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Children's Oncology Group's 2023 blueprint for research: myeloid neoplasms

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Abstract

During the past decade, the outcomes of pediatric patients with acute myeloid leukemia (AML) have plateaued with 5-year event-free survival (EFS) and overall survival (OS) of approximately 46% and 64%, respectively. Outcomes are particularly poor for those children with high-risk disease, who have 5-year OS of 46%. Substantial survival improvements have been observed for a subset of patients treated with targeted therapies. Specifically, children with *KMT2A*-rearranged AML and/or *FLT3* internal tandem duplication (*FLT3*-ITD) mutations benefitted from the addition

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AUTHOR CONTRIBUTIONS

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of gemtuzumab ozogamicin (GO), an anti-CD33 antibody-drug conjugate, in the AAML0531 clinical trial (NCT00372593). Sorafenib also improved response and survival in children with *FLT3*-ITD AML in the AAML1031 clinical trial (NCT01371981). Advances in characterization of prognostic cytomolecular events have helped to identify patients at highest risk of relapse and facilitated allocation to consolidative hematopoietic stem cell transplant (HSCT) in first remission. Some patients clearly have improved survival with HSCT, although the benefit is largely unknown for most patients. Finally, data-driven refinements in supportive care recommendations continue to evolve with meaningful and measurable reductions in toxicity and improvements in EFS and OS. As advances in application of targeted therapies, risk stratification, and improved supportive care measures are incorporated into current trials and become standard-of-care, there is every expectation that we will see improved survival with a reduction in toxic morbidity and mortality. The research agenda of the COG Myeloid Diseases Committee continues to build upon experience and outcomes with an overarching goal of curing more children with AML.

INTRODUCTION

State of Disease: Clinical

Myeloid malignancies account for approximately 20% of all childhood leukemias and include four general categories defined by molecular pathology and treatment: (1) acute promyelocytic leukemia (APL), (2) myeloid leukemia of Down Syndrome (ML-DS), (3) chronic myeloid leukemia (CML) and (4) AML.[1] The risk- and therapy-defining molecular events described over the past 10 years in childhood AML are different from adults with the same diagnosis.[2] Historically, therapy for childhood AML was adapted from data generated from the older adult AML experience. Recent comprehensive genomic characterization of AML across the lifespan demonstrates that AML in older adults and that in infants and young children less than 3 years are unique and genomically defined entities with distinct pathology. AML in older children, adolescents and young adults share more similarities than differences that are driven by genomic alterations that transcend age alone and impart distinct genomically driven phenotype, pathology, and outcome.

Current Outcomes in Pediatric AML—Clinical outcomes of children, adolescents, and young adults with AML have changed in the past 20 years with a 5-year overall survival (OS) of approximately 60% (Figure 1).[1,3,4] Conventional chemotherapy regimens, reliant on high doses of cytarabine and anthracyclines, have changed little during this period. Progress has focused on the dose and schedule intensification of conventional therapy, improved identification of patients with higher risk of relapse, advances in HSCT, and enhanced supportive care. Major recent advances in elucidation of predictive biomarkers of treatment response and survival have led to further therapy refinements.[5,6]

Patients with nucleophosmin 1 (*NPM1*) mutations,[7,8] CCAAT enhancer-binding protein alpha *(CEBPA)* biallelic mutations,[9] and core-binding factor (CBF) leukemias (*RUNX1::RUNXT1* or *CBFB::MYH11* rearrangements) have more favorable outcomes.[1,5,6,10] This is in stark contrast to outcomes for children with high-risk (HR) cytomolecular alterations who continue to have unacceptably poor survival despite maximally intensive initial and relapse therapy.[3,4] The refractory nature of AML combined

with challenges to conduct relapsed trials have limited or ability to identify new active agents for children. Outcomes in pediatric AML and related myeloid disorders will improve only if we develop treatment approaches that are informed by disease biology and incorporate novel agents relevant to the unique AML biology observed in infants, children and young adults.

State of Disease: Biological

Molecular targets—AML is most commonly the result of cumulative chromosomal or genomic events that combine to impair differentiation and increase proliferation and/or cell survival. Animal modeling support the two-hit hypothesis where 2 or more cooperating mutations are required for myeloid pathogenesis[2,11-19]. Class I mutations lead to an activation of signal transduction and proliferation. RAS pathway genes (*NRAS, KRAS, PTPN11*, and *NF1*) and receptor tyrosine kinases (*FLT3* and *KIT*) are among the most common Class I mutations seen in childhood AML. Class II mutations may include small insertions or deletions in transcriptional regulators like *CEBPA* and *RUNX1* or result from large chromosomal translocations that lead to a new fusion oncogene that impairs hematopoietic differentiation.[14-19] The most common rearrangements in childhood AML are the core-binding factor translocations [t(8;21)(q22;q22)] and inv(16) that result in *RUNX1::RUNX1T1* and *CBFB::MYH11* fusion oncogenes, respectively. The *KMT2A* gene at 11q23 can rearrange to create novel fusion proteins with a number of partner genes. More recent data demonstrates that specific fusions in infant AML delivered in a context appropriate manner may indeed be sufficient for malignant transformation, where transduction of *CBFA2T3::GLIS2* or *NUP98::KDM5A* fusion transcript into normal cord blood stem cells generated leukemia phenotypically similar to *de novo* disease.[20]

Recent advancements in next generation sequencing (NGS) have improved our understanding of the genomic landscape of AML. Several recent publications have identified cryptic or previously undetected translocations using NGS approaches. These include, for example, *CBFA2T3*::*GLIS2, NUP98* family fusions, and *MLLT10* rearrangements, all of which predict poor outcomes with conventional therapy.[2,21-25] The COG Myeloid Disease Committee has contributed to major publications (Table 1) and has described AML-defining cytogenetic, molecular, and immunophenotypic changes (Table 2) that predict survival and offer unique vulnerabilities for therapeutic targeting (Table 3).

