Published in final edited form as:

Semin Oncol. 2010 February ; 37(1): 53–59. doi:10.1053/j.seminoncol.2009.12.007.

The use of central laboratories and remote electronic data capture to risk-adjust therapy for pediatric acute lymphoblastic leukemia and neuroblastoma

Meenakshi Devidas, PhD^{1,2}, Wendy B. London, PhD^{1,3}, and James R. Anderson, PhD^{1,4}

¹ Children's Oncology Group Statistics and Data Center

² University of Florida, Department of Epidemiology and Health Policy Research, College of Medicine

³ Harvard University, Dana-Farber Cancer Institute and Children's Hospital Boston

⁴ University of Nebraska Medical Center, College of Public Health

Abstract

The Children's Oncology Group (COG) is a National Cancer Institute sponsored cooperative clinical trials group with the primary mission of conducting pediatric cancer clinical trials. COG has complex risk classification systems that are used to deliver risk-stratified therapy for many pediatric cancers, including clinical trials for Acute Lymphoblastic Leukemia (ALL) and Neuroblastoma (NB). Classification of patients is based on biological, clinical, and genomic data obtained at initial diagnosis and during the initial phases of therapy. The COG web-based remote data entry (RDE) system enables submission of data in real time from central laboratories and treating institutions. The data are then used in an automated fashion to determine the risk group and corresponding treatment assignment for individual patients enrolled in COG clinical trials.

Introduction

The Children's Oncology Group (COG) is a National Institutes of Health (NIH)/National Cancer Institute (NCI) sponsored cooperative clinical trials group. The COG conducts clinical trials and linked correlative biology research in pediatric cancer, with the goal of improving the standard of care for and ultimately curing children with cancer. The COG was formed in 2000 when the four NCI-funded children's cancer groups, the Children's Cancer Group (CCG), the Pediatric Oncology Group (POG), the National Wilms' Tumor Study Group, and the Intergroup Rhabdomyosarcoma Study Group merged into a single cooperative group. It is the largest cooperative pediatric cancer study group in the world. The merging groups were the

The COG is a consortium of over 200 hospitals and medical centers that pool their patient resources and scientific expertise to study the natural history and biology of childhood cancer, to develop effective therapeutic regimens, and to develop clinical trials of new therapeutic

---

Address correspondence to Meenakshi Devidas, PhD, Resrch Assoc Prof & Assoc Prgm Director, COG and Dept of Epidemiology & Health Policy Research, College of Medicine, University of Florida, 104 N. Main Street, Suite 600, Gainesville, FL 32601., Ph: (352) 273.0551, fax:(352) 392.8162, mdevidas@cog.ufl.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

agents in children with cancer. COG has over 4,000 member investigators including pediatric oncologists, pathologists, surgeons, radiation oncologists, radiologists, epidemiologists, neurologists, cytogeneticists, immunologists, pharmacologists, psychiatrists, psychologists, clinical research associates, data managers, and statisticians. Reference laboratories for immunophenotyping, cytogenetics, flow cytometry, molecular genetics, pharmacology, and pathology classify childhood malignancies, perform quality control, and submit data to the COG Statistics and Data Center (SDC). More than 6,000 patients are registered annually in the COG cancer registry. Most of these patients ultimately accrue onto COG therapeutic trials.

Systems for remote web-based data submission for clinical trials have been in use since 1998 – first in the Pediatric Oncology Group and after 2000 in COG. Individual members from COG treating institutions, enter their username and password to log in to the COG members' website. Members with the appropriate level of access may select a protocol number, patient (COG) identification number (specific to the given members' institution), and a category of data they wish to submit, before being presented with a screen or series of screens for data entry. COG members at the reference laboratories must also present valid usernames and passwords, though their access to view/enter data will be permitted for all COG patients on particular biologic or therapeutic trials, regardless of the patient's treating institution.

