COG-ASCT2031: A Multi-Center, Phase 3, Randomized Trial of Matched Unrelated Donor (MUD) versus HLA-Haploidentical Related (Haplo) Myeloablative Hematopoietic Cell Transplantation for Children, Adolescents, and Young Adults (AYA) with Acute Leukemia or Myelodysplastic Syndrome (MDS)

FAST FACTS

Eligibility Reviewed and Verified By

_____ MD/DO/RN/LPN/CRA Date _____

_____ MD/DO/RN/LPN/CRA Date _____

Consent Version Dated_____

PATIENT ELIGIBILITY:

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

___1. Timing

Patients must be enrolled before randomization or treatment begins. If a patient meets eligibility criteria to be randomized, including having both a confirmed MUD and haplo donor available (Section 4.3), randomization will occur at the time of study enrollment. If a patient only has a haplo donor available, they will be nonrandomly assigned to Arm C. Once a patient is randomized it is anticipated to take 4-8 weeks for a patient to complete their pre-HCT therapy, work-up for HCT, and the donor to complete their HCT work-up.

Prior to initiation of the HCT conditioning regimen, centers will consent patients to HCT using their institutional standard of care HCT consents. HCT eligibility must be entered into Medidata Rave and eligibility to start treatment confirmed within 4 weeks of starting protocol therapy (admission for HCT conditioning). There is no COG consent for the actual HCT. Centers will consent their subjects to the COG correlative lab/HRQOL studies along with the consent for enrollment.

___2. The eligibility criteria listed below are only for patients to enroll onto study. Once patient is deemed eligible and successfully enrolled onto study, patients will then need to meet criteria in Section 4.2 to be treated for HCT on this study.

___3. Age

6 months to <22 years at enrollment.

___4. Diagnosis

- Diagnosed with ALL, AML, or MDS for which an allogeneic hematopoietic stem cell transplant is indicated. For disease eligibility to proceed to transplant see Sections 4.2.4-4.2.5. Complete Remission (CR) status will not be confirmed at the time of enrollment. CR as defined in these sections is required to proceed with the actual HCT treatment plan.
- Has not received a prior allogeneic hematopoietic stem cell transplant.
- Does not have a suitable HLA-matched sibling donor available for stem cell donation.
- Has an eligible haploidentical related family donor based on at least intermediate resolution HLA typing.

___5. Patients who also have an eligible 8/8 MUD adult donor based on confirmatory high resolution HLA typing are eligible for randomization to Arm A or Arm B.

___6. Patients who do not have an eligible MUD donor are eligible for enrollment to Arm C.

___7. **Co-Enrollment on other trials**

Patients will not be excluded from enrollment on this study if already enrolled on other protocols for treatment of high risk and/or relapsed ALL, AML and MDS. This is including, but not limited to, COG AAML1831, COG AALL1821**,** the EndRAD Trial**, as well as local institutional trials**. We will collect information on all co-enrollments.
Patients will not be excluded from enrollment on this study if receiving immunotherapy prior to transplant as a way to achieve remission and bridge to transplant. This includes CAR T cell therapy and other immunotherapies.

___8. **Patient Criteria to proceed to HCT**

Patients must meet criteria for HCT within 12 weeks of randomization
The eligibility criteria for patients to enroll onto study are listed in Section 3.2. Once a patient is deemed eligible and successfully enrolled onto study, patient will then need to meet criteria listed below to be treated for HCT on this study.

___9. **Laboratory Studies**
All of the treatment criteria to begin HCT conditioning regimen must be performed within 4 weeks of starting this therapy, See Table 7.1.

If the result of a laboratory study that is repeated at any time *post-enrollment* and prior to the *start of protocol therapy* is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to initiating protocol therapy. The results of the recheck must be within the limits of criteria to proceed. If the result of the recheck is outside the limits of criteria, the patient may not receive protocol therapy until they meet criteria.

___10. **Clinical Studies**
Clinical studies (e.g., cardiac imaging, pulmonary function tests), if applicable, must be obtained within 28 days prior to *start of protocol therapy* (repeat if necessary).

___11. **Disease/Staging Imaging**
Disease/staging imaging studies, if applicable, must be obtained within 28 days prior to *start of protocol therapy* (repeat if necessary).

___12. Disease criteria as per Section 4.2.4-4.2.5.

___13. Performance Level
Karnofsky Index or Lansky Play-Performance Scale ≥ 60 on pre-transplant evaluation. Karnofsky scores must be used for patients ≥ 16 years of age and Lansky scores for patients < 16 years of age.

___14. Organ Function Requirements

- Adequate renal function defined as:
  - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.