Recent Findings

Clinical Achievements

De novo AML: Starting with AAML03P1 (NCT00070174) and AAML0531, COG trials adopted the Medical Research Council (MRC) chemotherapy backbone, which continues to be the foundation for trial objectives that utilize both randomized comparisons as well as comparisons informed by historical datasets.[4,26] In a randomized comparison, COG AAML0531 demonstrated that the addition of the anti-CD33 antibody-drug conjugate GO to the MRC backbone significantly improved EFS, relapse rate (RR), and disease-free survival (DFS) in children with high CD33 expression, *FLT3*-ITD mutations, and those with *KMT2A* rearrangements.[27-30] The successor AAML1031 randomized phase 3 trial (NCT01371981) investigated whether the addition of bortezomib to the MRC backbone could improve

survival[3]. While bortezomib did not improve outcomes, AAML1031 results led to many other important findings that are summarized in Table 1.

Acute Promyelocytic Leukemia: Acute promyelocytic leukemia (APL) accounts for 10-20% of cases of childhood acute myeloid leukemia and is characterized by the recurrent t(15;17) resulting in a *PML::RARA* oncoprotein. Historically, APL had poor cure rates with high rates of relapse and early death from complications of the disease and treatment. Presenting white blood cell (WBC>10,000 cells/uL) count has consistently proven to be a risk marker for survival with APL. Outcomes improved with treatment including all-trans retinoic acid (ATRA)[31] and arsenic trioxide (ATO). The COG AAML0631 (NCT00866918) trial incorporated an ATO consolidation cycle while decreasing total anthracycline dose and demonstrated very high cure rates for both patients with standard risk (SR) APL and those with HR APL.[32] The 3 year event free survival was 95% for SR APL and 83% for HR APL. Relapse rate was low at 4% and similar between the two risk groups, but survival was lower in the HR APL group due to increased number of early death events, predominately from coagulopathy.

The most recent COG AAML1331 phase 3 clinical trial (NCT02339740) for children with newly-diagnosed APL used an ATRA and ATO based treatment regimen with a non-inferiority comparison to AAML0631. All patients received daily dosing of ATRA and ATO in induction until achievement of hematologic remission and then intermittent ATRA and ATO treatments during 4 consolidation cycles. There was no maintenance therapy. Patients with HR APL received 4 doses of idarubicin during induction only. Cytotoxic chemotherapy was thus able to be eliminated for patients with SR APL and was significantly reduced for those with HR APL. Patients with SR APL had 2-year EFS and OS rates of 98% and 99% with one death during induction and one relapse. Patients with HR APL had a 2-year EFS and OS rates of 96% and 100% with no deaths and two relapses.[33] Eliminating maintenance therapy also shortened treatment duration to approximately 9 months. Detailed and intensive supportive care to manage coagulopathy and differentiation syndrome resulted in low rates of early death.

Myeloid Leukemia of Down Syndrome (ML-DS): ML-DS evolves from a subclone of the preleukemic neonatal disorder transient abnormal myelopoiesis (TAM) as a result of co-operation between somatic mutations of *GATA1* and mutations in genes encoding cohesin complex components, epigenetic modifiers and signal transducers including RAS pathway genes.[34,35] Persistence of TAM blasts for longer than 3 months after diagnosis (detectable by flow cytometry or PCR) was found to correlate with a three-fold increased risk of progression to ML-DS.[36,37]

There has been significant progress in the treatment and survival of children with ML-DS. Reduction of treatment intensity, from A2971 (NCT00003593)[38] and AAAML0431 (NCT00369317),[39] reduced the cumulative anthracycline dose from 320 to 240 mg/m^2. Despite this reduction of treatment intensity, 5-year EFS was 89.9% and OS 93%. Flow cytometric measurable residual disease (MRD) correlated with outcome and 5-year DFS was 92.7% for MRD-negative patients. Treatment-related mortality (TRM) remained <1% while the majority of ≥ grade3 febrile neutropenic episodes (30%) and microbiologically

confirmed infections at sterile sites (23% of patients) were associated with the high dose cytarabine/asparaginase course.

AAML1531 (NCT02521493) introduced a MRD-based risk stratification of treatment intensity for ML-DS based on flow cytometric MRD after the first course of induction therapy.[40] The 85% of patients with negative MRD received 1 less high dose cytarabine/asparaginase course compared to AAML0431. Interim analysis, however, revealed that 2-year EFS among MRD-negative (standard risk) patients (85.6%) was inferior to the predecessor study AAML0431 (93.5%)[39] due to an increased relapse rate and prompted the closure of the standard risk arm. Standard risk patients who relapsed were more likely to have a complex karyotype and had a low probability of survival (1-year OS 16.7%). Data evaluating the intensification of treatment for patients with positive MRD are not yet available.

Three successive trials (A2971[38], AAML0431,[39] and AAML1531[40]), each implementing a reduction of treatment intensity for ML-DS, confirm that TRM is no longer a dominant cause of treatment failure. Additionally, given the unsatisfactory outcome of patients after relapse of ML-DS[41], future trials must focus on prevention of relapse instead emerges as a priority given the unsatisfactory outcome of patients after relapse of ML-DS (with the possible exception of those achieving a second remission prior to HSCT.[41] Finally, flow cytometric MRD did not identify a favorable prognostic group for treatment de-intensification. A clinically applicable risk stratification of ML-DS therefore remains to be established.

Chronic Myeloid Leukemia: Like other myeloid diseases, the relative rarity of CML in children compared to adults means that management recommendations are derived from adults. Younger patients, however, often have a more aggressive clinical presentation. Tyrosine kinase inhibitors (TKIs) are highly effective in inducing deep molecular remissions. The current standard of care in children is continuous TKI though transition to adult oncology care, where trials without TKI are standard practice.[42] Prolonged exposure to TKIs in children during growth and development can have profound effects on bone growth and metabolism and endocrine function.[43,44] The current COG AAML18P1 (NCT03817398) pilot trial focuses on identifying children who can stop TKI without disease recurrence.