The COG reference laboratories receive biologic specimens from patients on particular biology or therapeutic trials as specified in the respective protocol document. Protocol-mandated specimens are collected primarily for two purposes: either to allow real-time assignment of patients to specific treatment approaches or to address specific correlative science aims embedded in the therapeutic research trial. Voluntary banking of specimens occurs largely through banking protocols, and these samples are then available for laboratory-based research, often incorporating information on the patients and their treatment outcome from the protocol research databases. In some diseases, like ALL and NB, specimen submission is a requirement because the specimen biologic and genetic results are needed in order to determine the appropriate intensity of subsequent therapy. When specimen submission is required, consent forms include the option for patients and/or their parent or guardian to consent to banking of leftover biological material for future research

Real-time laboratory data used for patient treatment assignment

Children's Oncology Group ALL and NBL treatment protocols integrate patient clinical features, laboratory results from the local institution, data regarding early response to treatment, and information generated by COG reference laboratories to assign patients to specific treatments or to allocate them to a specific risk stratum. In most cases, the reference laboratories receive patient specimens directly from the local institution and generate the laboratory information required for stratification and/or patient treatment assignment. The laboratory then enters the information directly into the RDE system in time for these data to be used in directing patient treatment. In this report, we detail the process used in these two disease areas for real-time risk stratification via the COG remote data entry system.

Current Risk Classification for Acute Lymphoblastic Leukemia

Although risk stratification was to some degree a part of treatment assignment in the legacy groups that merged to form the COG, this was not achieved in real time with the use of a web-based remote data entry system for ALL studies until 1999 when POG developed the P9900 classification trial. This classification trial for newly diagnosed ALL utilized a real-time risk classification system based on diagnostic data from the local institution including immunophenotype, initial white blood cell count (WBC), age at diagnosis, presence/absence of central nervous system (CNS) involvement, and central reference laboratories (cytogenetics

and molecular screening for prognostically important chromosome alterations). All patients were required to submit diagnostic samples (bone marrow and peripheral blood) to the reference laboratories for diagnostic testing and optional specimen for banking. Infants (≤ 1 year of age at diagnosis) and patients with T-cell ALL were assigned to separate protocols for infant ALL and T-ALL, at diagnosis. Patients with B-precursor ALL received a 29 day induction therapy on the classification study P9900. At the end of induction therapy, these B-precursor ALL patients were risk assigned to be eligible for post-induction therapy on one of three therapeutic trials for Low, Standard or High risk groups. Patients who were Philadelphia chromosome (Ph+) positive (BCR/ABL) were assigned to a separate study for very high risk ALL. The creation of COG in 2000 allowed for the analysis of clinical, biological, and early response data predictive of event-free survival (EFS) in acute lymphoblastic leukemia (ALL), and the development of a new classification system and treatment algorithm. Schultz et al [1] present the results of combined analyses of data from the Pediatric Oncology Group and Children's Cancer Group and the resultant biology-driven classification of ALL based on prognostic markers identified.

