COG-ANBL2131: A Phase 3 Study of Dinutuximab Added to Intensive Multimodal Therapy for Children with Newly Diagnosed High-Risk Neuroblastoma

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. Enrollment on APEC14B1 and Sample Submissions for Molecular Testing

All patients must be consented and enrolled on Project:EveryChild (APEC14B1) Part A Molecular Characterization Initiative (MCI) prior to enrollment on ANBL2131.

See APEC14B1 Manual of Procedures for required materials for MCI testing performed on APEC14B1.

- **It is strongly recommended that sites submit tissue on APEC14B1 and commence the process of enrollment as soon as a diagnosis of HRNBL is suspected. It is imperative that the appropriate samples for germline testing are submitted with the tumor tissue so that MCI testing is not delayed.**

- *ALK* and *MYCN* testing on this study for treatment randomization stratification will be performed using tumor tissue submitted for APEC14B1. It is **STRONGLY RECOMMENDED** that these specimens are shipped to the BPC within 48-72 hours after the diagnostic procedure occurs**.**

  MYCN testing for ANBL2131 eligibility purposes will not be performed through central *MYCN* testing as part of APEC14B1 and may be performed by the site or at a site-preferred laboratory (see Section 3.1.3.2 for information regarding *MYCN* testing for eligibility). However, these *MYCN* results will not be used for stratification.

  ALK and *MYCN* results are expected to be available within 18 days of receipt of all required materials (tumor and germline sample) by the BPC. Results from the CCDI MCI testing on APEC14B1 will be accessed by sites via a secure web portal. Refer to the APEC14B1 Manual of Procedures for complete details. Molecular Characterization Initiative testing results must be redacted and uploaded to the ANBL2131 CRFs as soon as they are available, and no later than Cycle 1, Day 24. **Hence, it is imperative to submit adequate tumor tissue and a germline sample as soon as possible after the diagnostic confirmation of neuroblastoma has occurred.**

___2. Timing

Patients must be enrolled onto APEC14B1 prior to enrollment on ANBL2131. Once enrolled on APEC14B1, biology results will be returned to the institution. Shortly thereafter, a risk group analysis will be performed based upon the age, stage, and biology results. Risk group assignment will then be made available to the institution.

Consent can be obtained and the patient can be enrolled on both APEC14B1 and ANBL2131 on the same day if the patient is considered to have HRNBL by virtue of BOTH stage (INRG Stage M) and age (≥547 days) prior to release of biology results.
When ANBL2131 enrollment is completed prior to the start of protocol therapy, the date protocol therapy is projected to start must be no later than **five (5)** calendar days after enrollment. In the event that an investigator determines that emergency therapy is required, protocol therapy may start before enrollment on ANBL2131. However, consent for ANBL2131 *must* be obtained prior to start of therapy AND enrollment must take place as soon as possible, but within **five (5)** calendar days of beginning protocol therapy.

For clinically stable patients ≥ 547 days of age who were initially diagnosed with INRG L1 or L2 disease but progress to Stage M, enrollment must take place within 4 weeks of progression to Stage M and prior to the start of ANBL2131 protocol therapy.

Patients < 547 days of age with INRG Stage M or MS disease and patients of any age with INRG L2 disease will only be eligible for this study with documentation of *MYCN* amplification obtained from testing by site-preferred laboratory prior to enrollment (see Section 3.1.3.2). For these patients for whom *MYCN* status is required to determine eligibility, but in whom the index of suspicion for high-risk disease is high and emergency therapy is clinically indicated, therapy as per ANBL2131 may be initiated prior to enrollment. However, consent for ANBL2131 *must* be obtained prior to start of therapy. Enrollment to ANBL2131 must take place when *MYCN* amplification has been documented by testing in site-preferred laboratory within **fourteen (14)** calendar days of beginning the emergent ANBL2131 protocol therapy.

For clinically stable patients initially thought to have non-high-risk disease but subsequently found to have *MYCN* amplified tumors on testing in site-preferred laboratory, study enrollment must occur after a maximum of **one (1)** cycle of intermediate-risk chemotherapy and prior to the start of ANBL2131 protocol therapy.

Clinically stable patients initially diagnosed with *MYCN* amplified INRG L1 disease who develop progression to Stage M must be enrolled within 4 weeks of progression and prior to the start of ANBL2131 therapy.

___3. Randomization and Callbacks

There are two Callbacks on ANBL2131:

(1) a Treatment Arm Randomization Callback for all patients
(2) an End of Induction Callback

- Treatment Randomization and Callback
  Random assignment to either Arm A or Arm B will take place after Induction Cycle 1 via Callback through OPEN. **Patients may not proceed to Cycle 2 of Induction until the Treatment Arm Randomization Callback Form has been completed.**

  It is expected that *ALK* and *MYCN* status will be designated prior to the start of Induction Cycle 2 chemotherapy. If a specimen is determined to be inadequate for testing, the treating site will be asked to submit an alternative specimen. In the event that *ALK* or *MYCN* status (obtained as part of APEC14B1) is unknown by Induction Cycle 1, Day 24, then sites will select status "unknown/pending" on the Treatment Arm Randomization Callback Form and proceed with randomization to Arm A or Arm B.