Relapsed/refractory AML: Although clinical outcomes for pediatric patients with newly-diagnosed AML have improved due to advances in cytomolecular- and MRD-based risk stratification and enhanced supportive care, nearly half of children continue to relapse and have dismal long-term clinical outcomes.[2,45] Importantly, the prognostic significance of some cytomolecular alterations appears to be maintained at relapse. For example, recent studies have reported 4-year 80% OS in patients with relapsed AML harboring *RUNX1::RUNXT1* or *CBFB::MYH11* rearrangements.[46,47] However, the duration of first remission is the most robust prognosticator in children with relapsed AML. Survival is particularly poor for children who relapse at <12 months from initial AML diagnosis (20-30% OS versus 50-60% for relapse ≥12 months).[46,48]

While no uniform salvage therapy approach(es) for first AML relapse in children has/have been adopted due to differing strategies by pediatric oncology cooperative groups and lack of universally-defined response criteria, consolidation of second remission with allogeneic HSCT (or second HSCT) remains the standard-of-care. Most first relapse regimens include fludarabine with cytarabine (FLA), and/or anthracycline chemotherapy depending on prior cumulative dose exposure with or without GO.[47,49] The COG AAML1421 phase 1/2 trial of liposomal daunorubicin/cytarabine (cycle 1) and FLA (cycle 2) for pediatric patients with first relapse of AML (n=37) reported a 81% CR/CRp/CRi with 80% MRD negative. The 2-year OS was 53%. These promising data led to an FDA label extension for pediatric patients >=1 year and to frontline investigation of liposomal daunorubicin/cytarabine in the randomized AAML1831 phase 3 trial. Current and recent pediatric trials are also exploring venetoclax-based salvage therapies given their emerging success.[50] Approaches to second or greater AML relapse are far more variable and have included phase 1 clinical trial investigation of new agents when available.[51,52]

COG and other international consortia have focused upon defining the genetic and immunophenotypic landscape of childhood AML, aligning these biologic characteristics with clinical outcomes data, and investigating precision medicine approaches for relevant high-risk subtypes. Current high-priority pediatric AML targets for which there are active and developing clinical trials are summarized in Figure 2. Several other targeted inhibitors in combination with chemotherapy are also under current investigation via early-phase clinical trials (Table 3). The APAL2020SC Screening Trial (NCT04726241), sponsored by the Leukemia & Lymphoma Society and conducted through COG, provides an opportunity for broad, centralized screening of genomic and cell surface targets for rapid eligibility determination for targeted therapy trials.

Supportive Care: Advances in supportive care have contributed to improved survival outcomes in COG pediatric AML trials. The COG Myeloid Disease Committee has led and facilitated supportive care research in two primary ways. First, COG phase 3 AML trials were used as a platform for secondary data analyses and embedded supportive care studies. Second, collaboration with the COG Cancer Control and Supportive Care (CCSC) Committee has yielded highly impactful supportive care interventional trials. Secondary data analyses of COG trial data provided supporting data for two randomized clinical through the COG CCSC Committee [53]. Specifically, a recently published randomized clinical trial of levofloxacin versus no prophylaxis in pediatric patients with high-risk neutropenia and demonstrated that levofloxacin was associated with a decreased risk of bacteremia in patients with acute leukemia [54]. A second COG trial demonstrated that, in pediatric patients with AML, caspofungin reduced the risk of invasive fungal infections relative to fluconazole [55]. These two trials have been practice defining for the pediatric AML community and set the foundation for subsequent trials testing novel antibiotics and antifungals.

Recent published secondary data analyses from COG AML clinical trials have reported clinically important cardiac toxicity outcomes during and shortly after completion of front link therapy. Analyses of AAML0531 data demonstrated a higher rate of left ventricular systolic dysfunction (LVSD) than previously reported and that early LVSD was associated with decreased survival outcomes.[56] Secondary data analyses from the AAML1031

trial demonstrated a cardioprotective effect of dexrazoxane with compromising survival outcomes.[57] These data to the required inclusion of dexrazoxane as a supportive care measure in the standard chemotherapy arm of AAML1831 and embedded cardiotoxicity studies.

Embedded supportive care studies included an analysis of quality of life (QoL) in the recent AAML1031 clinical trial. This study included 505 guardians and 348 children who completed a series of QoL surveys that revealed an association between adverse event frequency and lower QoL.[58] This work has set the foundation for an ongoing embedded study of neurocognitive function in the current AAML1831 trial. Secondary data analyses of multiple COG trials have demonstrated a consistent disparity in outcomes by race and ethnicity, serving as proxies for systemic racism and barriers to optimal care. Work by many investigators, including the Myeloid Diseases Disparity Committee, seeks to identify modifiable drivers of these disparities.[59] Moving forward, the COG Myeloid Diseases Committee will continue to utilize a two-pronged strategy of advancing supportive care with specific emphases on infection prevention and management, cardio-oncology, neurological outcomes, and addressing disparities.

Biological Achievements

Cytogenetic and molecular landscape in Childhood AML—The procurement of bone marrow samples for correlative biologic studies on serial COG trials has resulted in invaluable access to diagnostic and remission specimens that have further informed our understanding of disease biology and prognostic features. Major findings from AML biology-defining studies incorporating COG samples are included in Table 1.

Risk Classification—Risk group assignments in childhood AML links specific disease characteristics to the risk of induction failure or relapse. Two general categories of data is used to determine risk status which include (1) Cytomolecular (CM) characteristics and (2) response to induction therapy. The assessment of response occurs after the initial induction regimen using a validated multiparameter flow cytometry (MPF) assay capable of reliably detecting malignant population at a sensitivity of 0.01-0.1%. With the exception of CM favorable risk (Table 2) AML, the assessment of response by MPF is a reliable and significant predictor of event-free and overall survival. The accurate assessment of risk for relapse in children with AML requires the interpretation and integration of cytogenetic and FISH data, with both traditional sequencing and next-generation sequencing along with immunophenotyping for initial phenotype and end of induction response assessment (Figure 3).

