achieved in these patients. CR was achieved in 44% (95% CI: 14%, 79%) of these patients following single agent ARRANON (Table 10).

The ability of a single agent to induce a CR or CR* in patients who are refractory to modern, multi-agent, induction therapy is indicative of clinical benefit.

4.4. ADDITIONAL STUDIES

4.4.1. PGAA1001

Activity of nelarabine was first demonstrated in patients with relapsed or refractory T-cell hematologic malignancies during the first Phase I study (PGAA1001). An overall 29% (8/28) response rate was observed in pediatric patients enrolled, with a CR rate of 33% (6/18) in pediatric patients with relapsed or refractory T-ALL/T-LBL. An overall response rate of 38% (25/65) was observed in patients >18 years of age, with a CR rate of 29% (4/14) in adult patients with relapsed or refractory T-ALL/T-LBL.

4.4.2. Special Exceptions

One center that has enrolled multiple patients on Special Exceptions Protocols has published results in 16 subjects with relapsed or refractory T-ALL [Goekbuget, 2003].

This report included 15 adults who received nelarabine 1500 mg/m^2/day on days 1, 3, and 5 of 21 day cycles, and one child who received 650 mg/m^2/day on days 1 to 5 of 21 day cycles via special exceptions protocols. Two subjects were primary refractory and 14 had early relapse, including two after allogeneic stem cell transplant. All subjects were relapsed following or refractory to at least one prior multi-agent salvage therapy that included high-dose cytarabine. Nine (56%) subjects achieved a CR, one additional subject achieved an unconfirmed CR, described as around 5% blasts. Of these ten subjects, eight proceeded to stem cell transplant, and seven of the eight were still alive in continuous complete remission at the time of publication. The overall conclusion was that nelarabine was "generally well tolerated despite extensive pretreatment" and a favorable remission rate could be achieved in these subjects with highly resistant T-ALL.

4.5. EFFICACY CONCLUSIONS

ARRANON demonstrated clinical benefit in patients who received the recommended adult and pediatric doses enrolled on these two independently conducted clinical trials, CALGB 19801, and COG P9673. In adult and pediatric patients with two or more prior inductions, single agent ARRANON induced a CR plus CR* rates of 21% and 23% respectively. A CR rate of 18% (95% CI: 6%, 37%) occurred in adult patients with duration of CR from 15 to more than 195 weeks with some patients continuing in remission at the time of analysis, and 29% survival rate at one year, indicative of clinical benefit in this heavily pretreated patient population. Similar results were observed in pediatric patients with two or more prior inductions (Stratum 02) where single agent ARRANON induced a CR rate of 13% (95% CI: 4%, 27%) with duration of CR from 4.7 to 36.4 weeks, and 14% survival at one year.

Of particular note, refractory patients whose most recent attempt at remission induction failed, showed impressive CR plus CR* rates to ARRANON therapy of 24% (95%CI:

7%, 50%) in adult and 27% (95%CI: 11%, 50%) in pediatric patients with two or more prior inductions, and 56% (95%CI: 21%, 86%) in pediatric patients with one prior induction. The majority of these patients with refractory disease achieved a CR. The CR rate following single agent ARRANON therapy was 18% in both adult (95%CI: 4%, 43%) and pediatric (95%CI: 5%, 40%) patients with refractory disease after multiple prior induction attempts.

Induction of response (CR and CR*) is meaningful in patients with relapsed or refractory T-ALL/T-LBL, since long-term benefit is typically sought through transplant. Allogeneic BMT performed in patients who have been re-induced into remission shows a survival benefit compared to continued chemotherapy without a transplant [Henze, 1991; Giona, 1997; Wheeler, 1998; Dopfer, 1991]. This benefit is mostly seen in the high-risk group and in patients with early relapse [Borgmann, 2003]. Patients who are transplanted in CR have a better probability of long term survival than those transplanted in relapse [Bortin, 1989], indicating a need for improvements in re-induction therapy.

ARRANON demonstrated clinically meaningful response rates in patients with T-cell hematologic malignancies during Phase I studies and in a published report from patients enrolled in Special Exception Protocols at a single institution.

In summary, ARRANON has demonstrated consistent clinically significant efficacy in the treatment of patients with relapsed or refractory T-ALL/T-LBL.

5. OVERVIEW OF SAFETY

5.1. INTRODUCTION

Safety was assessed in several defined populations of patients (Table 11). The safety information presented in this document is provided regardless of causal relationship, and for patients treated at the recommended doses and schedules (650 mg/m^2/dose for 5 consecutive days for pediatric patients, and 1500 mg/m^2/dose days 1,3,5 for adult patients), unless specifically noted otherwise.

Table 11 Description of Patient Groupings for Safety Summaries

Patient Safety Group	N	Description
Pediatric Dose	84	COG P9673, all patients dosed at 650 mg/m^2 regardless of Stratum
Adult Dose	103	CALGB 19801 and PGAA2003 patients dosed at 1500 mg/m^2
Integrated Safety Database	459	All patients, regardless of dose or schedule enrolled in studies for which a full database is available: COG P9673, CALGB19801, PGAA2003, PGAA1005, PGAA1003, PGAA1002, PGAA1001
SAE Safety Database	980	All patients, regardless of dose or schedule through data cut-off date for submission

The dose limiting toxicity for nelarabine is neurologic. Neurologic safety data is presented in a standard manner in Section 5.6.1 utilizing standardized toxicity grades and event terms. Additionally, further evaluation of neurologic events, including exploratory analyses of potential associated factors are presented in Section 5.6.2 through Section 5.6.5 of this document. Other adverse events (AEs) are observed with nelarabine treatment but they are typical for cytotoxic agents and of lesser clinical significance in this patient population. Foremost among these are frequent hematologic toxicities that are common in heavily pretreated patients with relapsed and refractory hematologic malignancies.

5.2. STANDARD SAFETY DATA PRESENTATIONS, BY POPULATION

5.2.1. Adverse Events and Hematologic Toxicity in Pediatric Patients

The safety of ARRANON in the pediatric, i.e., ≤ 21 years of age, population was characterized mostly by expected hematologic AEs (Study COG P9673). Of the non-hematologic AEs, the 3 most frequent events reported at the 650 mg/m^2 dose (n=84) were headache (17%), peripheral neurologic disorder (12%), and increased transaminase levels (12%) (Table 12). The most frequent non-hematologic grade 3 events were increased bilirubin (7%), and peripheral neurologic disorder (7%). The most frequent non-hematologic grade 4+ events were seizures (6%), including one fatal seizure event (Table 12).

Grade 3 and 4 hematologic toxicity was commonly reported in these patients (Table 13).

Table 12 Most Commonly Reported (>/= 5% Overall) Non-Hematologic Adverse Events in Pediatric Patients Treated with 650 mg/m^2 of ARRANON Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days

System Organ Class Preferred Term	Percentage of Patients: 650 mg/m^2; N = 84 Toxicity Grade		
	Grade 3 %	Grade 4+[a] %	All Grades %
Hepatobiliary Disorders			
Transaminases increased	4	0	12
Blood albumin decreased	5	1	10
Blood bilirubin increased	7	2	10
Metabolic/Laboratory			
Blood potassium decreased	4	2	11
Blood calcium decreased	1	1	8
Blood creatinine increased	0	0	6
Blood glucose decreased	4	0	6
Blood magnesium decreased	2	0	6
Nervous System Disorders			
Headache	4	2	17
Peripheral Neurologic Disorder[b]	7	0	12
Lowered Consciousness[b]	1	1	7
Seizures[b]	0	6	6
Hypoesthesia	4	0	6
Gastrointestinal Disorders			
Vomiting	0	0	10
General Disorders & Administration Site Conditions			
Asthenia	1	0	6
Infections & Infestations			
Infection	2	1	5

Grade 4+ = Grade 4 and Grade 5

a. Three (3) patients had a fatal event. Fatal events included neutropenia and pyrexia (n = 1), status epilepticus/seizures (n = 1), and fungal pneumonia (n = 1). The status epilepticus/seizure was thought to be related to treatment with nelarabine. All other fatal events were unrelated to treatment with nelarabine.

b. Peripheral Neurologic Disorder, Lowered Consciousness, and Seizures are Clinical Category terms each of which includes several clinically related component terms from the MedDRA Dictionary. See Table 16 for each of the component terms.