- Callback for End of Induction (EOI) Response Rapid Central Review
  At the EOI, the treating team will complete the Disease Evaluation and Response CRF. If this is an EOI CRF, a rapid central review of EOI response data (*the response evaluation CRF*, *not a central review of the images or bone marrows*) will be performed by the study committee to confirm the institutional designation of GEIR vs. PEIR. Once the review is complete, sites will be notified of the outcome of submitted data. Sites must complete Callback through OPEN before proceeding to the next phase of therapy:
  - Extended Induction if rapid review confirms PEIR on Arm A or B;
  - Consolidation if rapid review confirms GEIR on Arm A or B

___4. Laboratory Studies

All laboratory studies to determine eligibility must be performed within 7 days prior to *enrollment* unless otherwise indicated.

The following laboratory studies must be repeated prior to the *start of protocol therapy* if >7 days have elapsed from their most recent prior assessment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. Laboratory tests need not be repeated if therapy starts within seven (7) days of their most recent prior assessment.

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 for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

___5. **Clinical Studies**
Clinical studies (eg, cardiac imaging, pulmonary function tests), if applicable, must be obtained within 14 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

___6. **Disease/Staging Imaging**
Disease/staging imaging studies, with the exception of ^{123}I-MIBG or PET scans, if applicable, must be obtained within 14 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

For patients who received a single cycle of intermediate risk therapy prior to enrollment, imaging studies and bone marrow aspirates/biopsies must have been obtained within 21 days prior to the start of protocol therapy on ANBL2131 (repeat if necessary).

Note: Baseline ^{123}I-MIBG scans and PET scans, if applicable, can be obtained after the start of protocol therapy if unavailable prior to the start of therapy. If performed prior to start of therapy, then these scans must be performed within 14 days prior to start of therapy. If performed after start of therapy, then these scans should be performed within 14 days after the start of Cycle 1, but this timing will not impact eligibility.

___7. Curie Scoring Curie scoring will be determined by local institutions and retrospectively by a central imaging review committee. Determination of the Curie score will rely primarily on planar imaging, with SPECT imaging used to resolve any equivocal findings. Curie scoring will not be performed for patients who are found to have MIBG non-avid disease at diagnosis.
When a MIGB study is scheduled, please write 'please provide Curie scores' in the comment section.

See Section 4.2.2 for required studies to be obtained prior to starting protocol therapy.

Inclusion Criteria

___8. Enrollment on APEC14B1
Patients must be enrolled on APEC14B1 and have consented to testing through the Molecular Characterization Initiative (MCI), prior to enrollment on ANBL2131.

___9. Age
≤ 30 years at the time of initial diagnosis with high-risk disease

___10. Diagnosis

i. Must have a diagnosis of NBL or ganglioneuroblastoma (nodular) verified by tumor pathology analysis or demonstration of clumps of tumor cells in bone marrow with elevated urinary catecholamines

ii. Newly diagnosed, HRNBL defined as one of the following:

a. Any age with International Neuroblastoma Risk Group (INRG) Stage L2, MS, or M **and** *MYCN* amplification

b. Age ≥ 547 days and INRG Stage M regardless of biologic features (clinical *MYCN* testing not required prior to enrollment)

c. Any age initially diagnosed with INRG Stage L1 *MYCN* amplified NBL who have progressed to Stage M without systemic chemotherapy

d. Age ≥ 547 days of age initially diagnosed with INRG Stage L1, L2, or MS who have progressed to Stage M without systemic chemotherapy (clinical *MYCN* testing not required prior to enrollment)

See Appendix III for INRG Staging System.

See Section 3.1.3.2 for *MYCN* testing requirements to determine eligibility (if required to satisfy eligibility requirement) and information on central review of *MYCN* testing results that will occur through APEC14B1.

___11. BSA
Patients must have a BSA ≥ 0.25 m^2

___12. Prior Therapy
- No prior anti-cancer therapy except as outlined below:
  - Patients initially recognized to have high-risk disease treated with topotecan/cyclophosphamide initiated on an emergent basis and within allowed timing, and with consent as described in Section 3.1.5.
  - Patients observed or treated with a single cycle of chemotherapy per a low or intermediate risk neuroblastoma regimen (eg, as per ANBL0531, ANBL1232 or similar) for what initially appeared to be non-high-risk disease but subsequently found to meet the criteria in Section 3.2.3.
  - Patients who received localized emergency radiation to sites of life-threatening or function-threatening disease prior to or immediately after establishment of the definitive diagnosis.