Historically, risk assignment was based on cytogenetics alone. High risk features including the presence of monosomy 5/5q deletion and monosomy 7 have long been identified as prognostic features predicting a high risk of relapse, while CBF fusions have been considered a more favorable biomarker in all COG *de novo* AML studies. *FLT3*-ITD mutations, detected by polymerase chain reaction, were added as a high-risk variant during AAML0531. The AAML1031 trial was the first to incorporate response assessed by MPF into risk classification, and incorporated *NPM1* and *CEBPA* mutations as favorable

risk biomarkers. Improvements in cytogenetic and molecular diagnostic techniques have significantly expanded the number of risk stratifying lesions. Advances in next generation sequencing have been essential in validating traditional cytomolecular techniques as well as identifying cryptic risk-defining lesions not detected through traditional methods. In the current Phase 3 study AAML1831, COG incorporates a more comprehensive list of risk defining events using the diagnostic approach described in Figure 3. The complexity of risk classification reflects the heterogeneity of childhood AML and the necessity for all future trials to be informed by, and evaluated according to, standards developed for children.

Key Trials to be Pursued

Treatment Approach for AML: Recent successes in incorporating targeted therapies such as GO and/or sorafenib to intensive chemotherapy regimens have improved survival in subsets of patients, but with additive toxicity. Future strategies will continue to capitalize on identification of relevant therapeutic targets and the incorporation of novel therapies, such as menin inhibition for patients with *KMT2A* or *NUP98* rearrangements. Based upon FDA approval and wide clinical use of venetoclax in adults with AML, but a paucity of data in children, future trials will also aim to elucidate the therapeutic benefit of BCL-2 inhibition in pediatric AML. The COG Myeloid Diseases Committee anticipates that the successor phase 3 trial to AAML1831 will incorporate a design that tests targeted agents involving approximately 45% of patients with relevant genetic alterations. For the remaining 55% of patients who lack a known driver variant directly responsive to targeted therapies, candidate interventions are under consideration. However, future trials will need to balance efforts to utilize a dose and dosing schedule that will limit potential for toxicity, while maximizing efficacy of the targeted agent. The COG Myeloid Diseases Committee also plans to continue its focus upon reducing anthracycline-induced cardiotoxicity of through incorporation of cardioprotective strategies such as dexrazoxane and, possibly, liposomal anthracycline chemotherapeutics (*eg*, CPX-351). Early phase clinical trials will also investigate new immunotherapies that target critical cell surface targets, such as CD123, CD33, and FOLR1, with a continued emphasis on identifying novel targets through correlative biology studies.

Treatment approach for APL: APL is now one of the most curable forms of childhood cancer with the utilization of ATRA and ATO-based therapy. However, ATO infusions in medical settings create a significant burden of care for patients and their families. An oral formulation of ATO administered at home has the potential to significantly improve quality of life for patient. There are promising trials showing efficacy of oral arsenic compounds. Thus, it is a goal of the COG myeloid committee to evaluate oral ATO in pediatric patients with APL to determine if similar drug exposure (through pharmacokinetic analysis) is achieved with oral versus IV formulations of ATO.

Treatment approach for ML-DS: Building on the successful reduction of TRM in past ML-DS trials, the major objective of future trials is the prevention of relapse events. This goal can be accomplished by developing a clinically applicable risk stratification of ML-DS (similar to non-DS AML) by correlating the molecular subtypes of ML-DS with outcomes, implementing molecular MRD assays based upon measuring the size of cell clones with patient-specific *GATA1* and co-operating mutations by error-corrected NGS, and

by the introduction of new drugs into the treatment of ML-DS (*e.g.*, liposomal cytarabine/daunorubicin, GO, inhibitors of pathways activated in ML-DS blasts[60]). Judicious inclusion of patients with ML-DS in early phase trials is essential to assure access to new forms of AML therapy also for this vulnerable group.

Summary and Future Directions

During the past decade, the COG Myeloid Disease Committee has improved outcomes for some children with AML via therapeutic clinical trials, increased understanding of the cytomolecular features of pediatric AML and correlation with clinical outcomes, and intercalation of critical supportive care measures. The continued evaluation of targeted strategies requires an expert and experienced network of collaborating pediatric institutions joined as the COG with aspirations for more global trials to better study children the growing number of rare molecular subsets. Effective development of new precision medicine approaches for children with relapsed AML and other acute leukemias will also be further facilitated by efforts of the ACCELERATE Pediatric Strategy Forum[6] and the recently-created international consortium created by the Leukemia & Lymphoma Society to facilitate international collaborations involving the COG.[61] This innovative international cooperative infrastructure has successfully engaged academic pediatric oncologists, federal regulatory agencies, and pharmaceutical companies to (1) standardize relapse definitions, response criteria, and outcomes reporting, (2) hasten pediatric-specific drug development and clinical investigation, and (3) increase enrollment efficiency of rare high-risk subtypes of childhood acute leukemias within specific trials. Taken together, the COG Myeloid Diseases Committee continues to leverage critical lessons learned, new biologic understanding, and access to new chemotherapies and targeted therapies with an overarching goal of curing more children with AML.