Table 13 Summary of On-Therapy Hematologic Toxicity Regardless of Attribution for Pediatric Patients Treated with 650 mg/m^2 of ARRANON by Maximum Severity

Hematologic Toxicity Preferred (Category) Term Subterm	Percentage of Patients; N = 84				
	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4+ %	All Grades %
Anemia	12	29	45	10	95
Neutropenia	6	10	17	62	94
Thrombocytopenia	23	6	27	32	88

Note: Hematologic toxicity was derived from both adverse event reports and laboratory data. Maximum severity is reported.

5.2.2. Adverse Events and Hematologic Toxicity in Adult Patients

The most common non-hematologic events in the adult Phase II studies at the 1500 mg/m^2 dose (n=103), regardless of drug relationship, were: lowered consciousness (63%); GI disorders, i.e., nausea (41%), pyrexia (23%), diarrhea and vomiting (22% each), and constipation (21%); respiratory disorders, i.e., cough (25%) and dyspnea (20%), dizziness (21%), and peripheral neurologic disorders (18%) (Table 14). The most frequent grade 3 non-hematologic events in these patients were lowered consciousness (11%) and febrile neutropenia (9%). The most frequent grade 4 non-hematologic event in this population was lowered consciousness (3%) (Table 14).

Grade 3 and 4 hematologic toxicity was commonly reported in these patients (Table 15).

Table 14 Most Commonly Reported (> / = 5% Overall) Non-Hematologic Adverse Events in Adult Patients Treated with 1,500 mg/m^2 of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days

System Organ Class Preferred Term	Percentage of Patients; N = 103 Toxicity Grade Grade 3 %	Grade 4+[a] %	All Grades %
Blood and Lymphatic System Disorders			
Febrile neutropenia	9	1	12
Cardiac Disorders			
Sinus tachycardia	1	0	8
Gastrointestinal Disorders			
Nausea	0	0	41
Vomiting	1	0	22
Diarrhea	1	0	22
Constipation	1	0	21
Abdominal Pain	1	0	9
Stomatitis	1	0	8
Abdominal distension	0	0	6
General Disorders and Administration Site Conditions			
Pyrexia	5	0	23
Asthenia	0	1	17
Edema, peripheral	0	0	15
Pain	3	0	11
Edema	0	0	11
Rigors	0	0	8
Gait, abnormal	0	0	6
Non-cardiac chest pain	0	1	5
Chest pain	0	0	5
Infections			
Infection	2	1	9
Pneumonia	4	1	8
Sinusitis	1	0	7
Hepatobiliary Disorders			
AST increased	1	1	6
Metabolism and Nutrition Disorders			
Anorexia	0	0	9
Dehydration	3	1	7
Hyperglycemia	1	0	6
Musculoskeletal and Connective Tissue Disorders			
Myalgia	1	0	13
Arthralgia	1	0	9
Back pain	0	0	8
Muscular weakness	5	0	8
Pain in extremity	1	0	7

Table 14 Most Commonly Reported (>/=5% Overall) Non-Hematologic Adverse Events in Adult Patients Treated with 1,500 mg/m^2 of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days (continued)

System Organ Class Preferred Term	Percentage of Patients; N = 103 Toxicity Grade Grade 3 %	Grade 4+[a] %	All Grades %
Nervous System Disorders			
Lowered Consciousness[b]	11	3	63
Dizziness	0	0	21
Peripheral Neurologic Disorders[b]	2	0	18
Hypoesthesia	2	0	17
Paresthesia	0	0	15
Headache	1	0	15
Ataxia	2	0	9
Tremor	0	0	5
Psychiatric Disorders			
Confusional state	2	0	8
Depression	1	0	6
Insomnia	0	0	7
Respiratory, Thoracic and Mediastinal Disorders			
Cough	0	0	25
Dyspnea	4	2	20
Pleural effusion	5	1	10
Epistaxis	0	0	8
Dyspnea, exertional	0	0	7
Wheezing	0	0	5
Vascular Disorders			
Petechiae	2	0	12
Hypotension	1	1	8

Grade 4+ = Grade 4 and Grade 5

a. Grade 5 (fatal) events included hypotension (n = 1) and respiratory arrest (n = 1).

b. Peripheral Neurologic Disorder and Lowered Consciousness are Clinical Category terms each of which includes several clinically related component terms from the MedDRA Dictionary. See Table 17 for each of the component terms.

Table 15 Summary of On-Therapy Hematologic Toxicity Regardless of Attribution for Adult Patients Treated with 1,500 mg/m^2 of ARRANON by Maximum Severity

Hematologic Toxicity Preferred (Category) Term Subterm	Percentage of Patients; N = 103 Grade 1 %	Grade 2 %	Grade 3 %	Grade 4+ %	All Grades %
Anemia	30	35	20	14	99
Thrombocytopenia	15	13	37	22	86
Neutropenia	3	16	14	49	81

Note: Hematologic toxicity was derived from both adverse event reports and laboratory data. Maximum severity is reported.

5.3. SERIOUS ADVERSE EVENTS

Serious adverse events, regardless of causal relationship, were reported for 20% of pediatric patients in 650 mg/m^2 dose group in COG P9673. The most common serious adverse events were peripheral sensory neuropathy (6%), convulsion (4%), and hypoesthesia (4%). Serious adverse events possibly attributable to treatment with ARRANON that occurred in more than one patient were peripheral sensory neuropathy reported in 5 patients (6%), hypoesthesia reported in 3 patients (4%) and convulsion and peripheral motor neuropathy, each reported in 2 patients (2%).

Serious adverse events were reported for 42% of the patients in the 1500 mg/m^2 dose group in adult Phase II studies. The most frequent serious adverse events, regardless of drug relationship, were pyrexia (8%), febrile neutropenia (5%), pneumonia (5%), dyspnea (5%), dehydration (4%), and pleural effusion (4%). Serious adverse events possibly attributable to treatment with ARRANON that occurred in more than one patient included pyrexia (5%), febrile neutropenia (3%), dehydration (3%), pneumonia (2%), pancytopenia (2%), and ataxia (2%).

5.4. DEATHS

In the pediatric population treated in 650 mg/m^2 dose group (n=84), eight (10%) patients died within 30 days of nelarabine treatment, one of which was due to drug related AE (1%, status epilepticus in patient 1055 in Stratum 04). The other deaths were unrelated to nelarabine treatment.

In the adult population treated at the 1500 mg/m^2 dose (n=103), 10 patients (10%) died within 30 days of nelarabine treatment, one of which was due to a drug related AE (1%, leukoencephalopathy in patient 1712 on Study PGAA2003). The other deaths among pediatric patients were unrelated to nelarabine treatment.

