

COG-AAML1831: A phase 3 randomized trial for patients with de novo AML comparing standard therapy including gemtuzumab ozogamicin GO to CPX-351 with GO, and the addition of the FLT3 inhibitor gilteritinib for patients with FLT3 mutations

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. **Amendment #1**
As of Amendment #1, The Safety Phase has been completed. The RP2D dose for the Efficacy Phase was determined to be DL1 of DA+GO or CPX-351 + GO with **Gilteritinib: 2 mg/kg/dose daily (120 mg max dose).**
- ___ 2. **Patients who plan to enroll on AAML1831 MUST consent to eligibility screening (Part A) and be enrolled on APEC14B1 before receiving any systemic protocol therapy on AAML1831.**
- ___ 3. Patients must be enrolled **before** treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment.
- ___ 4. All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.
- ___ 5. **Timely identification of FLT3 activating mutations and other risk stratifying lesions will require that sites obtain access to the Foundation Medicine Portal upon local study activation. See Section 16.0 for additional detail.**
- ___ 6. **Summary of Required Consents for AAML1831**

Population for Consent	Consent Document	Time Point for Obtaining Consent
All AML patients to be enrolled on AAML1831.	APEC14B1	Prior to submission of protocol required diagnostic specimens.
All AML patients to be enrolled on AAML1831.	<u>Consent #1</u> Arm A or B	Prior to the start of Induction 1 therapy.
Patients ≥ 2 years old who have FLT3-ITD allelic ratio greater than 0.1 regardless of any coexisting genetic markers.	<u>Consent #3</u> Arm C – Efficacy Phase	Efficacy Phase: After FLT3-ITD allelic ratio results are back and prior to initiation of gilteritinib.
Patients ≥ 2 years old who have clinically relevant non-ITD FLT3 Activating Mutations (see Appendix VIII for list of clinically relevant FLT3 activating mutations)	<u>Consent #5</u> Arm D – Efficacy Phase	Efficacy Phase: After the FLT3 mutation results are available and prior to the initiation of gilteritinib.
Any patient who will proceed to HSCT	<u>Consent #6</u> HSCT	Prior to HSCT

- ___ 7. Evaluation for CNS Disease at Diagnosis
It is strongly recommended that the diagnostic lumbar puncture for evaluation of CNS disease be performed on day 8 of Induction 1 (rather than day 1 or prior to initiation of systemic therapy) **EXCEPT in the case of patients with overt signs of CNS disease** (cranial nerve palsy, seizures, etc.) who require rapid CNS treatment. Deferment of the LP for patients without CNS symptoms will allow cyto-reduction of the peripheral blasts and thus decrease the risk of contaminating the CSF sample with peripheral blood blasts that would appear on the cytospin CSF sample. Since patients may have diagnostic evaluations including lumbar puncture prior to definitive diagnosis of the type of leukemia and/or consideration for enrollment onto a therapeutic study, it will NOT be a protocol violation (or eligibility exclusion) if a patient has a diagnostic lumbar puncture with intrathecal chemotherapy (either intrathecal cytarabine or ITT) prior to day 8 of induction. However, when possible this protocol recommendation should be followed.
- ___ 8. **NOTE:** The baseline ECHO must be ordered out of the 1831 template so the study is obtained using the AAML1831 required techniques
Notify cardiology at: lindsey.vanlente@helendevoschildrens.org
- ___ 9. **Patient Eligibility Criteria**
Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.
- ___ 10. **Laboratory Studies**
All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated.
Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > seven (7) days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.
- ___ 11. **Clinical Studies**
Clinical studies (e.g., cardiac imaging, pulmonary function tests), if applicable, must be obtained within 21 days prior to enrollment and start of protocol therapy (repeat if necessary).
- ___ 12. **Bone Marrow Evaluations**
Bone marrow aspirate and biopsy must be obtained within 14 days prior to enrollment. Attempts to obtain bone marrow by aspirate and biopsy must be made unless clinically prohibitive. In cases where it is clinically prohibitive, peripheral blood with an absolute blast count $\geq 1000/\square L$ (i.e., a WBC count $\geq 10,000/\mu L$ with $\geq 10\%$ blasts or a WBC count $\geq 5,000/\mu L$ with $\geq 20\%$ blasts) and morphology and/or phenotype consistent with AML is sufficient. Alternatively, diagnosis can also be made if peripheral blood molecular testing, FISH and/or cytogenetic testing is consistent with AML.
- ___ 13. **Isolated Granulocytic Sarcoma**
Patients with isolated granulocytic sarcoma are eligible. (Table 1 in [Appendix IV](#)). For patients with isolated granulocytic sarcoma, a biopsy must be obtained within 21 days prior to study enrollment. Please refer to APEC14B1 MOP for sample requirements.