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Glossary

AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
ATO	arsenic trioxide
ATRA	all-trans retinoic acid
CBF	core binding factor
CM	cytomolecular
CML	chronic myeloid leukemia
CBF	core-binding factor
CR	Complete Response
CRp	complete response without platelet recovery
CRi	complete response with incomplete count recovery
CCSC	Cancer Control and Supportive Care
COG	Children’s Oncology Group
DFS	disease-free survival
EFS	event free survival
FLA	fludarabine and cytarabine
GO	gemtuzumab ozogamicin
HR	high risk
HSCT	hematopoietic stem cell transplant
ITD	internal tandem duplication
LVSD	left ventricular systolic dysfunction
MLDS	myeloid leukemia of Down syndrome
MRC	Medical Research Council
MRD	minimal residual disease
MPF	multiparameter flow cytometry
NGS	next generation sequencing
OS	overall survival
PCR	polymerase chain reaction

QoL	quality of life
RR	relapse rate
SR	standard risk
TAM	transient abnormal myelopoiesis
TRM	treatment-related mortality

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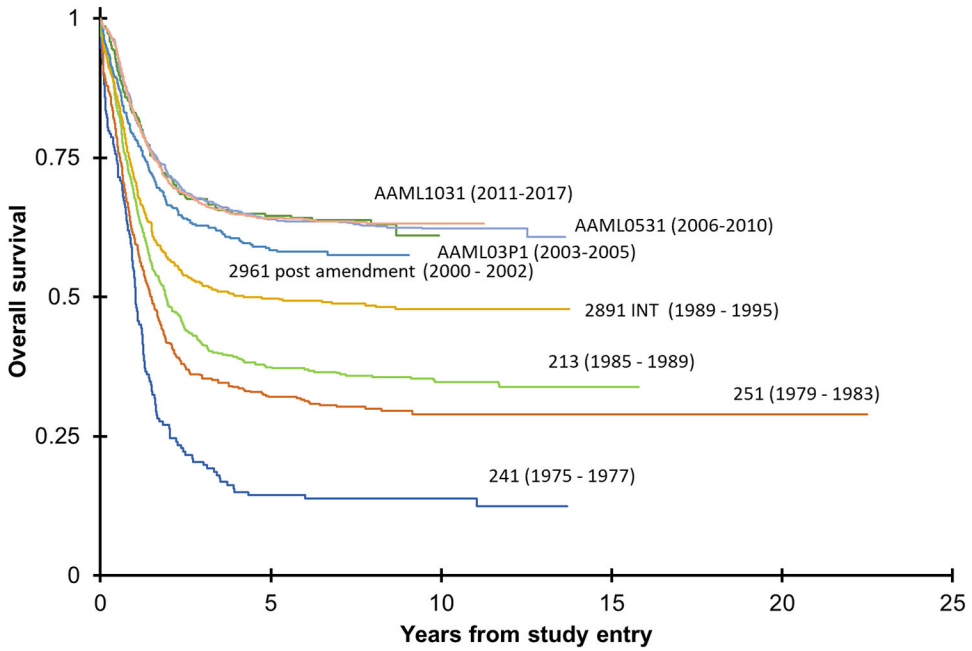

Figure 1.
Overall survival on successive clinical trials since 1975.

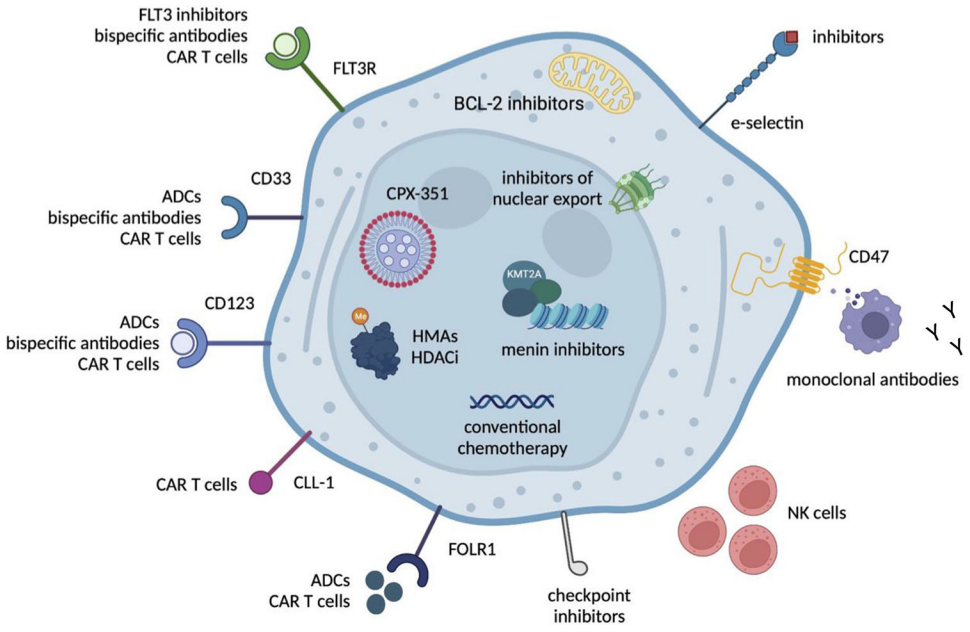

Figure 2. Therapeutic targets in relapsed pediatric AML and precision medicine therapies under current or planned clinical investigation.

ADCs = antibody-drug conjugates, CAR = chimeric antigen receptor, FLT3R = FLT3 receptor, FOLR1 = folate receptor 1, HDACi = histone deacetylase inhibitors, HMAs = hypomethylating agents, KMT2A = lysine methyltransferase 2A, NK = natural killer. *Figure was created using* BioRender.com.