5.5. POST TRANSPLANT HEMATOLOGIC RECOVERY

Transplantation is often a desired clinical outcome for the population studied in the ARRANON program, even though it was not a prospectively defined part of the pivotal studies. It is important to understand whether stem cell transplants following ARRANON treatment can be successful. One measure of success is post transplant myeloid recovery. The pivotal trial protocols were amended to allow post hoc collection of transplant outcomes. Myeloid engraftment data were available only on a subset of patients who underwent transplantation. In the adult population, 3 of 7 patients achieved myeloid engraftment, while 18 of 19 pediatric patients achieved myeloid engraftment. Note also that two of the adult patients who did not have defined myeloid recovery nonetheless experienced greater than 2 year survival periods. These data suggest that ARRANON does not interfere with the potential success of transplantation efforts in these heavily pretreated patients, and provides the necessary efficacy to allow patients to receive a stem cell transplant.

5.6. NEUROLOGIC ADVERSE EVENTS

Neurologic adverse events have been a focus throughout the development of ARRANON. Dose limiting toxicity in human Phase I dose rising studies was neurologic, similar to that seen in preclinical studies in primates. Early experiences in Phase II studies included severe neurologic toxicity necessitating a decrease in the recommended doses for pediatric and adult patients, and implementation of guidance on discontinuation of treatment for certain grade 2 or greater neurologic toxicities that persist or worsen. These changes were implemented following communications from NCI and GSK that occurred in mid 1998. This experience may be reminiscent of early experiences of fludarabine, now a widely used commercially available agent, which "was almost discarded following initial Phase I trials because of prohibitive toxicities, particularly neurotoxicity" [Cheson, 1994].

Because of the significant neurologic toxicity profile observed in the clinical development of ARRANON, especially in the earlier studies and at higher dose levels, multiple analytic approaches have been taken to better characterize and understand this aspect of the safety profile of ARRANON. The results from these analyses have been reported in the submission and are summarized in this document, including standard presentation of neurologic adverse events occurring in patients treated at the recommended doses (n=84 pediatric dose, n=103 adult dose, and n=459 any dose), as well as results from Exploratory Analyses of Potential Risk Factors Associated with Neurologic Events (n=459), and a Neurologic Adverse Event Case Review (n=980).

5.6.1. Standard Presentation of Neurologic Events

Among the 84 pediatric patients treated at the 650 mg/m^2 dose, the most frequent nervous system AEs at the 650 mg/m^2 dose were headache (17%), peripheral neurologic disorders (12%), lowered consciousness (7%), hypoesthesia (6%), and seizures (6%) (Table 16). Of note, peripheral neuropathy resolved in 1 patient after 8 months and in 2 patients after approximately 1 year. Neurologic serious adverse events (SAEs), regardless of drug relationship were reported for 15% of the pediatric patients. The most common serious nervous system events were peripheral sensory neuropathy (6%), convulsion (4%), and hypoesthesia (4%). Five patients (6%) in the 650 mg/m^2 dose group had seizure or related term serious adverse events; in the case of 3 patients, the events were judged by the investigator to be at least possibly related to treatment with ARRANON, including one fatal seizure event.

Table 16 Neurologic Adverse Events in Pediatric Patients Treated with 650 mg/m^2 of ARRANON Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days

Nervous System Disorders Preferred (Category) Term Subterm	Percentage of Patients; N = 84					
	Grade Unknown %	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4+ %	All Grades %
Headache	**0**	**8**	**2**	**4**	**2**	**17**
Peripheral Neurologic Disorders	**0**	**1**	**4**	**7**	**0**	**12**
Neuropathy, peripheral	0	0	4	2	0	6
Peripheral sensory neuropathy	0	0	0	6	0	6
Peripheral motor neuropathy	0	1	0	2	0	4
Lowered Consciousness	**0**	**1**	**4**	**1**	**1**	**7**
Somnolence	0	1	4	1	1	7
Fatigue	0	0	1	0	0	1
Lethargy	0	1	0	0	0	1
Hypoesthesia	**0**	**1**	**1**	**4**	**0**	**6**
Seizures	**0**	**0**	**0**	**0**	**6**	**6**
Convulsion	0	0	0	0	4	4
Grand mal convulsion	0	0	0	0	1	1
Status epilepticus	0	0	0	0	1	1
Motor dysfunction	**0**	**1**	**1**	**1**	**0**	**4**
Nervous system disorder	**0**	**1**	**2**	**0**	**0**	**4**
Paresthesia	**0**	**0**	**2**	**1**	**0**	**4**
Tremor	**0**	**1**	**2**	**0**	**0**	**4**
Ataxia	**0**	**1**	**0**	**1**	**0**	**2**

Among the 103 adult patients who received the 1500 mg/m^2 dose, the most frequent nervous system AEs, regardless of drug relationship, were lowered consciousness (63%), dizziness (21%), peripheral neurologic disorders (18%), hypoesthesia (17%), paresthesia (15%), and headache (15%) (Table 17). Neurologic SAEs, regardless of drug relationship, were reported for 8% of the adult patients; and included ataxia occurring in 2 patients and several other events occurring in only one patient Of note, only one patient at the 1500 mg/m^2 dose in the adult Phase II studies had a seizure or related term event.

Table 17 Neurologic Adverse Events in Adult Patients Treated with 1,500 mg/m^2 of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days

Nervous System Disorders System Organ Class Preferred (Category) Term Subterm	Percentage of Patients; N =103					
	Grade Unknown %	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4+ %	All Grades %
Lowered Consciousness	**0**	**33**	**17**	**11**	**3**	**63**
Fatigue	0	23	15	10	2	50
Somnolence	0	20	3	0	0	23
Depressed level of consciousness	0	4	1	0	1	6
Coma	0	0	0	0	1	1
Lethargy	0	0	1	0	0	1
Loss of consciousness	0	0	0	1	0	1
Dizziness	**0**	**14**	**8**	**0**	**0**	**21**
Peripheral Neurologic Disorders	**0**	**8**	**9**	**2**	**0**	**18**
Peripheral sensory neuropathy	0	7	6	0	0	13
Peripheral motor neuropathy	0	3	3	1	0	7
Neuropathy, peripheral	0	2	2	1	0	5
Hypoesthesia	**1**	**5**	**10**	**2**	**0**	**17**
Headache	**0**	**11**	**3**	**1**	**0**	**15**
Paresthesia	**0**	**11**	**4**	**0**	**0**	**15**
Ataxia	**0**	**1**	**6**	**2**	**0**	**9**
Tremor	**0**	**2**	**3**	**0**	**0**	**5**
Neuropathy	**0**	**0**	**4**	**0**	**0**	**4**
Amnesia	**0**	**2**	**1**	**0**	**0**	**3**
Dysguesia	**0**	**2**	**1**	**0**	**0**	**3**
Balance disorder	**0**	**1**	**1**	**0**	**0**	**2**
Sensory loss	**0**	**0**	**2**	**0**	**0**	**2**
Seizures	**0**	**0**	**0**	**1**	**0**	**1**
Convulsion	0	0	0	1	0	1

Grade 4+ = Grade 4 and Grade 5

Among the 459 patients in the safety database across patient populations, doses and schedules, the most frequent nervous system AEs, regardless of drug relationship were lower consciousness (47%), headache (18%), and dizziness (14%). Eleven percent (11%) of patients had an event of peripheral neurologic disorders, with 3% having a grade 3 and 1% a grade 4 event. Three percent (12 of 459) had seizure or related term. Nervous system SAEs occurred in 14% of the patients in the safety database.

Nervous system disorders occurring in patients treated with ARRANON resolved in most (65%) cases, while 21% were known to have not resolved, and 1% were fatal. The results are displayed by study and dose (Table 18, Table 19, Table 20).