  - OR a 24 hour urine Creatinine clearance ≥ 60 mL/min/1.73 m^2
  - OR a GFR ≥ 60 mL/min/1.73 m^2. GFR must be performed using direct measurement with a nuclear blood sampling method OR direct small molecule clearance method (iothalamate or other molecule per institutional standard).
    Note: Estimated GFR (eGFR) from serum creatinine, cystatin C or other estimates are not acceptable for determining eligibility
- Adequate liver function defined as:
  - SGOT (AST) or SGPT (ALT) < 5 x upper limit of normal (ULN) for age. Total bilirubin < 2.5 mg/dL, unless attributable to Gilbert's Syndrome.
- Adequate cardiac function defined as:
  - Shortening fraction of ≥ 27% by echocardiogram or radionuclide scan (MUGA) or
  - Ejection fraction of ≥ 50% by echocardiogram or radionuclide scan (MUGA), choice of test according to local standard of care.
- Adequate pulmonary function defined as:
  - FEV1, FVC, and corrected DLCO must all be ≥ 50% of predicted by pulmonary function tests (PFTs).
  - For children who are unable to perform for PFTs (e.g., due to age or developmental delay), the criteria are: no evidence of dyspnea at rest, O2 Sat > 92% on room air by pulse oximetry, not on supplemental O2 at rest, and not on supplemental O2 at rest.

___15. ALL Criteria

- ALL high-risk in CR1* for whom transplant is indicated. Examples include: induction failure, treatment failure as per minimal residual disease by flow cytometry >0.01% after consolidation and not eligible for AALL1721 or AALL1721 not available/unwilling to enroll, hypodiploidy (<44 chromosomes) with MRD+ >0.01% after induction, persistent or recurrent cytogenetic or molecular evidence of disease during therapy requiring additional therapy after induction to achieve remission (e.g. persistent molecular BCR-ABL positivity), T cell ALL with persistent MRD>0.01% after consolidation.
- ALL in CR2* for whom transplant is indicated. Examples include: B-cell: early (<36 months from initiation of therapy) BM relapse, late BM relapse (≥ 36 months) with MRD >0.1% by flow cytometry after first re-induction therapy; T or B-cell: early (<18 months) IEM, late (≥ 18 months) IEM, end-Block 1 MRD ≥ 0.1%; T-cell or Ph+: BM relapse at any time.
- ALL in > CR3*
- Patients treated with CART cells for whom transplant is indicated. Examples include: transplant for consolidation of CART, loss of CART persistence and/or B cell aplasia <6 months from infusion or have other evidence (e.g., MRD+) that transplant is indicated to prevent relapse.

___16. AML/MDS Criteria

- AML in CR1* for whom transplant is indicated. Examples include those deemed high risk for relapse as described in AAML1831:
  - FLT3/ITD+ with allelic ratio > 0.1 without bZIP CEBPA, NPM1
  - FLT3/ITD+ with allelic ratio > 0.1 with concurrent bZIP CEBPA or NPM1 and with evidence of residual AML (MRD ≥ 0.05%) at end of Induction
  - Presence of RAM phenotype or unfavorable prognostic markers (other than FLT3/ITD) per cytogenetics, FISH, NGS results, regardless of favorable genetic markers, MRD status or FLT3/ITD mutation status
  - AML without favorable or unfavorable cytogenetic or molecular features but with evidence of residual AML (MRD ≥ 0.05%) at end of Induction
  - Presence of a non-ITD FLT3 activating mutation and positive MRD (≥ 0.05%) at end of Induction 1 regardless of presence of favorable genetic markers.
- AML in > CR2
- MDS with <5% blasts by morphology and flow cytometry (if available) on the pre-transplant bone marrow evaluation

*Complete remission (CR) is defined as <5% blasts by morphology and flow cytometry (if available) on the pre-transplant bone marrow evaluation with minimum sustained ANC of 300 cells/microliter for 1 week or ANC >500 cells/microliter. We will be collecting data from all approaches to MRD evaluation performed including NGS and PCR.

Assent: The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

EXCLUSION CRITERIA:

___1. Patients with genetic disorders (generally marrow failure syndromes) prone to secondary AML/ALL with known poor outcomes because of sensitivity to alkylator therapy and/or TBI are not eligible (Fanconi Anemia, Kostmann Syndrome, Dyskeratosis Congenita, etc). Patients with Downs syndrome because of increased toxicity with intensive conditioning regimens.

___2. Patients with any obvious contraindication to myeloablative HCT at the time of enrollment

___3. Pregnant and Breastfeeding

- Female patients who are pregnant are ineligible as many of the medications used in this protocol could be harmful to unborn children and infants
- Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

___4. Patients with uncontrolled fungal, bacterial, viral, or parasitic infections are excluded. Patients with history of fungal disease during chemotherapy may proceed if they have a significant response to antifungal therapy with no or minimal evidence of disease remaining by CT evaluation.

___5. Patients with active CNS leukemia or any other active site of extramedullary disease at the time of initiation of the conditioning regimen are not permitted. Note: Those with prior history of CNS or extramedullary disease, but with no active disease at the time of pre-transplant workup, are eligible.