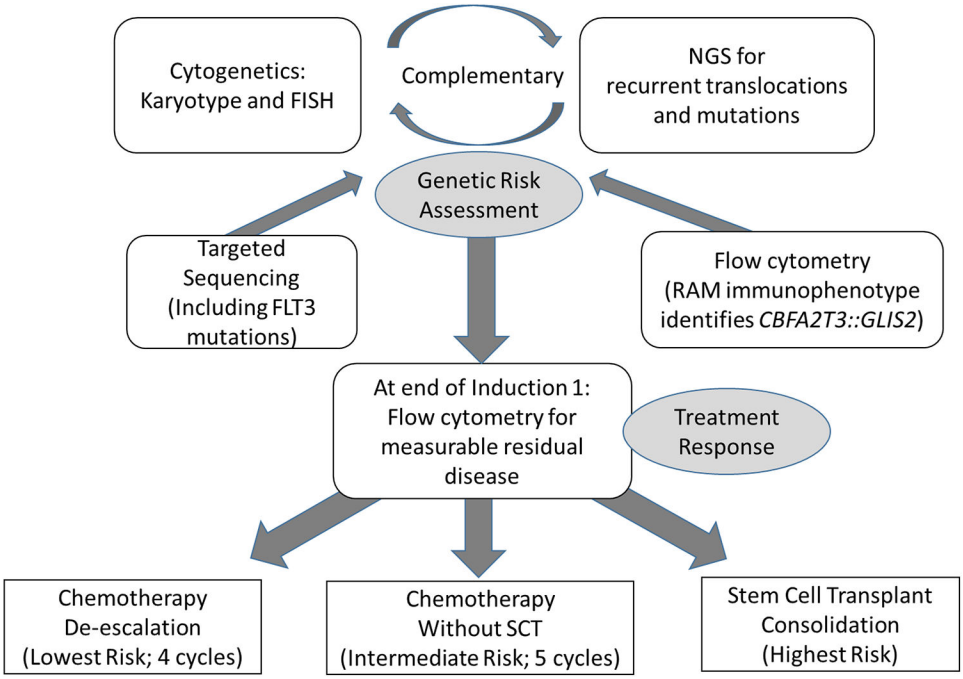

Figure 3. Flow diagram for diagnostic and end of induction response assessments to accurately risk stratify patients in the AAML1831 Phase 3 trial.

Table 1.

A summary of key publications from the past 10 years that inform the current standard of care and result from COG data and specimen requests, and utilize the COG Statistics and Data Center.

Citation	Clinical Data Sets	Key Findings
Biomarkers		
Ostronoff *et al*, 2014	CCG-2941/2961 AAML03P1, AAML0531	The *NUP98::NSD1* chimeric oncogene commonly co-occurs with the *FLT3*-ITD mutations, is common adolescents and predicts a poor survival when occurring alone or co-occurring with *FLT3*-ITD
Tarlock *et al*, 2014	CCG-2861, -2891, -2961, POG-9421, AAML03P1 AAML0531	The t(6;9)(p23;q34) translocation resulting in the *DEK::NUP214* fusion product co-occurs commonly with the *FLT3*-ITD, and is an independent predictor of poor survival
Brodersen *et al*, 2016[62]	AAML0531	A recurrent diagnostic immunophenotype (CD56+, HLA-DR+, CD38+) identifies a group of patients with a distinctively poor outcome. This is now called the RAM phenotype in current trials.
Pollard *et al*, 2016[30]	AAML0531	Patients with higher CD33 expression have a reduction in relapse risk and improvement in EFS when treated with GO.
Tarlock *et al*, 2016[27]	AAML03P1, AAML0531	GO reduces the relapse risk for patients with *FLT3*-ITD.
Lamba *et al*, 2017[63]	AAML0531	A CD33 single nucleotide polymorphism (rs12459419 C>T) occurring in the splice enhancer region predicts EFS in patient treated with GO. This alternatively spliced CD33 isoform lacks expression of the antibody binding site for GO.
Bolouri *et al*, 2018[2]	AAML03P1, AAML0531	This was the most comprehensive genomic profiling of childhood AML, and it demonstrated the differences in mutations across the lifespan.
Tarlock *et al*, 2019 [64]	AAML0531	Exon 17 and not exon 8 KIT mutation co-occurring with core-binding factor mutations predicts a higher rate of relapse following conventional therapy with or without GO.
Brodersen *et al*, 2020 [65]	AAML0531	Compared to standard morphology, difference-from normal flow cytometry was a better predictor of OS in children with AML. In fact, there was a significant false negative and false positive rate by morphology when confirmed by flow.
Tarlock *et al*, 2020 [66]	AAML0531, AAML1031	Colony-stimulating factor 3 receptor (*CSF3R*) activating mutations co-occur with *CEBPA* and t(8;21) mutations, but predict poor outcomes in the patients with a co-occurring *CEBPA* mutation.
Huang *et al*, 2021	2961, AAML03P1 AAML0531, AAML1031	The co-occurrence of the *CBFB-MYH11* re-arrangement and *KIT* mutations in AML in children predicts a higher risk for relapse.
Noort *et al*, 2021	AAML03P1, AAML0531, AAML1031, and European samples *	Childhood AML with the *NUP98::KDM5A* fusion tends to occur in younger patient with a higher rate of acute megakaryocytic AML. OS and EFS is reduced.
Pollard, *et al* 2021[29]	AAML0531	Gemtuzumab ozogamicin improves overall outcomes in pediatric *KMT2A*-rearranged AML and in high-risk vs. not high-risk fusions.
Tarlock et al 2021[9]	AAML03P1, AAML0531, AAML1031	Described favorable CEBPA-bZIp mutations regardless of monoallelic or biallelic status. Described high relapse risk observed when co-occurring CSF3R mutation is present.
Umeda *et al*, 2022[67]	AAML1031	A multi-group analysis identifying exon 13 tandem duplications in upstream binding transcription factor (*UBTF*)as a recurring mutation in AML that predict poor outcomes
Lamble *et al*, 2022[68]	AAML1031	The authors establish that higher CD123 expression correlates with high risk cyto-molecular events in childhood AML.
Huang *et al*, 2022[69]	AAML03P1, AAML0531, AAML1031	With diagnostic cytogenetics and RNA sequencing from more than 1500 patients, the authors identify a cytomolecular risk prediction model for childhood AML utilizing a leukemic stem cell signature based on AML cytomolecular subtypes.