The current COG ALL classification study (AALL03B1) was activated on 12/29/2003. It has enrolled over 9000 patients with newly diagnosed ALL from more than 200 COG institutions. To date, it has proven to be a robust mechanism to accomplish risk stratification of all newly diagnosed children with ALL (infant, B-lineage, T-lineage) who are subsequently enrolled on frontline COG ALL clinical trials, based on age, WBC, and blast genetics at diagnosis, and response to induction therapy. AALL03B1 requires that bone marrow and/or peripheral blood samples at diagnosis, at protocol day 8/15, and at the end of induction (protocol day 29), be submitted to specific flow cytometry and molecular reference laboratories. Due to the large number of participating treating institutions, and hence volume of patients with ALL, two flow cytometry and two molecular reference laboratories are used, one each to service the treating institutions within COG from the Western United States and Canada (and centers in Australia and New Zealand) and Eastern United States and Canada (and centers in Western Europe). These samples are sent to the reference laboratories with the patient's COG identification number, COG study number, study accession number and the date sample was drawn. Patients with newly diagnosed ALL are first classified into strata (B-precursor NCI standard risk or high risk – based on age and WBC, infant, or T-ALL) based upon immunophenotype, age at diagnosis, and WBC at diagnosis. Initial induction therapy is then initiated on an appropriate therapeutic protocol. The reference/institutional laboratories process the samples from diagnosis to confirm immunophenotype, determine DNA index, the presence of favorable cytogenetics (Trisomies of chromosomes 4, 10 and 17; or ETV6-RUNX1 fusion), unfavorable cytogenetics/translocations (MLL translocation, t(9;22) and/or BCR-ABL) and/or host polymorphisms. End induction marrow samples are analyzed to detect the presence of minimal residual disease (MRD). These data are entered directly into the RDE system by the laboratories and can be viewed by the patient's treating institution. Some of the fluorescence in-situ hybridization (FISH) testing previously performed in central COG reference laboratories are now done at COG approved institutional cytogenetic laboratories. COG moved towards using institutional data for some tests previously performed centrally, with some duplication for quality control purposes. As of 2007, all FISH testing available at commercial cytogenetics laboratories are now done at approved institutional cytogenetics). By protocol day 35 (prior to starting post-induction therapy), data from the institution and the reference laboratories are all submitted into the RDE system. Appropriate study personnel are informed via automatic emails of the submission of each piece of data used in risk stratification. Once all data are available the end of induction, a short summary of all diagnostic, clinical response and biology data together with the calculated preliminary risk assignment for the patient are automatically made available to the study chairs of the COG ALL classification protocol (AALL03B1) using a pre-defined algorithm (Tables 1A and 1B). The study chairs approve (or modify) these risk assignments and enter them into the RDE system by protocol day 35. Submission of these data

generates an automatic email notification to the treating institution, giving the risk assignment and corresponding stratum/treatment assignment recommending appropriate post-induction therapy for the patient. The institution uses this to inform patients/parents about the proposed post-induction therapy for the patient, obtains informed consent as needed and commences recommended therapy. In studies involving a randomization to therapy at the end of induction for certain risk groups (e.g. protocols for NCI standard risk B-precursor ALL and for T-cell ALL), when the treating institution personnel submit the late-randomization form, the risk assignment for the patient is pulled into the form at the back end and validation rules are run to ensure that the stratum assignment and corresponding treatment randomization are appropriate for the risk group assigned. This ensures that the institution does not make an error and choose the incorrect stratum and hence has the patient randomized or assigned to the incorrect post-induction therapy. Using the RDE system 97% of patients on the ALL biology protocol have been successfully risk assigned in a timely manner for start of appropriate post-induction therapy on COG therapeutic trials.

Future Plans for Risk Stratification in Acute Lymphoblastic Leukemia

AALL08B1 is the successor classification protocol to AALL03B1. AALL08B1 seeks to improve and simplify risk stratification using the framework of AALL03B1 with the incorporation of mature outcome data from P9900. Enrollment on AALL08B1 is required for enrollment on all frontline COG treatment trials for newly diagnosed ALL. All participants will have a uniform set of clinical and biologic variables determined both at their local institution and COG Reference Laboratories, for risk-group and treatment assignment. Diagnostic data, cytogenetic and response data will be used to determine the risk group for each patient in the RDE system. Each patient with newly diagnosed B-precursor ALL will be assigned to one of the following risk groups – Low, Average, High, and Very High. Each corresponds to a specific treatment strategy (either randomized or assigned). The objective is to have the risk group computed automatically by the RDE system with an email notification going out to the treating institution with the risk classification and subsequent treatment protocol assignment for the patient.

Data captured on AALL08B1 will be used in the therapeutic trials, in cross era analysis, and in international collaborations to further define the prognostic importance of biologic features in ALL. The biologic variables assessed in this study will be correlated with outcome within the context of uniform treatment strategies. Data from this study will also be used to characterize samples used for cell bank and other biology studies.