Table 18 Summary of Resolution of On-therapy Nervous System Disorder Events Regardless of Attribution (Events Occurring in N=84 Pediatric Patients who Received 650 mg/m^2 in COG P9763)

	650 mg/m^2 Events=80
Resolution	**n (%)**
Fatal	1 (1%)
Not Resolved	13 (16%)
Resolved	50 (63%)
Unknown	16 (20%)

Note: Resolved with Sequelae included in Resolved count.
Note: n = number of events (not patients).
Note: Data represent events occurring in 84 pediatric patients.

Table 19 Summary of Resolution of On-therapy Nervous System Disorder Events Regardless of Attribution (Events Occurring in N=103 Adult Patients who Received 1500 mg/m^2 in CALGB 19801 and PGAA2003)

	CALGB 19801 Events=61	PGAA2003 Events=156	Total Events=217
Resolution n (%)			
Fatal	0 (0%)	3 (2%)	3 (1%)
Not Resolved	0 (0%)	50 (32%)	50 (23%)
Resolved	0 (0%)	103 (66%)	103 (47%)
Unknown	61 (100%)	0 (0%)	61 (28%)

Note: Resolved with Sequelae included in Resolved count
Note: n = number of events (not patients)
Note that for Study CALGB 19801, events were recorded only during the cycle in which they occurred, and date of resolution *per se* was not reported.
Note: Data represent events occurring in 103 adult patients.

Table 20 Summary of Resolution of On-Therapy Nervous System Disorder Events Regardless of Attribution (Events Occurring in All Treated Subjects, N=459, Across All Phase I and Phase II Studies with Available Database)

	PGAA1001 Events=227	PGAA1002 NEvents=35	PGAA1003 Events=132	PGAA1005 Events=30	COG P9673 Events=142	CALGB 19801 Events=63	PGAA2003 Events=216	Total Events=845
Resolution n (%)								
Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (2%)	0 (0%)	3 (1%)	6 (1%)
Not Resolved	43 (19%)	5 (14%)	35 (27%)	5 (17%)	24 (17%)	0 (0%)	68 (31%)	180 (21%)
Resolved	182 (80%)	30 (86%)	92 (70%)	25 (83%)	77 (54%)	0 (0%)	142 (66%)	548 (65%)
Unknown	2 (1%)	0 (0%)	5 (4%)	0 (0%)	38 (27%)	63 (100%)	3 (1%)	111 (13%)

Note: Resolved with Sequelae included in Resolved count.

Note: n = number of events (not patients).

Note: In Study CALGB 19801, events were recorded only during the cycle in which they occurred, and date of resolution *per se* was not reported.

Note: Data represent events occurring in 459 adult and pediatric patients.

5.6.2. Exploratory Analysis of Neurologic Event Covariates

5.6.2.1. Methods

Neurologic AE terms in the Medical Dictionary for Regulatory Activities (MedDRA) were reviewed and categorized based on the following categories: peripheral nervous system (PNS), central nervous system (CNS), mental status change (MSC, typically somnolence or related) and uncategorized. All events were considered, regardless of attribution, across the seven studies in the safety database. Prescribed dosing, prior therapy, concomitant therapy, and baseline characteristic variables were examined as potential risk factors for the occurrence of any neurologic AE (any event) (grade ≥3), any event (any grade), CNS events (grade ≥3), CNS events (any grade), MSC events (grade ≥3), MSC events (any grade), PNS Events (grade ≥3), or PNS Events (any grade). Separate analyses were performed for each of the eight categories described above.

Please see ATTACHMENT 2 for further details on the methods utilized for this analysis.

5.6.2.2. Results

The potentially relevant characteristics were evaluated, but only three were shown to be associated with multiple categories of neurologic adverse events; namely: age, cycle dose, and CNS disease (i.e., CNS leukemia) at baseline (Table 21). Cycle dose is defined as the dose in mg/m^2 given over the full 21 day cycle. Cycle dose was associated with all categories except CNS events. Increasing age was associated with increasing incidence of neurologic events, but was not associated with the severe events. CNS disease at baseline, however, was associated with severe neurologic events, with an odds ratio of 3.35 and $p = 0.0002$. Among the other baseline features identified to be associated with only a single category of neurologic adverse event, several features would be expected to be correlated to the presence of baseline CNS disease (i.e., concomitant intrathecal cytarabine and methotrexate, and prior intrathecal therapy).

Modeling of data from the safety database suggests that 25% of patients in this heavily pretreated population would be expected to have a neurologic adverse event of any grade and 10% a grade 3 or 4 event, in the absence of ARRANON treatment.

Cumulative dose does not appear to be associated with an increased risk of neurologic events. Further details are provided in the Exploratory Analyses of Potential Risk Factors Associated with Neurologic Events.

Table 21 Odds Ratios and 95% Confidence Intervals for Risk Factors Identified from Logistic Modeling

Model Parameter	Any Event		MSC Events		CNS Events		PNS Events	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Prescribed Cycle Dose (g/m^2)	**1.20 (1.09, 1.31)**	**1.23 (1.11, 1.35)**	**1.33 (1.21, 1.46)**					**1.22 (1.07, 1.39)**
Age (years)	**1.03 (1.02, 1.04)**		**1.03 (1.02, 1.03)**		**1.02 (1.01, 1.04)**			
Age Category (ped. ≤16 vs. adult >16)							0.238 (0.14, 0.41)	
CNS at Baseline (Y vs. N)[a]		**3.35[b] (1.97, 5.69)**				**2.67[d] (1.24, 5.75)**		**2.64[c] (1.11, 6.26)**
Prior Cranial Radiation (Y vs. N)								2.48 (1.23, 5.00)
Concomitant IT ara-C and IT MTX (Y vs. N)[e]		4.07[e] (2.15, 7.72)						
Baseline sodium[a]				0.86[a] (0.77, 0.96)				
Infusion Duration (2 hr vs. 1 hr)					0.28 (0.16, 0.50)			
Hydration Status at Baseline (≥20 vs. < 20)[a]						2.40[d] (1.12, 5.13)		
Prior IT ara-C, IT HC or IT MTX (Y vs. N)[e]							1.87[e] (1.03, 3.39)	
Prior IT MTX and IT ara-C (Y vs. N)[e]								2.47[e] (1.25, 4.89)

a. Data available on only 70% to 80% of patients.
b. Model evaluated with CNS at baseline, cycle dose, and infusion duration. Cycle dose and infusion duration not significant once adjusted for CNS at baseline
c. Model evaluated with CNS at baseline, cycle dose, and infusion duration. Infusion duration significant when adjusted for CNS at baseline while cycle dose is not significant once adjusted for CNS at baseline
d. Examined individually in separate models due to limited data
e. Unknown vs. N also examined. Many patients treated with MTX and/or Ara-C with route of admin unknown

5.6.3. PK/PD Analysis of Neurologic Events

A cross-study PK/PD analysis was performed on three Phase I studies to look for relationships between plasma nelarabine, plasma ara-G, or intracellular ara-GTP exposure and several functional categories of neurologic events using logistic regression models. The data from the nelarabine-fludarabine combination study (Study PGAA1005) were excluded as they had the potential to confound the PK/PD relationship.

5.6.3.1. Methods

The exposure measures evaluated were Cmax and AUC(0-t) values for nelarabine, ara-G, and intracellular ara-GTP. The categories of neurologic events evaluated were peripheral nervous system events, mental status changes, or any neurologic event during Course 1 or at any time during the study. Pharmacokinetic measures of exposure, demographics (age, gender, race, BSA), disease category, and study were included in the full model. Each exposure measure was evaluated separately. Stepwise analysis was used to identify the factors associated with each neurologic event category; factors with $p<0.05$ were considered statistically significant.