Citation	Clinical Data Sets	Key Findings
Elsayed, *et al*, 2022[70]	AAML0531	In this multi-group trial, the authors validate pharmacogenomic markers involved in cytarabine metabolism as prognostic for survival.
Gbadamosi *et al*, 2022[71]	AAML03P1, AAML0531	The authors identified a scoring system best on expression of 10 genes involved in DNA damage response to predict survival following treatment that includes GO.
Marrero *et al*, 2023[72]	AAML1031, St Jude AML02 and AML08	A multi-group analysis describing the effect of *SAMHD1,* which participates in cytarabine metabolism, polymorphisms on survival in childhood AML.
Farrar *et al* JCO 2023[73]	AAML03P1, AAML0531 AAML1031	Long noncoding RNA expression enhances predictive power of traditional cytogenetic and mutation defined risk and may be comparable to historical cytogenetic/molecular risk characteristics
Bertrums *et al*, 2023[74]	AAML03P1, AAML0531, AAML1031	A multi-group analysis describing the poor outcomes associated with NUP98 fusions and describing the commonly occurring co-mutations.
Chisholm *et al*, 2023[75]	AAML0531, AAML1031	Described cases of non-DS AMKL by molecular and cytogenetic subtypes and reported their corresponding EFS and OS
Lamble *et al*, 2023[76]	AAML03P1, AAML0531, AAML1031	Described prognostic significance of *CREBBP* sequence variants and their impact on co-occurring mutations in AML . Demonstrated that such mutations are associated with similar high risk as that of *CREBBP::KAT6A* fusions
Therapy and Supportive Care		
Gamis et a, 2014l[4]	AAML0531	GO improves event free survival in children with *de novo* AML when combined with conventional therapy.
Guest et al, 2017[77]	AAML03P1 and AAML0531	GO was well tolerated in infant AML and was associated with favorable outcomes.
Taub *et al,* 2017[39]	AAML0431	Use of high dose cytarabine early in treatment for DS- ML improved outcomes from historical studies with manageable toxicities.
Kutny *et al*, 2017[32]	AAML0631	Arsenic consolidation allowed for cumulative reduction in anthracyclines with comparable outcomes in pediatric APL
Getz *et al,* 2019[56]	AAML0531	Early treatment-related cardiotoxicity may be associated with decreased EFS and OS.
Getz *et al*, 2020[57]	AAML1031	Dexrazoxane preserved cardiac function without compromising EFS and OS or increasing noncardiac toxicities.
Elgarten *et al*, 2021[78]	AAML0531, AAML1031	Intensifying a second induction course does not improve survival in children with high-risk AML
Hitzler *et al*[79]	AAML1531	Dose reduction of cytarabine treatment for Downs Syndrome patients with ML-DS who were MRD negative at end induction lead to higher rates of relapse establishing importance of this treatment in ML-DS
Getz *et al,* 2022[57]	AAML0531, AAML1031	Capizzi AraC can be eliminated in patients who low risk molecular/cytogenetic risk features who are MRD negative after Induction I
Pollard *et al,* 2022[80]	AAML0531, AAML1031	The addition of sorafenib to conventional therapy improves induction response and survival in patient with *FLT3*-ITD with an allelic ratio greater than 0.4.
Kutny *et al* 2022[33]	AAML1331	Arsenic and ATRA are sufficient treatment for standard-risk APL and can be a mainstay of therapy in high-risk APL

* Includes samples from IEOP (Associazione Italiana di Ematologia e Oncologia Pediatrica), BFM (Berlin-Frankfurt-Münster) group, CPH (Czech Pediatric Hematology Working Group), DCOG (Dutch Childhood Oncology Group) and LAME (Leucémie Aiquë Myéloblastique Enfant).

Table 2.

Risk Stratification for Pediatric Patients with Newly-Diagnosed AML Used in the COG AAML1831 Clinical Trial.

Primary Risk Marker	Modifying Risk Marker	Comment
RUNX1::RUNXT1 and *CBFB:MYH11* mutations *	MRD+ at EOI1	End-induction 1 (EOI1) MRD-negative complete remission indicates that treatment de-escalation possible with 4 (not 5) cycles of chemotherapy without HSCT
	KIT exon 17 mutation	Presence of *CKIT* mutation indicates need for 5 cycles of chemotherapy, but HSCT in CR1 not indicated
	Unfavorable cytogenetic and/or NGS marker	Presence of an unfavorable genetic marker (see below) supersedes risk group and these patients are recommended to receive HSCT in CR1
NPM1 or *CEBPA* bZIP mutation	MRD+ at EOI1	MRD negative response indicates that treatment de-escalation possible with 4 (not 5) cycles of chemotherapy without HSCT
	Unfavorable cytogenetic and/or NGS marker	Presence of any additional unfavorable genetic marker (see below) supersedes risk group and these patients are recommended to receive SCT.
FLT3-ITD	*NPM1* or *CEBPA* bZIP mutation AND MRD+ at EOI1	Co-occurring *NPM1* or *CEBPA* bZIP mutation allows 5 cycles of chemotherapy without HSCT only if MRD negative, otherwise HSCT recommended
Unfavorable cytogenetic and/or NGS marker	None	HSCT recommended if any of the following are present: t(3;21)(26.2;q22) *RUNX1::MECOM* t(3;5)(q25;q34) *NPM1::MLF1* t(6;9)(p22.3;q34.1) *DEK::NUP214* t(8;16)(p11.2;p13.3) *KAT6A::CREBBP* (if 90 days or older at diagnosis) t(16;21)(p11.2;q22.2) *FUS::ERG* inv(16)(p13.3q24.3) *CBFA2T3::GLIS2* t(4;11)(q21;q23.3) *KMT2A::MLLT2* t(6;11)(q27;q23.3) *KMT2A::MLLT4* t(10;11)(p12.3;q23.3) *KMT2A::MLLT10* t(10;11)(p12.1;q23.3) *KMT2A::ABI1* t(11;19)(q23.3;p13.3) *KMT2A::ENL* 11p15 rearrangement (*NUP98* with any partner gene) 12p13.2 rearrangement (*ETV6* with any partner gene) deletion 12p to include 12p13.2 (loss of *ETV6*) monosomy 5/del(5q) to include 5q31 (loss of *EGR1*) monosomy 7 10p12.3 rearrangement (*MLLT10* with any partner gene)

* previously referred to as core binding factor (CBF) AML, t(8;21) or inv(16)/t(16;16)

MRD measurable residual disease, HSCT hematopoietic stem cell transplant, NGS next generation sequencing

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Table 3.