Risk Classification for Neuroblastoma

For NB, patients are required to be enrolled on biology study ANBL00B1 prior to enrollment on a COG therapeutic NB study. According to the criteria in ANBL00B1, patients are categorized as either low, intermediate, or high-risk (Table 2). The outcome for these groups is disparate, with 3-year event-free survival (EFS) ranging from about 95% for low-risk [2] and 88% for intermediate-risk [3] to approximately 40% for high-risk [4]. Treatment is much more intense for the high-risk patients, including 5–6 courses of high-dose induction, radiation therapy, surgery, one or more autologous stem cell transplants, and maintenance biologic therapy or chemotherapy, compared to low and intermediate-risk patients who receive surgery alone, or as few as two cycles of induction chemotherapy and surgery, respectively. Therefore, it is very important to discriminate as accurately as possible between the low- or intermediate-risk patients versus the high-risk patients.

The COG NB treatment trials use the following factors to assign patients to low, intermediate, or high-risk therapy: age at diagnosis, INSS stage, *MYCN* status, ploidy, and INPC histology. When a new patient is being considered for treatment on a COG NB treatment study, the

institution provides information on the patient's age and INSS stage at the same time as the various required specimens are submitted for processing at the reference laboratories. The Neuroblastoma Reference Laboratory at the COG Biopathology Center in Columbus, OH performs assessments of *MYCN* status, and ploidy, 11q (LOH), and 1p LOH and enters those data directly into the RDE system. INPC histology is assessed at a separate central laboratory and data are entered into the RDE system. Treatment level is determined in a two-step process:

1. An automated computer algorithm (based on the risk assignment table in the ANBL00B1 biology protocol) determines the assignment of risk (low, intermediate, or high) based on RDE data on age at diagnosis, INSS stage, *MYCN* status, ploidy, and INPC histology. An automated report is generated and sent by e-mail message to the Neuroblastoma Tracking Center at the University of Chicago. There, the correct risk group assignment is checked and confirmation of the risk group assignment is entered into the RDE system. The entry of confirmation triggers an automated e-mail message to be sent with the patient's risk group assignment to the treating institution. All institutions have "view access" to all of the RDE laboratory results for the patients at their respective institution as soon as the laboratories have entered the data. This real-time exchange of laboratory results via the system permits assignment of the patient to a risk group (allowing entry onto the appropriate treatment protocol), usually within 14 days of diagnosis. The protocols are designed so that this information is assumed to be available within at most 28 days of diagnosis.
2. For intermediate-risk patients, the COG is currently testing the use of 11q loss of heterozygosity (LOH) and 1p LOH to determine the number of initial cycles of therapy to be administered. All intermediate-risk patients receive at least two cycles of therapy. The 11q and 1p assessments are more complex and require more time to perform, and the COG Biopathology Center enters the results into the RDE within 6 weeks of receipt of the specimens, well before the 8-week time point at which intermediate-risk patients have completed the first two cycles of therapy. Analogous to the first step of risk-group assignment, the number of cycles for intermediate-risk patients is determined using an automated computer algorithm based on the five risk factors in step 1 above, plus 11q LOH, 1p LOH, degree of initial surgical resection of the tumor, and whether the patient has any overt adverse symptoms. An automated report is generated and sent by e-mail message to the Neuroblastoma Tracking Center, the number of cycles is confirmed by a clinician-expert, and confirmation is entered into the RDE system. This triggers an automated e-mail message to be sent to the treating institution with information on the number of initial treatment cycles to be administered to the patient.

ANBL00B1 and the associated RDE risk assignment and communication system were activated in 1998. Initially, annual enrollment to ANBL00B1 averaged less than 500 per year, with annual incidence of NB estimated at about 600. Current enrollment on ANBL00B1 exceeds 600 patients per year, and incidence estimates are being revised. Over 95% of the NB patients who enroll on ANBL00B1 have sufficient known data to be successfully assigned to a risk group. Because ANBL00B1 is such a critical element of the treatment assignment and NB research process of the COG, there is currently no enrollment goal, with plans to keep the study open indefinitely, and intermittent amendments as needed to modify the risk stratification as new and improved prognostic factors are identified.

