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. **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.**
___2. **Risk stratification will not be possible without the submission of viable samples via APEC14B1. Given there are multiple required samples, bone marrow acquisition techniques such as frequent repositioning or performing bilateral bone marrow testing should be considered to avoid insufficient material for required studies. Consider a repeat marrow prior to starting treatment if there is insufficient diagnostic material for the required studies.**
___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. **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.	Consent #1 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.	Consent #2 Arm C – Safety Phase Consent #3 Arm C – Efficacy Phase	Safety Phase: After FLT3-ITD allelic ratio results are back and prior to initiation of gilteritinib. 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)	Consent #4 Arm D – Safety Phase Consent #5 Arm D – Efficacy Phase	Safety Phase: After the FLT3 mutation results are available and prior to the initiation of gilteritinib. Efficacy Phase: After the FLT3 mutation results are available and prior to the initiation of gilteritinib. After the FLT3
Any patient who will proceed to HSCT	Consent #6 HSCT	Prior to HSCT

___6. 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 prior to day 8 of induction. However, when possible this protocol recommendation should be followed.

___**7.** **NOTE:** The baseline ECHO must be ordered out of the 1831 template so the study is obtained using the AAML1831 required techniques

___8. **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.

___9. **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.

___10. **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).

___11. **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 ≥ 1000/□L (i.e., a WBC count ≥ 10,000/µL with ≥ 10% blasts or a WBC count ≥ 5,000/µL with ≥ 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.

___12. 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). Risk stratification will not be possible without the submission of viable samples. Given there are multiple required samples, bone marrow acquisition techniques such as frequent repositioning or performing bilateral bone marrow testing should be considered to avoid insufficient material for required studies. Consider a repeat marrow prior to starting treatment if there is insufficient diagnostic material for the required studies.
- 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) ≥ 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/□L (i.e., a WBC count ≥ 10,000/μL with ≥ 10% blasts or a WBC count of ≥ 5,000/μL with ≥ 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.

- Patients with myeloid neoplasms with germline predisposition are not eligible.
- Fanconi anemia
- Shwachman Diamond syndrome
- Patients with constitutional trisomy 21 or with constitutional mosaicism of trisomy 21
- Any other known bone marrow failure syndrome

___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. 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.

___4. 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).

REQUIRED OBSERVATIONS:

Required Observations - Arm A: Induction 1

- Physical exam with vital signs, height and weight.
- CBC, differential and platelets.
- AST, ALT, bilirubin (total and direct), amylase, lipase.
- Electrolytes, calcium, magnesium, phosphate.
- BUN, creatinine.
- ECG. Prior to start of Induction 1, Day 8* of Induction 1
  *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 of > 30 ms higher than baseline, obtain repeat ECGs daily, until QTc has returned to a range of < 30 ms from baseline in order to remain eligible for 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.
- Echocardiogram. Prior to the start of Induction 1. See Section 18.1
- 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.
- Bone marrow for MRD (required). Day 29-36 depending on count recovery and repeated as needed for disease evaluation. **Send to Hematologics. 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: evaluable marrow requires 10% cellularity on biopsy OR peripheral blood sample must demonstrate an absolute phagocyte count (APC) of > 300 within 5 days of procedure.
- Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment.
- 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.
- Radiographic evaluation of extramedullary disease, if applicable. See Section 21.0.

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 mimimum 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:
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
Pheresis or Exchange Transfusion Products [2]	As Available	SM or EDTA	Future Research	COG Leukemia Biospecimen Bank