5.6.3.2. Results

Measures of nelarabine, ara-G, or ara-GTP exposure were not generally associated with the various categories of neurologic events, with the exception of the following apparent relationships:

- higher nelarabine plasma Cmax and AUC(0-t) values and the occurrence of mental status changes at any time during the study;
- higher intracellular ara-GTP Cmax and AUC(0-t) values and the occurrence of peripheral nervous system events at any time during the study.

No measures of nelarabine, ara-G, or ara-GTP exposure were associated with the "any neurologic event" category.

Analyses of the combined Phase I/II dataset to look for relationships between neurologic events and baseline characteristics, nelarabine dose, and other potential risk factors were performed and are described in Section 5.6.2.

5.6.4. Neurologic Adverse Event Case Review

Particularly informative cases of neurologic adverse events were identified from all available neurologic adverse event reports for patients treated with ARRANON. Selection criteria included absence of alternative etiology of the event, and documentation of results from additional neurologic investigation(s). Several important observations have been made based on this review.

The reports demonstrate that there can be multiple neurologic events observed in an individual patient. These events are not always reversible within the often short life span of the patient, and the events can be fatal.

Several cases clinically reported as PNS events were, upon objective testing, found to involve some degree of central demyelination.

When the peripheral nervous system is involved, there can be both axonal and demyelinative features. Some reports describe a demyelinative picture that resembles Guillain-Barré Syndrome (GBS).

There was evidence of central demyelination, primarily involving the cervical and thoracic cord. In one case, this demyelination pathologically involved the white matter tracts in a pattern like that seen in reports of vitamin B12 deficiency. The spinal MRI scan descriptions were also consistent with the involvement expected with vitamin B12 deficiency. A very similar histologic pattern was also seen in the non-human primate toxicology studies (as reviewed by Dr. Herb Schaumberg, personal communication).

5.6.5. Guillian-Barré-like Syndrome Events

As noted above, several events consistent with the ascending peripheral neuropathy seen in GBS have been identified among the over 980 patients treated with ARRANON. The rate of 1.4% overall (14/980) suggests a low incidence of GBS-like events. When these events do occur, they can be severe and disabling, and in at least one case of an adult in the Special Exceptions Program, the event was judged to have contributed to death. Over the course of ARRANON development, these cases appear to have become less frequent. This may be partially due to the refinement of the dose regimens, together with increased awareness of the potential for severe neurologic toxicity and the limitation of ARRANON use to the proposed indications.

5.7. SAFETY CONCLUSIONS

In conclusion, ARRANON is a member of a class of drugs, the nucleoside analogs, known to be associated with hematologic and neurologic toxicity. In addition, the patients treated with ARRANON were pretreated with agents know to cause neurotoxicity. The ARRANON AE profile, with the exception of neurologic events which were dose limiting, was relatively unremarkable for this heavily pretreated population. The recommended doses for adult and pediatric patients in the proposed indicated population have shown a relatively low incidence of severe neurologic events. Efforts are ongoing to better understand the mechanism of the neurologic events associated with the use of nelarabine.

Close monitoring of patients using standard physical examination techniques, patient education, and scientific communication should allow for early detection of neurologic toxicities to minimize their severity. The treatment related death rate at the proposed dose and regimen (one case each from n=84 and n=103) was 1%. These two deaths occurred in patients who were outside of the proposed indicated population.

Historical data on patients who have failed multiple prior induction attempts suggests that some multi-agent treatment regimens carry a 10-20% treatment related mortality [Bernstein 1997, Thomas 1999].

Data for approved nucleoside analogues used as anti-tumor chemotherapeutics demonstrates neurologic toxicity is relatively common and occasionally severe (including fatal) at standard doses, and more frequently severe (including fatal) at higher Phase I doses [Cheson 1994].

Given the significant antitumor activity resulting in responses of sufficient duration and quality to allow for bone marrow transplantation in this heavily pretreated and often refractory population, the frequency and severity of the neurologic toxicity is acceptable. As clinical experience has been gained in the use of ARRANON, neurologic monitoring has been incorporated into practice, and the safety profile of ARRANON has improved. ARRANON has an acceptable risk to benefit ratio in patients with relapsed or refractory T-ALL/T-LBL.

6. BENEFIT AND RISK ASSESSMENT

Patients in the proposed indication with multiply relapsed or refractory T-ALL/T-LBL are in desperate need of efficacious treatment. At the time of ARRANON treatment, they have already undergone modern front-line therapy that has been risk adjusted (usually meaning increased intensity for patients with T-cell disease) designed to offer the best chance for cure. Upon failure (relapse or failure to respond), these patients were treated with individualized therapy based on their prior responses, and prior exposures, again designed to offer the best chance for cure. Patients whose disease is refractory after multiple best attempts at cure using multi-agent regimens are unlikely to respond to a single agent unless that agent is able to provide meaningful benefit.

Administration of ARRANON has resulted in CR plus CR* rates of 21% (95% CI: 8%, 41%) and 23% (95% CI: 11%, 39%) in adult and pediatric patients, respectively, whose disease persisted despite at least two prior chemotherapy regimens. The duration of remission induced by ARRANON was 4 to 195.4+ weeks and 3.3 to 42.1 weeks in adult and pediatric patients, respectively, allowing those patients for whom it was an option to receive a stem cell transplant. Myeloid engraftment was demonstrated in the majority of these patients and did not appear to be compromised by prior receipt of ARRANON.

As demonstrated by the results of two independently conducted trials, administration of ARRANON has resulted in CR plus CR* rates of 24% (95% CI: 7%, 50%) and 27% (95% CI: 11%, 50%) in adult and pediatric patients, respectively, who had refractory disease after multiple prior best attempts at cure. In those pediatric patients who were refractory to one prior attempt at cure, the CR plus CR* rate for single agent ARRANON was 56% (95% CI: 21%, 86%).

Current multi-agent therapies used in patients who disease has failed to respond to one prior induction attempt can be associated with a 10% to 20% treatment related mortality rate. Administration of ARRANON has been associated with common and usually low grade neurologic toxicity. Among the 459 patients in the safety database and presented

without regard for causal relationship, only 13% of patients experienced a grade 3 neurologic AE and 7% a grade 4 neurologic AE. Similar values apply to the proposed labeled indication populations. Nonetheless, a thorough review of the information within the clinical trial dataset has been undertaken in an effort to best characterize the risk benefit for prescribers. As a result, potential risk factors for the more severe neurologic events are reported. Definitive guidance for prescribers aimed at mitigating the risk for severe events is also proposed.

Overall, ARRANON demonstrates substantial efficacy in heavily pretreated and refractory patients with a well described toxicity profile, allowing for informed treatment decisions in this highly underserved orphan population.

7. CONCLUSIONS

The proposed indication for ARRANON is for the treatment of patients with T-cell acute lymphoblastic leukemia or T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

Patients with T-ALL/T-LBL who have received multiple prior induction regimens and whose disease has continued to relapse, or has proven refractory, have a poor prognosis, and no standard of care. New treatments are needed for these patients with multiply relapsed or refractory T-ALL/T-LBL.

ARRANON was developed as a T-cell selective agent that has demonstrated a clinically meaningful level of anti-neoplastic activity beginning with the first clinical trial in 1994.