___ 14. Inclusion Criteria

- Eligibility Screening

All patients must be enrolled on APEC14B1 and consented to Eligibility Screening (Part A) prior to enrollment and treatment on AAML1831. Submission of diagnostic specimens must be done according to the Manual of Procedures (see [MOP on APEC14B1 web page](#)).

- Age

Patients must be less than 22 years of age at the time of study enrollment.

- Diagnosis

Patient must be newly diagnosed with *de novo* AML according to the 2016 WHO classification with or without extramedullary disease.

– Patient must have 1 of the following:

(a) $\geq 20\%$ bone marrow blasts

In cases where extensive fibrosis may result in a dry tap, blast count can be obtained from touch imprints or estimated from an adequate bone marrow core biopsy.

(b) $< 20\%$ bone marrow blasts with one or more of the genetic abnormalities listed in [Table 1](#) of [Appendix IV](#).

(c) A complete blood count (CBC) documenting the presence of at least 1,000/ μ L (i.e., a WBC count $\geq 10,000/\mu$ L with $\geq 10\%$ blasts or a WBC count of $\geq 5,000/\mu$ L with $\geq 20\%$ blasts) circulating leukemic cells (blasts) if a bone marrow aspirate or biopsy cannot be performed.

EXCLUSION CRITERIA:

- ___ 1. Patients with the following constitutional conditions are not eligible.
 - Fanconi anemia
 - Shwachman Diamond syndrome
 - Patients with constitutional trisomy 21 or with constitutional mosaicism of trisomy 21
 - Telomere disorders
 - Germline predispositions known, or suspected by the treating physician to increase the toxicity with AML therapy
- ___ 2. Patients with any of the following oncologic diagnoses are not eligible.
 - Any concurrent malignancy
 - Juvenile myelomonocytic leukemia (JMML)
 - Philadelphia chromosome positive AML
 - Mixed phenotype acute leukemia
 - Acute promyelocytic leukemia
 - Acute myeloid leukemia arising from myelodysplasia
 - Therapy-related myeloid neoplasms
- ___ 3. Cardiac Function

Patients with persistent cardiac dysfunction prior to enrollment, defined as ejection fraction (EF) < 50% (preferred method Biplane Simpson's EF) or if EF unavailable, shortening fraction (SF) < 24%. *Note: if clinically safe and feasible, repeat echocardiogram is strongly advised in order to confirm cardiac dysfunction following clinical stabilization, particularly if occurring in the setting of sepsis or other transient physiologic stressor. If the repeat echocardiogram demonstrates an EF ≥ 50%, the patient is eligible to enroll and may receive an anthracycline-containing Induction regimen.
- ___ 4. Prior Therapy

Administration of prior anti-cancer therapy except as outlined below:

 - Hydroxyurea
 - All-trans retinoic acid (ATRA)
 - Corticosteroids (any route)
 - Intrathecal therapy given at diagnosis

Please see [Section 4.4](#) for additional concomitant therapy restrictions for patients during treatment. In particular, strong inducers of CYP3A4 and/or P-glycoprotein (P-gp) should be avoided from the time of enrollment until it is determined whether the patient will receive gilteritinib. Patients receiving gilteritinib will be required to avoid strong CYP3A4 inducers and/or strong P-gp inducers for the duration of the study treatment. See [Appendix VII](#) for list of strong CYP3A4 inducers and P-gp inducers.
- ___ 5. Pregnancy and Breastfeeding
 - Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.
 - Lactating females who plan to breastfeed their infants.
 - Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

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

INDUCTION STRATIFICATION FACTORS:

At the time of enrollment, all patients will be randomized to receive treatment with the standard chemotherapy daunorubicin/cytarabine + GO (Arm A) or treatment with CPX-351 + GO (Arm B).