REQUIRED OBSERVATIONS:

Pre-HCT Within 4 weeks of start of conditioning
Study Evaluation

- History & Physical
- Performance Status Evaluation
- Pediatric Disease Risk Index [1]
- Anti-donor HLA antibody testing (DSA) [2]
- Infectious Disease Marker (IDM) Testing [3]
- Pregnancy test for FCBPs [4]
- Estimated creatinine clearance [5]
- EKG
- Cardiac function: ECHO/MUGA w/ LVEF
- PFTs (FEV1, FVC, DLCO) [6]
- CBC & Differential
- Serum chemistries (AST, ALT, Creatinine,Total/Direct Bilirubin)
- Product analysis [7]
- Chimerism analysis [8]
- Bone marrow examination with MRD assessment [9]
- Diagnostic lumbar puncture
- Health Related QOL Studies [10]

[1] 1 See Appendix IX.

[2] DSA: Refer to Section 4.3 for requirements.

[3] For IDMs, Infectious disease testing (NMDP Infectious Disease Markers):

1. Hepatitis: Hepatitis B surface antigen (HBsAg); Hepatitis B core antibody (anti-HBc); Hepatitis C antibody (anti-HCV)
2. Syphilis: Ab (rapid plasma reagin assay (RPR); non-treponemal testing per NMDP standard of care for syphilis screening to included VDRL or RPR
   *If positive, follow-up with confirmatory testing of treponemal-specific testing
3. HIV: HIV-1 and HIV-2b antibody and p24 antigen; plus HIV RNA or HIV nucleic acid test (NAT)
4. West Nile NAT
5. Serologies: CMV, HSV1/2, VZV, EBV, HTLV I/II, *T. Cruzi* (Chagas disease), *T. gondii* (toxoplasmosis) antibodies

[4] FCBP is defined as a female of childbearing potential is defined as a female of childbearing potential who:

1. has not undergone a hysterectomy or bilateral oophorectomy, or
2. has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months)

[5] Refer to Section 4.2.3 for requirements.

[6] For children who are unable to perform for PFTs (e.g., due to age or developmental delay), the criteria are: no evidence of dyspnea at rest, O2 Sat > 92% on room air by pulse oximetry, and not on supplemental O2 at rest.

[7] 12 CD3, CD34, total nucleated cells/ kg infused

[8] Pre-HCT: DNA for primer identification. Post-HCT: PB – whole blood and sorted chimerism (CD3, CD15, CD33, CD34, CD19, CD14, CD16 per institutional standards); BM - whole marrow chimerism (only if indicated per institutional standard of care when disease restaging is done).

[9] pre-HCT marrow should be done when the patient has a minimum sustained ANC of 300 cells/microliter for 1 week of ANC>500 cells/microliter. BM aspirate (BMA) to be sent for flow cytometry/MRD, cytogenetics, and FISH/molecular studies (FISH only in instances of a pre-existing known chromosomal abnormality). Additional studies are not required (i.e., NGS, PCR) but if performed, will be collected. BM biopsy only indicated if aspirate inadequate for clinical decision making such as in the setting of MDS.

[10] Includes self-reported COG Sociodemographic form

TREATMENT PLAN:
Timing of consent should be at the discretion of the site i.e. when it is convenient and bestfor the patient. We encourage centers to consent their patients at the time it is recognized they need a HCT. Patients with both available donor sources (8/8 MUD and haplo) will berandomized to Arm A (haploHCT) or Arm B (MUD HCT). We anticipate this consent will be while a patient is receiving chemotherapy. Enrollment and randomization should occur only when the site is ready to acquire a donor. The randomization will be stratified by patient age, CR status, and disease type. Patients enrolled on this study who only have an available haplo donor will be assigned to Arm C and receive a nonrandomized haploHCT. We anticipate it will take at least 4 weeks from the time of randomization until the patient begins the HCT myeloablative conditioning regimen. A patient must meet eligibility for HCT within 12 weeks of randomization or they will be removed from the study protocol therapy.

All transplants performed on COG trials must occur at COG Approved FACT- accredited SCT programs (Per COG Policy OM-003).

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0.

SPECIMEN REQUIREMENTS:

Timepoint	Test	Blood Volume	Shipping Destination
Pre-HCT patient[3] and donor	CTRA	1-2ml in shipping media tubes. See 15.2.2.	BPC
Day -4 (+/- 1 day)	ATG PKs[1]	1-2ml whole blood in sodium heparin tube	BPC
	CTRA	1-2ml in shipping media tubes. See 15.2.2.	
Day 0 (+/-1 day)	ATG PKs[1]	1-2ml whole blood in sodium heparin tube	BPC
	Graft Composition[1]	1ml in EDTA tube	
	Immune Functional Assessments[1]	4ml in EDTA tube	
	Extended Immune Cell Phenotyping[1]	4ml in EDTA tube	
	TCR and BCR receptor repertoire analysis[1]	1ml in EDTA tube	
	Cytokine analysis[2]	4ml in Red-top tube with no anticoagulant	
	GVHD biomarkers[2]	4ml in Red-top tube with no anticoagulant	