Current early-phase clinical trials for children with relapsed/refractory AML.

Targeted therapy	Target	Chemotherapy combination	Age	Clinicaltrials.gov identifier	Study group	Notes
Small molecule inhibitors						
venetoclax	BCL-2	cytarabine +/− idarubicin	2 - 20 years	NCT03194932	SJCRH	ALL also eligible
venetoclax	BCL-2	FLA + GO	29 days - 21 years	NCT05183035	LLS PedAL/EuPAL	CD33+ AML
selinexor, venetoclax	XPO1, BCL-2	FLA/FLAG	≤ 30 years	NCT04898894	SJCRH	ALAL also eligible
gilteritinib	FLT3	gilteritinib, FLAG	6 months - 21 years	NCT04240002	Astellas	*FLT3*-ITD or mutation
quizartinib	FLT3	FLA + etoposide	1 month - 21 years	NCT03793478	ITCC/COG	*FLT3*-ITD or mutation
pexidartinib	FLT3		3 - 35 years	NCT02390752	NCI	ALL and solid tumor also eligible
MRX-2843	FLT3		≥ 12 years	NCT04872478	Meryx	ALL and MPAL also eligible
enasidenib	IDH2		2 - 18 years	NCT04203316	COG	*IDH2* mutation
pevonedistat	NEDD8	azacytidine + FLA	1 month - 21 years	NCT03813147	COG/PEP-CTN	active, not recruiting
ALRN-6924	MDM2/MDMX	+/− cytarabine	1 - 21 years	NCT03654716	DFCI	CNS and solid tumors; lymphoma and leukemia also eligible
idasanutlin	MDM2	FLA or venetoclax	≤ 30 years	NCT04029688	Hoffmann-La Roche	ALL and solid tumor also eligible
revumenib (SNDX-5613)	menin		≥ 30 days	NCT04065399	Syndax	*KMT2A* rearrangement, *NUP98* rearrangement, or *NPM1* mutation; *KMT2A*-rearranged ALL also eligible
revumenib	menin	FLA	≥ 30 days	NCT05326516	Syndax	*KMT2A* rearrangement, *NUP98* rearrangement, or *NPM1* mutation; *KMT2A*-rearranged ALL or MPAL also eligible
revumenib	menin	decitabine + cedazuridine (ASTX727) + venetoclax	≥ 12 years	NCT05360160	MDACC	MPAL also eligible
niclosamide	CREB	cytarabine	2 - 25 years	NCT05188170	Stanford University	ALAL also eligible
Antibody and cellular immunotherapies						
GO	CD33	Liposomal daunorubicin and cytarabine	≤ 21 years	NCT04915612	MDACC	CD33+ AML
CD33 CAR T cells	CD33	fludarabine + cyclophosphamide LD	1 - 35 years	NCT03971799	CIBMTR multi-site	CD33+ AML
CD33xCD3 bispecific antibody	CD33xCD3		2 - 21 years	NCT05077423	Y-mAbs Therapeutics, COG/PEP-CTN	study terminated early due to financial decision by sponsor

Targeted therapy	Target	Chemotherapy combination	Age	Clinicaltrials.gov identifier	Study group	Notes
CD33 CAR T cells (DARIC)	CD33	rapamycin (activates DARIC)	≤ 30 years	NCT05105152	SCH	study terminated before expansion cohort due to financial decision by sponsor
flotetuzumab	CD123xCD3			NCT04158739	COG/PEP-CTN	active, not recruiting
CD123CART	CD123	fludarabine + cyclophosphamide LD, rituximab for T cell termination	≤ 21 years	NCT04318678	SJCRH	CD123+ AML/MDS; ALL and BPDCN also eligible
CD123CART	CD123	LD chemotherapy (fludarabine, cyclophosphamide)	1 - 29 years	NCT04678336	CHOP	CD123+ AML
SAR443579 (NK cell engager)	CD123		≥ 12 years	NCT05086315	Sanofi	B-ALL and high-risk MDS also eligible
CLL-1 CAR T cells	CLL-1 (CLEC12A, CD371)	fludarabine + cyclophosphamide LD	≤ 75 years	NCT04219163	BCM/TCH	CLL-1+ AML
CIML NK cells	AML cells	FLAG or fludarabine + cyclophosphamide LD	≥ 1 year	NCT03068819	WUSTL	post-HSCT relapse
CIML NK cells	AML cells	fludarabine + cyclophosphamide LD	≥ 1 year	NCT04024761	DFCI	post-HSCT relapse

ALAL = acute leukemia of ambiguous lineage, BCM/TCH = Baylor College of Medicine/Texas Children's Hospital, BPDCN = blastic plasmacytoid dendritic cell neoplasm, CHOP = Children's Hospital of Philadelphia, CREB = cAMP response element binding protein, CIBMTR = Center for International Blood and Marrow Transplant Research, CIML = cytokine-induced memory-like, COG = Children's Oncology Group, DARIC = dimerizing agent-regulated immune-receptor complex, DFCI = Dana-Farber Cancer Institute, FLA = fludarabine/cytarabine, FLAG = fludarabine/cytarabine + g-csf, HSCT = hematopoietic stem cell transplant, ITCC = Innovative Therapies for Childhood Cancer consortium, LD = lymphodepleting chemotherapy, LLS PedAL/EuPAL = Leukemia & Lymphoma Society Pediatric Acute Leukemia and European Pediatric Acute Leukemia consortium, MDS = myelodysplastic syndrome, MPAL = mixed phenotypic acute leukemia, NCI = National Cancer Institute, SCH = Seattle Children's Hospital, SJCRH = St Jude Children's Research Hospital, WUSTL = Washington University in St Louis.