During Induction 1, after results of FLT3 testing becomes available (from the central lab at Fred Hutchinson Molecular Oncology Laboratory and Foundation Medicine), those children ≥ 2 years of age with FLT3/ITD allelic ratio > 0.1 or other clinically relevant non-ITD FLT3 activating mutations (see [Appendix VIII](#) for the list of qualifying mutations) will be offered participation on 2 separate arms (Arm C or Arm D) of the trial; adding gilteritinib in combination with their assigned chemotherapy backbone. The dose of gilteritinib will be assigned during the initial safety phase (see [Section 4.2](#)) which will be conducted to determine the recommended Phase 2 dose (RP2D) of gilteritinib to be used in combination with Arms A and B chemotherapy. Upon completion of the safety phase, the study will move into the efficacy phase using the RP2D of gilteritinib.

Cytogenetics, molecular diagnostics, NGS, RAM phenotype, and end of Induction 1 MRD will be used to risk stratify all patients into high risk (HR) and low risk (LR) groups (see [Section 3.4](#) for risk stratification). Risk assignment will be done centrally and entered into RAVE. Risk assignment should be available no later than Day 14 of Induction 2. LR patients will receive 4 or 5 courses of chemotherapy as outlined below. HR patients should receive 3 courses of chemotherapy and proceed to HSCT (see [Section 19.0](#) for timing and guidelines for HSCT). Patients assigned to therapy with gilteritinib will receive gilteritinib maintenance following chemotherapy or HSCT.

Cytogenetics, molecular diagnostics, NGS, RAM phenotype, and end of Induction 1 MRD will be used to risk stratify all patients into high risk (HR) and low risk (LR) groups (see [Section 3.4](#) for risk stratification).

REQUIRED OBSERVATIONS:

Required Observations - Arm A: Induction 1

- a. Physical exam with vital signs, height and weight.
- b. CBC, differential and platelets.
- c. AST, ALT, bilirubin (total and direct), amylase, lipase.
- d. Electrolytes, calcium, magnesium, phosphate.
- e. BUN, creatinine.
- f. ECG. Prior to start of Induction 1, Day 8* of Induction 1
Day 8 ECG only required for patients identified to have a FLT3 mutation who intend to enroll on Arms AC/AD or BC/BD. If FLT3 mutation is not identified by Day 8, the pre gilteritinib ECG should be performed as soon as results return in order to maximize the opportunity to address QT prolongation prior to start of gilteritinib. In order to start gilteritinib-containing regimens, QTc needs to be less than 480 ms and less than 30 ms greater than baseline. If the Day 8 ECG shows a QTc \geq 480 ms or $>$ 30 ms higher than baseline, QTc must be calculated using the Fridericia formula (QTcF). If QTcF exceeds these parameters, obtain repeat ECGs daily, until QTcF has returned to a range of $<$ 30 ms from baseline and QTcF $<$ 480 ms in order to start gilteritinib-containing arms (AC/AD or BC/BD). Efforts should be made to correct any electrolyte abnormalities and/or remove any agents known to prolong QT interval. Note: Initial QTc calculation can be performed according to institutional standards. However, ECG-related delays and/or gilteritinib dose modifications should only be made for QT prolongation confirmed using the Fridericia formula (QTcF). (See [Section 5.10.1](#)) Please refer to cardiac manual for guidance around QTcF calculation when institutional ECGs do not meet criteria as outlined above.
- g. Echocardiogram. Prior to the start of Induction 1. See [Section 18.1](#) **Note: ECHO must be ordered “per COG-AAML1831 indication”.**
- h. Bone marrow aspirate/biopsy. Day 29-36 depending on count recovery and repeated as needed for disease evaluation. Send to Hematologics. See below (letter i) for further instructions regarding evaluable marrow.
- i. Bone marrow for MRD (required). Day 29-36 depending on count recovery and repeated as needed for disease evaluation. **This sample is necessary for Risk Assignment.** See [Section 15](#). It is recommended that patients have a marrow evaluation no later than Day 36 of this course, recognizing that patients with delayed count recovery may require repeat marrows for disease evaluation. See [Section 4.5](#): it is recommended evaluable marrow demonstrates 10% cellularity on biopsy OR peripheral blood sample must demonstrate an absolute phagocyte count (APC) of $>$ 300 within 7 days of procedure.
- j. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment.
- k. HLA-typing of the patient, siblings, and parents should be done at diagnosis. If HLA typing is not able to be performed at diagnosis, then this should be pursued as soon as possible upon recovery from Induction 1. See [Section 19.1.2](#) and [Section 19.1.3](#) for donor selection guidelines.
- l. Radiographic evaluation of extramedullary disease, if applicable. See [Section 21.0](#).
- m. Collection of samples for cardiac biomarkers is required at baseline-pre treatment. See [Section 18.2](#).