Extensive testing was performed on the automated risk assignment algorithm. Through repeated iterations of the algorithm, a comprehensive list of all possible combinations of the values of the risk factors and the resulting risk group assignment was generated, over 40,000 rows. This list was divided amongst several experts, who reviewed each row on the list to ensure that it produced the desired result according to the risk assignment table in the

ANBL00B1 protocol. This exercise also forced the clinicians to decide in advance how a patient should be assigned/treated if one or more of the risk factors were unable to be determined.

Discussion

Efficient and user-friendly systems have been developed by the COG for automated risk group assignment, including collection of risk factor data, automated implementation of an algorithm to assign the risk group and generate e-mail communications, manual verification of the correct risk/treatment group assignment, and automated communication of the final risk assignment to the treating institution. Over 97% of patients on the ALL biology protocol, and over 95% of patients on the NB biology protocol, have been successfully risk assigned in a timely manner for start of appropriate therapy on COG therapeutic trials.

Admittedly, this process did not work perfectly from its inception. For instance, in the NB system, there was resistance from the laboratories to entering the results into the RDE system, as the RDE data entry was viewed as extra work because they still had to enter the data into their own local systems. Some laboratories expressed concern for accurate identification of the patient because the RDE system did not include patient names (in compliance with COG data standards), and this was resolved by including multiple unique identifiers on the specimen shipping form and within the RDE system.

From an informatics standpoint, the development of access permissions was complex, requiring new layers of security and creation of new “roles” for the laboratory personnel to have write/edit access to the database. For the treating institutions standpoint, strict timeframes were imposed for specimen submission and entry of the clinical risk factors into the RDE. Deadlines were imposed for the laboratories to enter the results, and for the Tracking Center to enter confirmation of the risk group. The sequence of events had to be timed perfectly in order for the process to finish in time for the patient to enroll on the appropriate therapeutic study within the eligibility time window.

Initially, sometimes the treating institutions, the laboratory, and/or the Tracking Center were not able to make one or more of the deadlines, resulting in a slightly higher rate of ineligible patients. However, the learning curve improved, and currently a higher proportion of patients are eligible and enrolled on the biology risk assignment trial and therapeutic trials than before the automated risk assignment systems were implemented. The increased enrollment on ANBL00B1 might be attributed to the physician’s and patient’s desire to participate in cutting-edge NB therapies offered by COG NB trials, but may also be due to the ease and speed with which the RDE systems permit determination of the patient’s risk group. An enormous side benefit of the risk classification systems is the high level of completeness of the key prognostic factors data in the COG database. These data have played and will continue to play a pivotal role in the basic science and clinical research of ALL and NB, both within COG and in international data-sharing situations.

It is noteworthy that the specimen and data submission requirements of the COG ALL and NB trials are not purely for unspecified research purposes, but primarily to ensure that the patient is assigned to the correct research protocol, thus assuring appropriate clinical care in the context of the available treatment protocols. The RDE systems provide a faster, more straightforward way for the treating institution to determine appropriate treatment, and minimize the chance of error as opposed to doing the risk assignment manually via the table in the protocol. The COG RDE system permits rapid use of centralized systems, expertise in assessments by reference laboratories, and accuracy and reproducibility of risk/treatment group assignment.

The Children’s Oncology Group has been very successful in implementing and improving upon a system which uses clinical and biological data from treating institutions, central

laboratories and remote electronic data capture to risk-adjust therapy for pediatric patients with acute lymphoblastic leukemia and neuroblastoma. Following the example of these disease areas, plans are underway to implement similar systems in COG for some of the other pediatric cancers.