Among the studies conducted are two pivotal multi-center trials, Study COG P9673 conducted by Children's Oncology Group (COG) and Study CALGB 19801 an inter-group trial coordinated by Cancer and Leukemia Group B (CALGB). Patients who had relapsed or were refractory to two or more prior induction regimens achieved CR plus CR* rates of 21% (95%CI: 8%, 41%) in adult, and 23% (95%CI: 11%, 39%) in pediatric patients following treatment with single agent ARRANON. The majority of responses to single agent ARRANON were CRs, with CR rates of 18% and 13% in these adult (95%CI: 6%, 37%) and pediatric (95%CI: 4%, 27%) patients, respectively. Responses (CR plus CR*) were considered durable in these patients with aggressive disease (adults: 4.0 to 195.4+ weeks, pediatric: 3.3 to 42.1 weeks), and generally long enough to allow for arrangement of a stem cell transplant procedure, a frequent goal in this treatment setting. Patients with multiply relapsed or refractory disease who were treated on these two trials had median survival of 20.6 weeks for adults and 13.1 weeks for children following ARRANON. One-year survival in the pivotal trials was 29% in adults and 14% in children with multiply relapsed or refractory disease. These efficacy results compare favorably to results reported for clofarabine and for single agent data of approved drugs currently used in multi-agent treatment regimens.

Of particular note, refractory patients whose most recent attempt at remission induction failed, showed impressive CR plus CR* rates to ARRANON therapy of 24% (95%CI: 7%, 50%) in adult and 27% (95%CI: 11%, 50%) in pediatric patients with two or more

prior inductions, and 56% (95%CI: 21%, 86%) in pediatric patients with one prior induction. The majority of these patients with refractory disease achieved a CR. The CR rate following single agent ARRANON therapy was 18% in both adult (95%CI: 4%, 43%) and pediatric (95%CI: 5%, 40%) patients with refractory disease after multiple prior induction attempts.

The risk to benefit ratio of ARRANON was acceptable at the proposed doses in these patients with multiple prior induction attempts. Hematologic toxicity was the most common grade 3 or 4 adverse event, similar to other nucleoside analogs. The dose limiting toxicity of ARRANON is nervous system toxicity. The recommended doses for adult and pediatric patients in the proposed indicated population have shown a relatively low incidence of grade 3 or 4 neurologic events. Patients who received ARRANON on these trials were monitored by physical examination for neurologic adverse events. Dosing of ARRANON was discontinued when neurologic events of grade 2 or greater did not resolve. The same guidelines for ARRANON dosing are suggested post-approval.

In addition to the 588 patients who received ARRANON on GSK (n=268) or NCI (n=320) sponsored clinical trials, more than 392 patients have received ARRANON through special exceptions protocols world-wide. The continued investigational requests for ARRANON through the special exceptions mechanism demonstrates the assessment among physicians who care for these patients that ARRANON provides clinical benefit.

ARRANON demonstrates clinical benefit and an acceptable risk to benefit ratio in this group of heavily pretreated patients with multiply relapsed or refractory T-ALL/T-LBL who have a poor prognosis and no proven treatment options.

8. REFERENCES

Berg SL, Blaney SM, Devidas M et al. Phase II Study of Nelarabine (compound 506U78) in Children and Young Adults with Refractory T-Cell Malignancies: A Report From the Children's Oncology Group. Journal of Clinical Oncology. 2005;23:3376-3382.

Bernstein ML, Abshire TC, Pollock BH et al. Idarubicin and cytosine arabinoside reinduction therapy for children with multiple recurrent or refractory acute lymphoblastic leukemia: a Pediatric Oncology Group study. J Ped Hematol/Oncol. 1997;19:68-72.

Borgmann A, von Stackelberg A, Hartmann R et al. Unrelated donor stem cell transplantation compared with chemotherapy for children with acute lymphoblastic leukaemia in a second remission: a matched-pair analysis. *Blood*. 2003;101:3835-3839.

Bortin MM, Horowitz MM, Rimm AA. Report from the International Bone Marrow Transplant Registry. *Bone Marrow Transplant*. 1989;4:221-228.

Cheson BD, Vena DA, Foss FM, Sorensen JM. Neurotoxicity of purine analogs: a review. *J Clin Onc*. 1994;12(10):2216-28.

Colburn DE, Thomas DA and Giles F. Phase II study of single agent paclitaxel in adult patients with relapsed acute lymphoblastic leukemia. *Invest New Drug*. 2003;21:109-111.

DeAngelo DJ, Yu D, Dodge RK, et al. A phase II study of 2-amino-9-beta-D-arabinosyl-6-methoxy-9H-purine (506U78) in patients with relapsed or refractory T-lineage acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL): CALGB study 19801. Blood. 2002; 100(11):198a (Abstr. 743).

Dopfer R, Henze G, Bender-Götze W et al. Allogeneic bone marrow transplantation for childhood acute lymphoblastic leukemia in second remission after intensive primary and relapse therapy according to the BFM- and CoALL-protocols: results of the German Cooperative Study. *Blood*. 1991;78:2780-2784.

Frankel SR, Stock W, Byrd J, Bloomfield CD. Acute lymphoblastic leukemia. In Haskell CM (ed): Cancer Treatment, Fifth Edition, W.B. Saunders Co., Philadelphia, PA 2001.

Gandhi V, Plunkett W, Rodriguez, Jr., CO, et al. Compound GW506U78 in refractory hematologic malignancies: relationship between cellular pharmacokinetics and clinical response. *J Clin Oncol* 1998;16:3607-3615.

Giles FJ, Garcia-Manero G, Cortes JE et al. Phase II study of troxacitabine, a novel dioxolane nucleoside analog, in patients with refractory leukemia. J Clin Oncol. 2002;20:656-664.

Giona F, Testi AM, Rondelli R et al. ALL R-87 protocol in the treatment of children with acute lymphoblastic leukaemia in early bone marrow relapse. *Brit J Haematol*. 1997;99:671-677.

Goekbuget N, Al-Ali H, Atta J, Brueck P, Boehme A, Freund M, Gerhardt A, Hermann S, Horst H, Kaufmann M, Kotthoff, R, Koch U, Krauter J, Pfeifer H, Schmid M, Hoelzer D. Improved Outcome of Poor Prognostic Relapsed/Refractory T-All and T-Lymphoblastic Lymphoma (LBL) with Compound GW506U78 Followed by Immediate Stem Cell Transplantation (SCT). The Hematology Journal. 2003;4:Supp 2: 266.

Harris RE, Sather HN and Feig SA. High-dose cytosine arabinoside and L-asparaginase in refractory acute lymphoblastic leukemia: the Children's Cancer Group experience. *Med Ped Oncol*. 1998;30:233-239.

Henze G, Fengler R, Hartmann R et al. Six-year experience with a comprehensive approach to the treatment of recurrent childhood acute lymphoblastic leukemia (ALL-REZ BFM 85). A relapse study of the BFM group. *Blood.* 1991;78:1166-1172.

Hoogstraten B. Cyclophosphamide (cytoxan) in acute leukemia. *Cancer Chemo Reports*. 1962;16:167-171.

Jones B, Holland JF, Morrison AR et al. Daunorubicin (NSC 82151) in the treatment of advanced childhood lymphoblastic leukemia. *Cancer Res*. 1971;31:84-91.

Kantarjian HM, Estey EH, Plunkett W et al. Phase I-II clinical and pharmacologic studies of high-dose cytosine arabinoside in refractory leukemia. *Am J Med*. 1986;81:387-394.

Karon M, Freireich EJ, Frei E et al. The role of vincristine in the treatment of childhood acute leukemia. *Clin Pharmco Ther*. 1966;7:332-339.

Lauer SJ, Ochs J, Pollock BH et al. Recombinant alpha-2B interferon treatment for childhood T-lymphoblastic disease in relapse. A Pediatric Oncology Group Phase II Study. *Cancer*. 1994;74:197-202.

Miser JS, Smithson WA, Krivit W et al. Phase II trial of indicine N-oxide in relapsed acute leukemia of childhood. *Am J Clin Oncol*. 1992;15:135-140.