___13. HIV
HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

___14. Organ Function Requirements
- Adequate renal function defined as:
  - A serum creatinine based on age/sex as follows:

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
1 month to < 6 months	0.4	0.4
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

OR - a 24-hour urine creatinine clearance ≥ 70 mL/min/1.73 m^2

OR - a GFR ≥ 70 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:
  - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
  - SGPT (ALT) ≤ 10 x ULN*

  * *Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L*

- Adequate cardiac function defined as:
  - Shortening fraction of ≥ 27% by echocardiogram, or
  - Ejection fraction of ≥ 50% by echocardiogram or radionuclide angiogram.
- Ability to tolerate Peripheral Blood Stem Cell (PBSC) Collection:
  No known contraindication to PBSC collection. Examples of contraindications might be a weight or size less than the collecting institution finds feasible, or a physical condition that would limit the ability of the child to undergo apheresis catheter placement (if necessary) and/or the apheresis procedure.

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

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

EXCLUSION CRITERIA

___1. Patients who are 365-546 days of age with INRG Stage M and *MYCN* non-amplified NBL, irrespective of additional biologic features.
___2. Patients ≥547 days of age with INRG Stage L2, *MYCN* non-amplified NBL, regardless of additional biologic features.
___3. Patients with known bone marrow failure syndromes.
___4. Patients on chronic immunosuppressive medications (eg, tacrolimus, cyclosporine, corticosteroids) for reasons other than prevention/treatment of allergic reactions and adrenal replacement therapy are not eligible. Topical and inhaled corticosteroids are acceptable.
___5. Patients with a primary immunodeficiency syndrome who require ongoing immune globulin replacement therapy.
___6. 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 prior to enrollment 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.

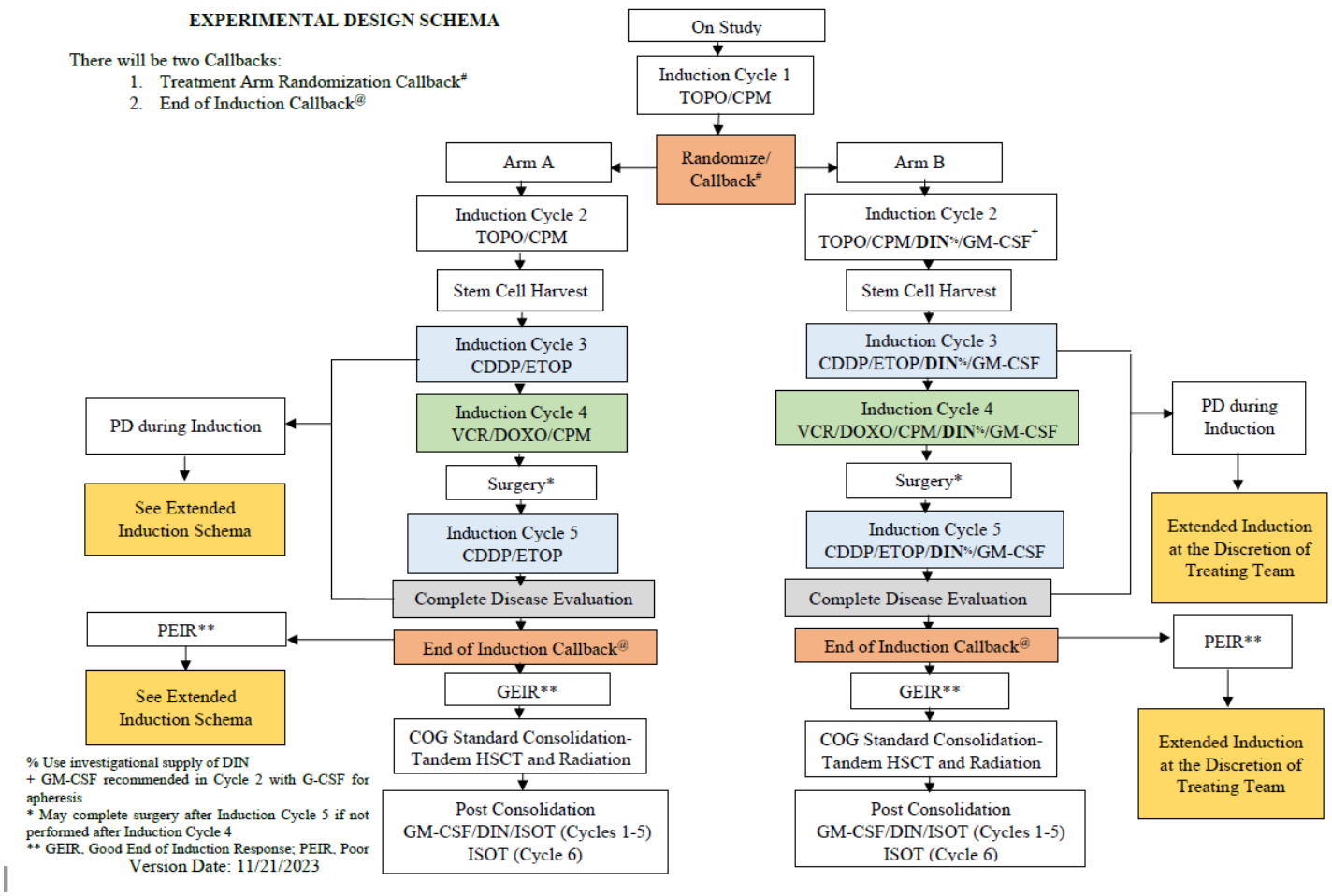
REQUIRED OBSERVATIONS:

Required Observations - Cycle 1 for All Patients

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical exam with vital signs, height, weight, and BSA. Note: Height is only required at the beginning of this cycle.
b. CBC, differential and platelets.
c. Electrolytes, BUN, creatinine, Ca++, PO4, Mg++
d. Total bilirubin, ALT, and AST
e. Urinalysis
f. GFR or creatinine clearance (obtain only if serum creatinine is above maximum for age/sex)
g. ECG
h. ECHO or MUGA
i. Audiogram or BAER (may be obtained during Cycle 1 or 2)
j. Bilateral bone marrow aspirates and biopsies (submit for central review; see Section 14.1.4)
k. Cross-sectional tumor imaging with CT/MRI (submit for central review; see Section 16.6)
l. ^{123}I-MIBG scan may be obtained within 14 days of starting treatment during Cycle 1 (**submit for central review; see Section 16.6**)
m. ^{18}F-FDG-PET scan for patients with ^{18}I-MIBG non-avid disease may be obtained within 14 days of starting treatment during Cycle 1 (**submit for central review; see Section 16.6**)
n. TSH/Free T4
o. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment.
p. Specimens for correlative studies. See Section 15.2 and Appendix X for specimen requirements.
q. Specimens for whole exome sequencing of diagnostic tumor and germline as part of APEC14B1 MCI, should be submitted 48-72 hours after diagnostic procedure. See Section 15.1.
r. Household Survey should be collected any time from enrollment until Day 14 of Cycle 1 (See Section 15.3.3).
s. Memorial Symptom Assessment Scale (Pediatric-MSAS) (may be collected any time from Cycle 1, Day 1 +/- 2 weeks; See Section 15.3)

TREATMENT PLAN:



TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

SPECIMEN REQUIREMENTS:
See APEC14B1 Manual of Procedures for required materials for MCI testing performed on APEC14B1.

BIOLOGY REQUIREMENTS:
Tumor and germline DNA obtained at diagnosis as part of APEC14B1 may be used. **All other specimens described in the following section are to be obtained <u>in addition to</u> samples submitted as part of APEC14B1 unless otherwise specified.** Each of these correlative studies is **<u>optional, but strongly encouraged</u>**.

Correlative Studies: Induction

	Time point	Sample Type	Total Volume	Quantity	Tube Type / Sample Prep	Notes	Destination lab	Section Number
CORRELATIVE STUDIES: INDUCTION	Diagnosis/ Pre-Tx	Tumor Tissue	-	2 slides	2 H&E stained slides		BPC	15.2.6.4
			-	6 slides	3-5 unstained slides AND 1 H&E stained slide	Ship within 4-6 weeks from surgical procedure	Goldsmith Lab	15.2.2
			-	5 slides	5 unstained slides		BPC	15.2.5
		Blood	4 mL	1 tube	Sodium heparin (green top)	Process for plasma	BPC	15.2.6.2
			8 mL	2 tubes (4 mL in each tube)	Sodium heparin (green top)	Same day shipping; 5 mL minimum	Goldsmith Lab	15.2.4
			6-10 mL	1 tube	CellRescue tube	Same day shipping	Crompton Lab	15.2.3
			6-10 mL	1 tube	Streck tube		BPC	15.2.6.5
			2.5 mL	1 tube	PAXgene RNA		BPC	15.2.5
		Bone Marrow	2 mL	1 tube	PAXgene bone marrow RNA		BPC	15.2.6.1

See Appendix X for Optional Correlative Biology Studies at timepoints during therapy.

<u>Maximum Blood Draw Volumes</u>

Age	Allowable blood volume drawn within 24 hours	Allowable blood volume drawn within 30 days
Newborn - < 3 months	2.25 mL/kg	4.5 mL/kg
≥ 3 months - < 18 years	2 mL/kg	4 mL/kg

Adults ≥ 18 years may have up to the lesser of 12 mL/kg, or 550 mL, drawn in an 8 week period.