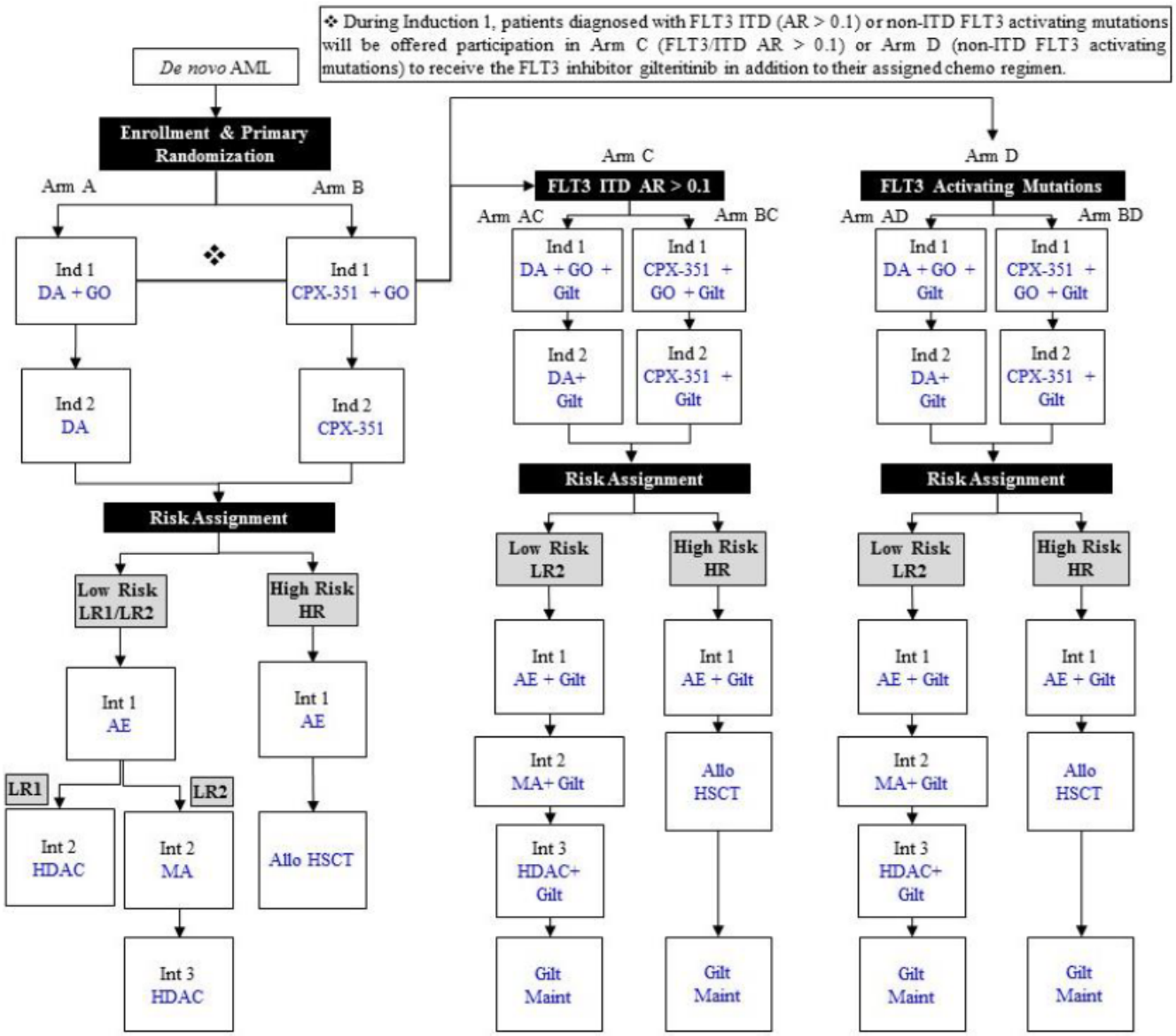
[1] If BM unattainable, submit 3-10 mL of PB in SM.
[2] Only if leukopheresis or exchange transfusion is performed for clinical indications. See Section IX for details.

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

BIOLOGY REQUIREMENTS:
Required material for Pathology Review – see Section 13.2.3

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 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.

Safety Phase – Modified Rolling 6 Design	
DL-1	DA + GO or CPX-351 + GO with **Gilteritinib: 1 mg/kg/dose daily (60 mg max dose)**
DL 0	DA+GO or CPX-351 + GO with **Gilteritinib: 1.5 mg/kg/dose daily (90 mg max dose)**
DL 1 (Starting dose)	DA+GO or CPX-351 + GO with **Gilteritinib: 2 mg/kg/dose daily (120 mg max dose)**

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