TOXICITIES AND DOSAGE MODIFICATIONS:

See [Section 5](#)

SPECIMEN REQUIREMENTS:

In addition to the local flow and COG approved cytogenetics, the following specimens are required:

AAML1831 Reference Lab Studies – Required for Eligibility Screening (see [Section VI iii](#) for details)

Specimen	Volume	Tube Type	Test	Laboratory
Bone Marrow ¹	Minimum 2-4 mL	Sodium Heparin (Green Top)	Central Flow Cytometry & RAM Phenotype	Hematologics, Inc.
Bone Marrow ²	4-8 mL	SM	NGS & Determination of FLT3-ITD Allelic Ratio, NPM1 and BZIP CEBPA	COG Leukemia Biospecimen Bank

¹ Peripheral blood (Diagnosis only-*only* if marrow specimen is not obtainable): collect a minimum of 5 mL of whole blood in a preservative-free sodium heparin vacutainer (green top).

² If bone marrow cannot be obtained and the peripheral blast count is at least 20%, send 8-16 mL of peripheral blood in an SM tube

The following specimens are optional:

As a reminder, the optional PK for CPX-351 starts on Day 5 of Induction 1. Be sure to order kits immediately after your patient is randomized to Arm B to allow sufficient time for the kit to arrive.

Biorepository – Optional for Banking (see [Section VI iv](#) for details)

Specimen	Volume	Tube Type	Test	Laboratory
Bone Marrow ¹	3-10 mL	SM	Future Research	COG Leukemia Biospecimen Bank
Peripheral Blood	7-10 mL	Red Top Tube Centrifuged and Serum Saved	Future Research	COG Leukemia Biospecimen Bank
Peripheral Blood (AAML1831 only)	10 mL	EDTA	Future Research	COG Leukemia Biospecimen Bank
Pheresis or Exchange Transfusion Products ²	As Available	SM or EDTA	Future Research	COG Leukemia Biospecimen Bank

¹ If BM unattainable, submit 3-10 mL of PB in SM.

² Only if leukopheresis or exchange transfusion is performed for clinical indications. See [Section IX](#) for details.

<p>Pharmacokinetics of CPX-351 See Section 26 for additional details</p>	<p>Induction 1: Day 5 CPX-351 dosing:</p> <ul style="list-style-type: none"> • Prior to CPX-351 Day 5 dosing • EOI (within 15 minutes from end of infusion) • 6 ± 1 hour calculated from start of infusion • 72 ± 24 hour calculated from start of infusion • 168 ± 48 hour calculated from start of infusion
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Also see APEC14B1 MOP