National Cancer Institute, SEER cancer prevalence database using SEER's cancer query system. 2003; http://srab.cancer.gov/prevalence/canques.html.

Pappo A, Dubowy R, Ravindranath Y. Phase II trial of trimetrexate in the treatment of recurrent childhood acute lymphoblastic leukemia: A Pediatric Oncology Group Study. *J Natl Cancer Inst*. 1990;82:1641-1642.

Sallan S. Presentation to Oncology Drug Advisory Committee. December 1, 2004.

Tan CTC, Hancock C, Steinherz P et al. Phase I and clinical pharmacological study of 4-demethoxydaunorubicin (idarubicin) in children with advanced cancer. *Cancer Res*. 1987;47:2990-2995.

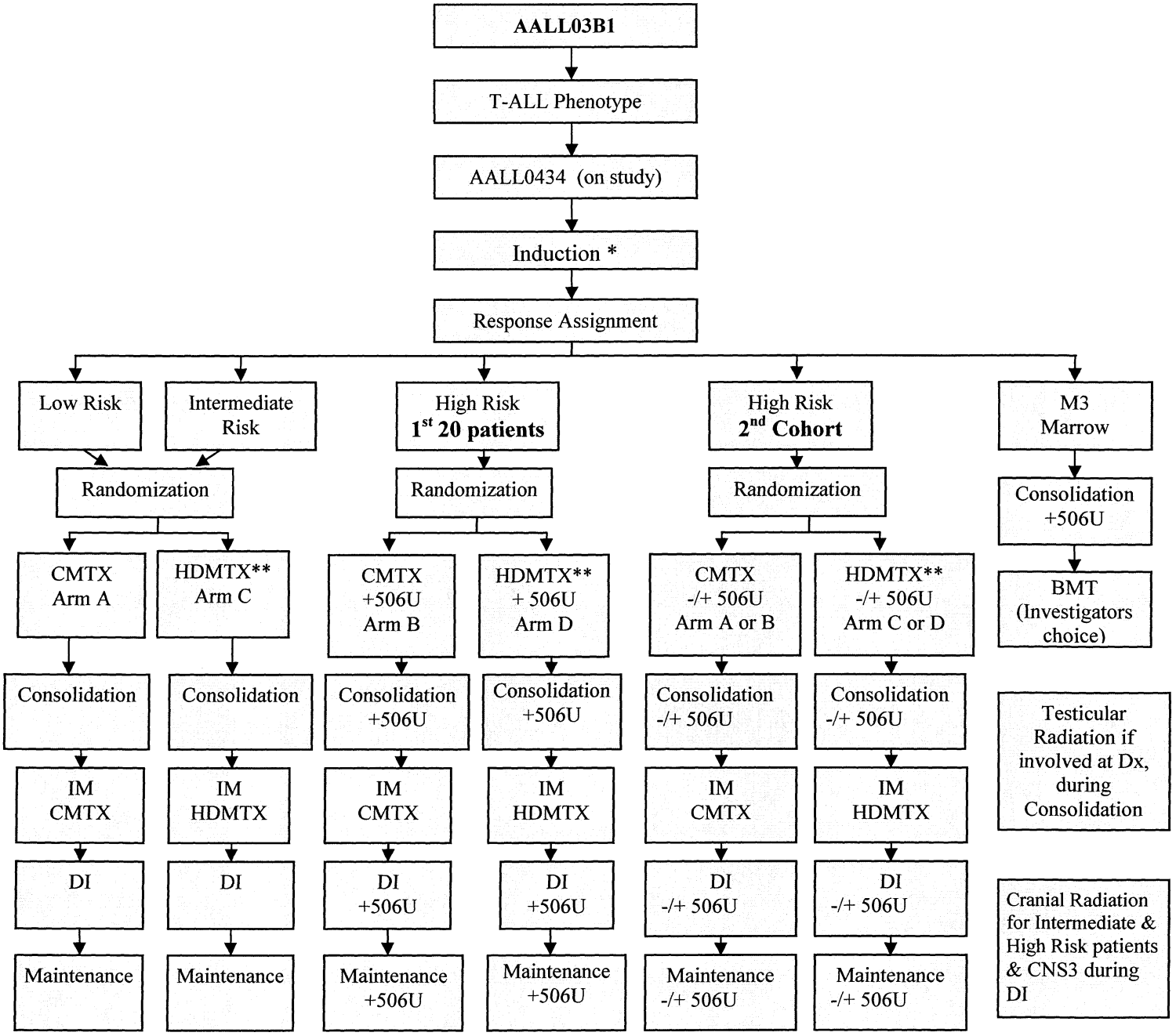
Thomas DA, Kantarjian H, Smith TL et al. Primary refractory and relapsed adult acute lymphoblastic leukemia: characteristics, treatment results, and prognosis with salvage therapy. *Cancer*. 1999;86:1216-1230.

Wheeler K, Richards S, Bailey C et al. Comparison of bone marrow transplant and chemotherapy for relapsed childhood acute lymphoblastic leukaemia: the MRC UKALL X experience. *Br J Haematol*. 1998;101:94-103.

ATTACHMENTS

Attachment 1: SCHEMA FOR DRAFT PROTOCOL AALL0434

EXPERIMENTAL DESIGN SCHEMA: SAFETY PHASE



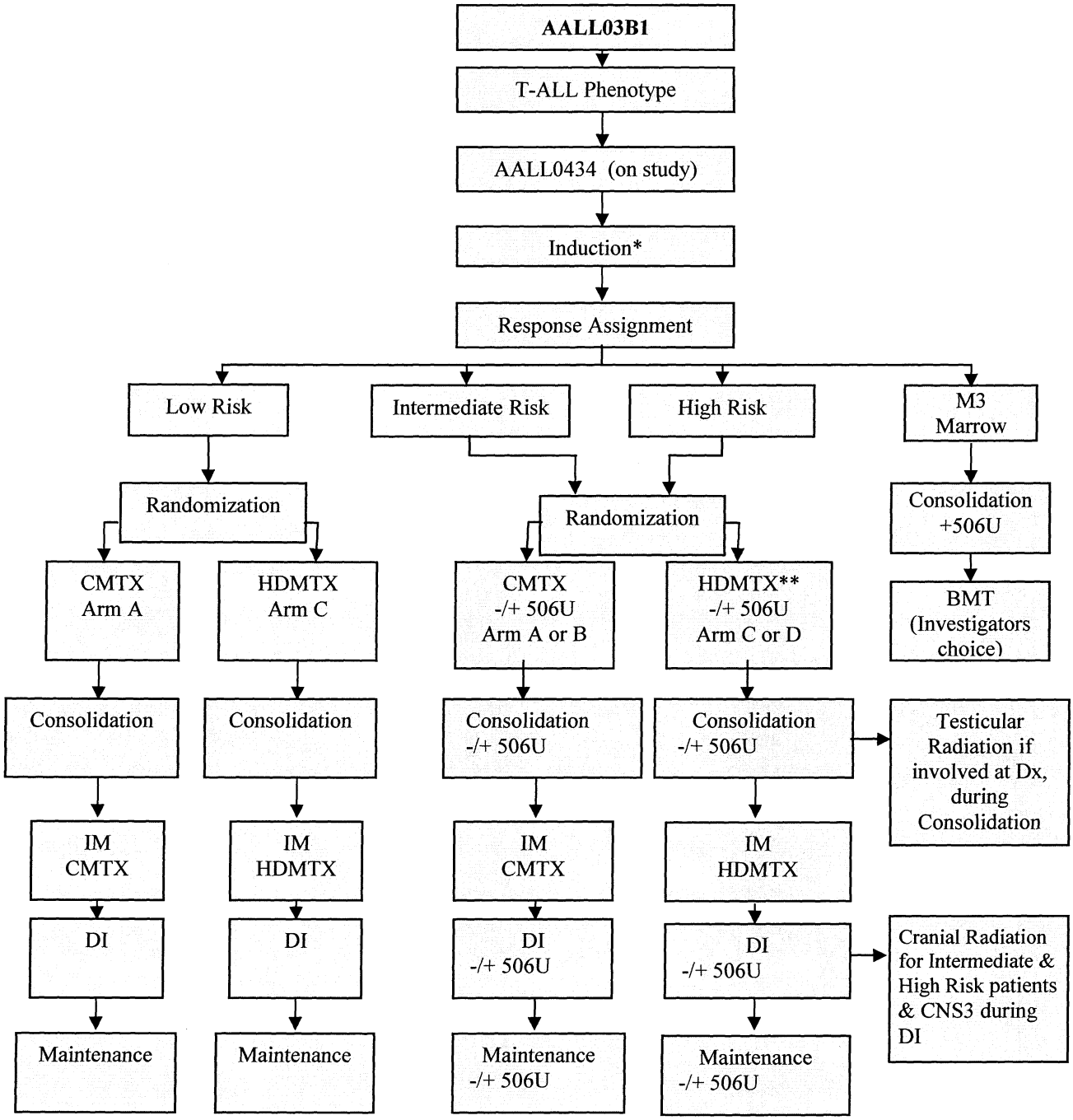
* Induction evaluation = Day 8 BMA; if not M1 then repeat on Day 15.
Evaluation of BMA and MRD on Day 29.
** Patients with CNS3 and/or testicular disease at Dx will be assigned to HDMTX arms
RER = M1 marrow on Day 8 and < 0.1% MRD on Day 29 OR
M2/M3 marrow on Day 8 and M1 marrow on Day 15 and
< 0.1% MRD on Day 29.
SER = M2/M3 on Day 15 OR positive MRD on Day 29.
Low Risk = RER, M1 on Day 15 and MRD < 0.1% on Day 29; and CNS 1 status.
Intermediate Risk = RER or SER with MRD < 1% on Day 29; any CNS status.
High Risk = M2 at end of Induction or MRD ≥ 1% on Day 29; any CNS status.