References

1. Schultz KR, Pullen J, Sather H, Shuster J, Devidas M, Borowitz M, Carroll AJ, Heerema NA, Loh M, Raetz E, Winick N, Hunger SP, Carroll WL, Gaynon P, Camitta BM. Biology-Driven Classification Of Childhood Acute Lymphoblastic Leukemia: A Combined Analysis Of Prognostic Markers From The Pediatric Oncology Group (POG) And Children's Cancer Group (CCG). *Blood* 2007;109(3):926–35. [PubMed: 17003380]
2. Strother, D.; London, WB.; Yap, J.; Schmidt, ML.; Shimada, HH.; Tagge, E.; Murray, K.; Rosen, N.; Matthay, KK.; Castleberry, RP.; Cohn, SL. Surgery and restricted use of chemotherapy as treatment of low-risk neuroblastoma: Preliminary results of Children's Oncology Group protocol 9641. Proceedings of the 38th Congress of the International Society of Paediatric Oncology;
3. Baker, DL.; Schmidt, M.; Cohn, S.; London, WB.; Buxton, A.; Sandler, A.; Shimada, H.; Matthay, K. A phase III trial of biologically-based therapy reduction for intermediate risk neuroblastoma. American Society of Clinical Oncology Annual Meeting Proceedings. Part I; 2007. abstract #9504
4. Kreissman, SG.; Villablanca, JG.; Diller, L.; London, WB.; Maris, JM.; Park, JR.; Reynolds, CP.; von Allmen, D.; Cohn, SL.; Matthay, KK. Response and toxicity to a dose-intensive multi-agent chemotherapy induction regimen for high risk neuroblastoma (HR-NB): A Children's Oncology Group (A3973) Study. American Society of Clinical Oncology Annual Meeting Proceedings. Part I; 2007. abstract #9505

Table 1

Table 1A. Day 29 Risk Assignment for B-Precursor ALL patients	
Standard Risk-Low: Randomized Treatment Assignment	
Features Present	• Age 1–9.99 years, and • WBC < 50,000/μl, and • Triple Trisomies (4,10,17) or <i>TEL AML1</i>, and • Day 8 or 15 marrow M1, Day 29 marrow M1 and • Day 29 MRD < 0.1% • No CNS2, CNS3 or other extramedullary disease
Standard Risk Average: Randomized Treatment Assignment	
Features Present	• Age 1–9.99 years, and • WBC < 50,000/μl, and • Day 8 or 15 marrow M1, Day 29 marrow M1 and • Day 29 MRD < 0.1% • Triple Trisomies (4,10,17) or <i>TEL AML1</i> with CNS2 status • No overt testicular disease
Standard Risk-High: Non-Random Assignment to Augmented Therapy	
Features Present	• Age 1–9.99 years and • WBC < 50, 000/μl, and • CNS 3 OR • Day 15 marrow M2/M3, or Day 29 MRD $\geq$ 0.1% and < 1% or • Any <i>MLL</i> translocation with a RER or • Steroid pretreatment as defined in 4.6.3.6 OR • Day 29 M2 marrow and/or Day 29 MRD $\geq$ 1% with both M1 marrow on Day 43 and Day 43 MRD < 1% • No overt testicular disease
High Risk: Randomized Treatment Assignment	
Features Present	• Age 10.00 – 30.99 years, and/or • WBC $\geq$ 50,000/μl, and • Day 8 or 15 marrow M1, Day 29 marrow M1 and • Day 29 MRD < 0.1%
High Risk: Assignment to Augmented Therapy	
Features Present	• Age 10.00 – 30.99 years, and/or