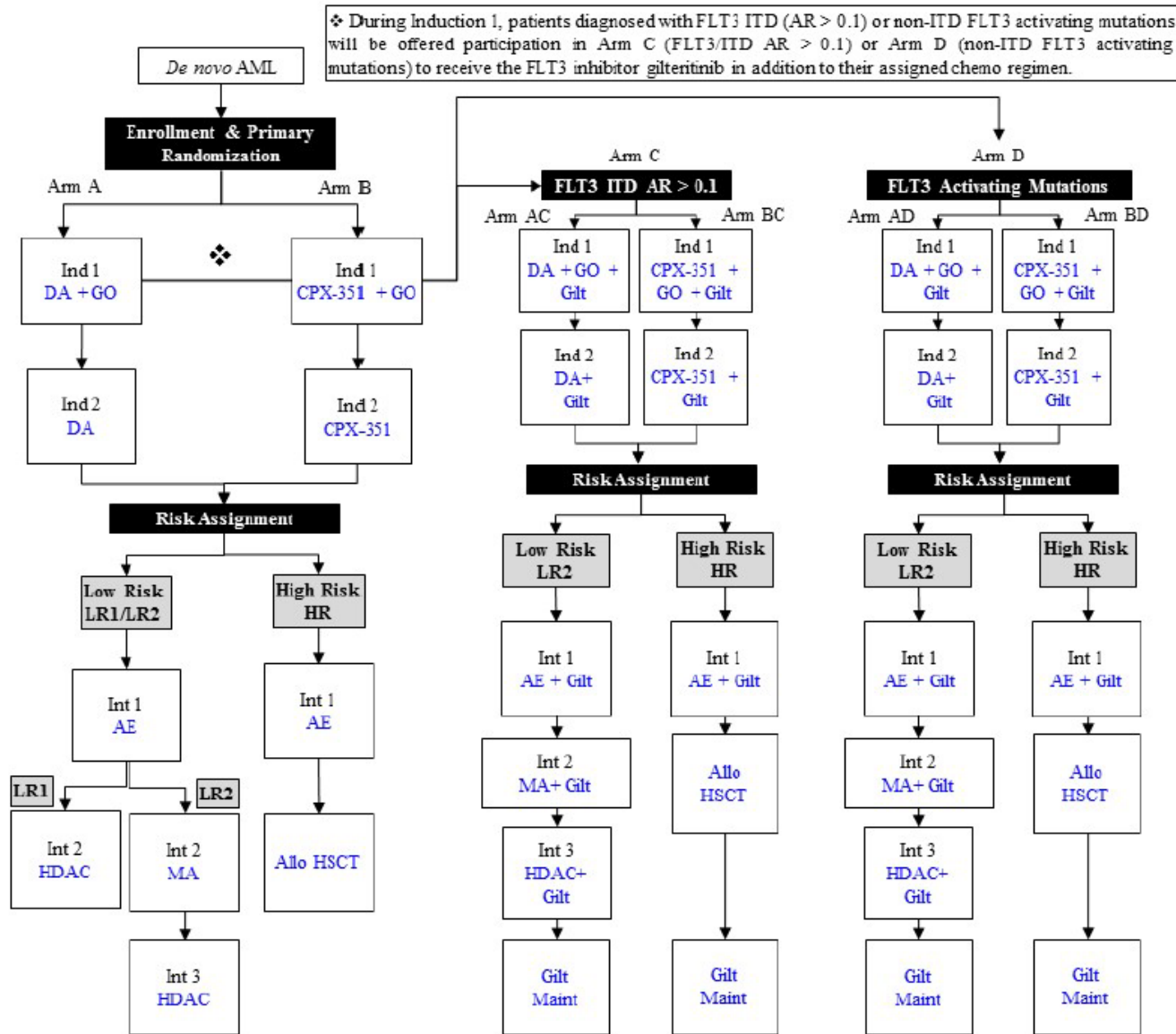
Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See [Appendix XIV](#).

BIOLOGY REQUIREMENTS:

Note: Slides for central review are not needed.

TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA



See [Section 3.4](#) for Details Regarding Risk Assignment

Safety Phase and Efficacy Phase

Patients must be ≥ 2 years of age to receive gilteritinib. The Safety Phase was completed with Amendment #1.

For the Efficacy Phase, the Phase 2 dose (RP2D) of gilteritinib to be used in combination with Arms A and B chemotherapy was determined to be DL1 of DA+GO or CPX-351 + GO with Gilteritinib: 2 mg/kg/dose daily

Legend: AE= cytarabine/etoposide, Allo= allogeneic, AR= allelic ratio, DA= daunorubicin/ cytarabine, DL= dose level, Gilt= gilteritinib, GO= gemtuzumab ozogamicin, HDAC= high dose cytarabine/ asparaginase (Capizzi II), HSCT= hematopoietic stem cell transplant, Ind= induction, Int= intensification, ITD= internal tandem duplication, MA= mitoxantrone/cytarabine, Maint=maintenance