CMTX = Capizzi escalating MTX
HDMTX = High dose MTX
506U = Compound 506U78
IM = Interim Maintenance
DI = Delayed Intensification

Patients with Down Syndrome will not Receive HDMTX
Patients with a prior seizure disorder will Not receive 506U

The safety phase ends when the 1st 20 HR pts have been evaluated for 8 weeks past week 36 506U

EXPERIMENTAL DESIGN SCHEMA: EFFICACY PHASE



* Induction evaluation = Day 8 BMA; if not M1 then repeat on Day 15.
Evaluation of BMA and MRD on Day 29.
** Patients with CNS3 and/or testicular disease at Dx will be assigned to HDMTX arms
RER = M1 marrow on Day 8 and < 0.1% MRD on Day 29 OR
M2/M3 marrow on Day 8 and M1 marrow on Day 15 and
< 0.1% MRD on Day 29.
SER = M2/M3 on Day 15 OR positive MRD on Day 29.
Low Risk = RER, M1 on Day 15 and MRD < 0.1% on Day 29; and CNS 1 status.
Intermediate Risk = RER or SER with MRD < 1% on Day 29; any CNS status.
High Risk = M2 at end of Induction or MRD ≥ 1% on Day 29; any CNS status.

CMTX = Capizzi escalating MTX
HDMTX = High dose MTX
506U = Compound 506U78
IM = Interim Maintenance
DI = Delayed Intensification

Patients with Down Syndrome will not Receive HDMTX
Patients with a prior seizure disorder will Not receive 506U

Attachment 2: METHODS OF EXPLORATORY ANALYSIS OF NEUROLOGIC EVENT COVARIATES

The following methods were utilized for the Exploratory Analysis of Neurologic Event Covariates described in Section 5.6.2.

Neurologic AE terms in the Medical Dictionary for Regulatory Activities (MedDRA) were reviewed and categorized based on the following categories: peripheral nervous system (PNS), central nervous system (CNS), mental status change (MSC, typically somnolence or related) and uncategorized. All events were considered, regardless of attribution, across the seven studies in the safety database. Prescribed dosing, prior therapy, concomitant therapy, and baseline characteristic variables were examined as potential risk factors for the occurrence of any neurologic AE (any event) (grade ≥3), any event (any grade), CNS events (grade ≥3), CNS events (any grade), MSC events (grade ≥3), MSC events (any grade), PNS Events (grade ≥3), or PNS Events (any grade). Separate analyses were performed for each of the eight categories described above.

Correlations between prescribed dose scales and the occurrence of an event along with clinical reasoning were used to determine one prescribed dose scale for use in all analyses. All dose related parameters were then evaluated in a logistic regression model using the logit link and forward selection. In the initial models the prescribed dose parameter was forced into the model allowing other parameters to enter the model using forward selection with entry criteria of a 0.05 significance level. If the prescribed dosing parameter was not significant (after being forced into the model) the model was re-run, evaluating all parameters (including prescribed dose) for inclusion in the model using forward selection. The results from these models along with clinical judgment were used to determine final dosing parameter models for each of the eight neurologic endpoints under consideration.

The correlations between other potential risk factors and the occurrence of an event were examined. A significance level of 0.25 was used to identify potential risk factors to evaluate in logistic regression models. All parameters that were found to be non-significant were discarded and no longer considered in the analysis. Significant parameters with less than 10% missing data were added to a model with any dosing parameters identified as significant in previous models. If prescribed dose was previously identified as significant, it was forced into the model. All other dosing parameters found significant along with potential risk factors identified in correlation analyses with less than 10% missing data were considered for entry into a model using the forward selection procedure and entry criteria of alpha=0.10. The rationale was to allow other covariates, which may be highly correlated with the dosing parameters under consideration or may be better predictors of neurologic events, to enter the model instead of dosing parameters such as infusion duration or schedule. At each step, consideration was given to clinical and biologic rationale when selecting which covariate to retain in the model i.e., if two covariates were significant at a given step, adjustments could be made to override the forward selection procedure and ensure that the covariate entering the model was more meaningful from a biologic/clinical perspective..

Significant parameters identified in the correlation analyses with greater than 10% missing data that were of clinical interest were examined individually in a model with prescribed dosing parameters.

Additional analyses were provided as necessary.

The second analysis of neurologic AEs involved estimating the distribution of cumulative dose to event (mg/m^2 and mg). Consideration was given only to on-therapy AEs. Separate analyses were performed for each of the eight categories of interest (any event [grade ≥3], any event [any grade], CNS events [grade ≥3], CNS events [any grade], MSC events [grade ≥3], MSC events (any grade), PNS events [grade ≥3], and PNS events [any grade]). A censoring variable was employed to discriminate between patients who had an event and those who did not have an event. The cumulative dose for patients who did not experience an event was the total cumulative dose received on study. For those who had multiple events, only the first event was considered (e.g. first PNS event [any grade], first PNS event [grade ≥3], etc). Quartiles of cumulative dose and their confidence intervals are provided.

Cumulative doses were split into intervals chosen in an attempt to have an adequate number of events to estimate the hazard across a broad range of cumulative doses. The ranges of observed cumulative doses were split into groups in order to provide a hazard analysis. Estimates of the hazard and 95% confidence intervals for each group were provided. Groups were chosen in an attempt to have a balanced sample sizes across groups.