Table 1A. Day 29 Risk Assignment for B-Precursor ALL patients

	- WBC $\geq 50,000/\mu\text{l}$, and - CNS 3 or testicular disease (including NCI SR patients) *, OR - Day 15 marrow M2/M3, or Day 29 MRD $\geq 0.1\%$ and $< 1\%$ **, OR - Any <i>MLL</i> translocation with a RER **, OR - Steroid pretreatment as defined in 4.6.3.6 *, OR - Day 29 M2 marrow and/or Day 29 MRD $\geq 1\%$ with both M1 marrow on Day 43 and Day 43 MRD $< 1\%$ *Non random assignment. **Assignment to augmented therapy with randomization to steroid and methotrexate schedule
Very High Risk	
Features Present	- Cytogenetic, FISH or molecular evidence of a t(9;22) and/or <i>BCR/ABL</i> fusion (T ALL patients with this feature are also eligible) (eligible for AALL0622 provided all eligibility criteria are met) or - DNA index < 0.81 or < 44 chromosomes or other clear evidence of a hypodiploid clone, OR - Cytogenetic, FISH or molecular evidence of an <i>MLL</i> translocation with a SER - Induction failure defined as M3 bone marrow aspirate on Day 29, regardless of cellularity, or - M2 marrow Day 29 and/or Day 29 MRD burden $\geq 1\%$, with M2/3 marrow Day 43 and/or Day 43 MRD burden $\geq 1\%$

Table 1B. Day 29 Risk Assignment for T-ALL

T-ALL-Low Risk: Treatment Assignment	
Features Present	- Age 1–9.99 years, and - WBC $< 50,000/\mu\text{l}$, and - Day 8 or 15 marrow M1, Day 29 marrow M1 and - Day 29 MRD $< 0.1\%$ - No CNS2, CNS3 or other extramedullary disease - No identified <i>BCR/ABL</i> fusion
T-ALL-Intermediate Risk: Randomized Treatment Assignment	
Features Present	- Any Age - Any WBC - Day 8 or 15 marrow M1, M2, or M3, Day 29 marrow M1 and - Day 29 MRD $< 1\%$ - CNS 1, 2, or 3 - No identified <i>BCR/ABL</i> fusion
T-ALL-High Risk: Randomized Treatment Assignment	

Table 1B. Day 29 Risk Assignment for T-ALL

Features Present	• Any Age • Any WBC • Day 15 marrow M1, M2, or M3, and Day 29 marrow M2 or • Day 29 MRD $\geq 1\%$ • Steroid pretreatment as defined in 4.8.2.4 • No identified <i>BCR/ABL</i> fusion
T-ALL-Induction Failure: Non-Random Assignment to Augmented Therapy	
Features Present	• Any Age • Any WBC • Day 15 marrow M1, M2, or M3, and Day 29 marrow M3 • Steroid pretreatment as defined in 4.8.2.4 • No identified <i>BCR/ABL</i> fusion

Table 2

The ANBL00B1 stratification for NB risk group assignment (1998–2006*)

INSS Stage	Age (days)	MYCN status	Ploidy	Shimada histology	Other factors	Risk Group
1	any	any	any	any		Low
2A/2B	any	not amp	any	any	resection ≥50%	Low
2A/2B	any	not amp	any	any	resection <50%	Intermediate
2A/2B	any	not amp	any	any	biopsy only	Intermediate
2A/2B	any	amp	any	any	any degree of resection	High
3	<547d	not amp	any	any		Intermediate
3	≥547d	not amp	any	Fav		Intermediate
3	any	amp	any	any		High
3	≥547d	not amp	any	Unfav		High
4	<365d	amp	any	any		High
4	<365d	not amp	any	any		Intermediate
4	365–<547d	amp	any	any		High
4	365–<547d	any	DI=1	any		High
4	365–<547d	any	any	Unfav		High
4	365–<547d	not amp	DI>1	Fav		Intermediate
4	≥547d	any	any	any		High
4S	<365d	not amp	DI>1	Fav	asymptomatic	Low
4S	<365d	not amp	DI=1	any	asyp or symp	Intermediate
4S	<365d	missing	missing	missing	too sick for biopsy	Intermediate
4S	<365d	not amp	any	any	symptomatic	Intermediate
4S	<365d	not amp	any	Unfav	asyp or symp	Intermediate
4S	<365d	amp	any	any	asyp or symp	High

* The previous risk stratification is presented because validation of the current risk stratification is ongoing.