

**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 Eligibility Screening and 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 concurrently with the tumor tissue so that MCI testing is not delayed.

ALK and MYCN testing for treatment randomization stratification on ANBL2131 and for eligibility determination for ANBL1531 Arm E will be performed using tumor tissue submitted for APEC14B1 MCI testing; outside testing results will not be accepted. It is STRONGLY RECOMMENDED that these specimens are shipped to the BPC within 48-72 hours after the diagnostic procedure occurs. Submission of frozen tumor tissue is strongly encouraged to facilitate ALK testing; use of an alternative source of tumor material, such as bone marrow, for such testing is expected to be a rare occurrence. Additional samples to support correlative biology work on ANBL2131 are outlined in Section 15 and Appendix X.

ALK and MYCN testing results for stratification on ANBL2131 and eligibility determination for ANBL1531 Arm E are expected to be available within 18-21 days of receipt of sufficient samples for 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. The MCI Somatic Disease/Germline Comparator Exome (SDGC) Clinical Report must be redacted and uploaded to the ANBL2131 CRFs as soon as the report is available, and no later than Cycle 1, Day 24 (see Section 3.1.7.1 for information regarding process for Treatment Arm Randomization Callback

- ___ 2. Timing Patients must be enrolled onto APEC14B1 prior to enrollment on ANBL2131 and patients must consent to participate in Eligibility Screening and MCI. Once enrolled on APEC14B1, risk classification will be returned to the institution but this is not required to have been completed prior to enrollment on ANBL2131.

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, prior to the start of ANBL2131 protocol therapy, and within 6 months of original diagnosis.

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 3.1.3.1). 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 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 may only take place when MYCN amplification has been confirmed by APEC14B1 central review of the site-preferred laboratory report and 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 confirmed MYCN amplified tumors after APEC14B1 central review of the site-preferred laboratory testing results, study enrollment must occur after a maximum of one (1) cycle of intermediate-risk chemotherapy and prior to the start of ANBL2131 protocol therapy.

If a patient who is ≥ 547 days is diagnosed with neuroblastoma or nodular ganglioneuroblastoma (unfavorable subtype) and is believed to have INRG Stage L1 or L2 disease, but has not yet completed the metastatic work-up (123I-MIBG or 18F-FDG PET, bilateral bone marrow aspirates and biopsies), administration of one (1) cycle of intermediate-risk chemotherapy will not preclude eligibility for this trial. If the patient is found to have Stage M disease, 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, prior to the start of ANBL2131 therapy, and within 6 months of original diagnosis. Enrollment to ANBL2131 may only take place when MYCN amplification has been confirmed by APEC14B1 central review of the site-preferred laboratory report.

All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

3. Randomization and Callbacks

There are three Callbacks on ANBL2131:

- (1) a Treatment Arm Randomization Callback for all patients
- (2) an End of Induction Callback
- (3) an End of Extended 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.** However, patients \geq 1 year of age whose tumors are determined to have an ALK aberration prior to Induction Cycle 2 will be removed from ANBL2131 protocol therapy (see Section 8.1) prior to randomization and will be offered treatment on ANBL1531 Arm E until the required number of patients have been accrued to ANBL1531 Arm E.

* See 3.1.7.1 for definition and steps for randomization call back

- The MCI results (including ALK and MYCN status for stratification purposes and eligibility for ANBL1531 Arm E) are expected to be designated prior to the start of Induction Cycle 2 chemotherapy. The Central Review Form MCI Report will be completed by the IGM on or before Induction Cycle 1, Day 24. In the event that the MCI results (obtained as part of APEC14B1) are unknown by Induction Cycle 1, Day 24, the IGM central reviewers will select status “unknown/pending” for ALK and/or MYCN on the Central Review Form MCI Report
- For patients with ALK and/or MYCN status of “unknown/pending”, a Central Review Form MCI Report must still be completed by the IGM before the Treatment Arm Randomization Callback can be completed. The site will receive notification that the Central Review Form MCI Report has been completed. The site will then complete the Stratum Assignment Prior to Callback CRF in Rave, and subsequently the Treatment Arm Randomization Callback Form in OPEN 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. A rapid central review of EOI response data (the Disease Evaluation and Response CRF, not a central review of the images or bone marrows) will be performed by the study committee to confirm the institutional designation of the revised International Neuroblastoma Response Criteria (INRC) overall response and GEIR vs. PEIR. In order for the EOI rapid central review of response data to be completed, the Disease Evaluation and Response CRF at both Baseline AND the EOI must be completed. Once the treating team completes the Disease Evaluation and Response CRF at the EOI, the study team will be notified and will complete the Central Review Disease Evaluation CRF. When the rapid central review is complete, sites will be notified via email of the outcome of submitted data. Sites must then complete the EOI Callback through OPEN before proceeding to the next phase of therapy:
 - Extended Induction for patients with PD during Induction Cycles 3-5;
 - Extended Induction if rapid review confirms PEIR on Arm A or B;
 - Consolidation if rapid review confirms GEIR on Arm A or B.

Callback at End of Induction must occur before proceeding to either Extended Induction or Consolidation.

Callback for End of Extended Induction For patients who receive Extended Induction, there will be another callback via OPEN in which sites must input information indicating that the patient has completed Extended Induction therapy (ie, when the patient stops the use of investigational dinutuximab).

___ 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 123I-MIBG or PET scans, if applicable, and bone marrow aspirates/biopsies must be obtained within 14 days prior to enrollment and start of protocol therapy (repeat if necessary).

___ 7. 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).

___ 8. Note: Baseline 123I-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.

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

Inclusion Criteria

Enrollment on APEC14B1 Patients must be enrolled on APEC14B1 and have consented to Eligibility Screening and 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 and within 6 months of original diagnosis
 - 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) and within 6 months of original diagnosis

See Appendix III for INRG Staging System.

See Section 3.1.3.1 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 Eligibility Screening

11. BSA
Patients must have a BSA ≥ 0.25 m².

12. Prior Therapy

- No prior anti-cancer therapy except as outlined below:
 - o 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.
 - o 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.
 - o 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
Known 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

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

OR - a 24-hour urine creatinine clearance ≥ 70 mL/min/1.73 m²

OR - a GFR ≥ 70 mL/min/1.73 m². 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 $\geq 27\%$ by echocardiogram, or
 - Ejection fraction of $\geq 50\%$ 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:

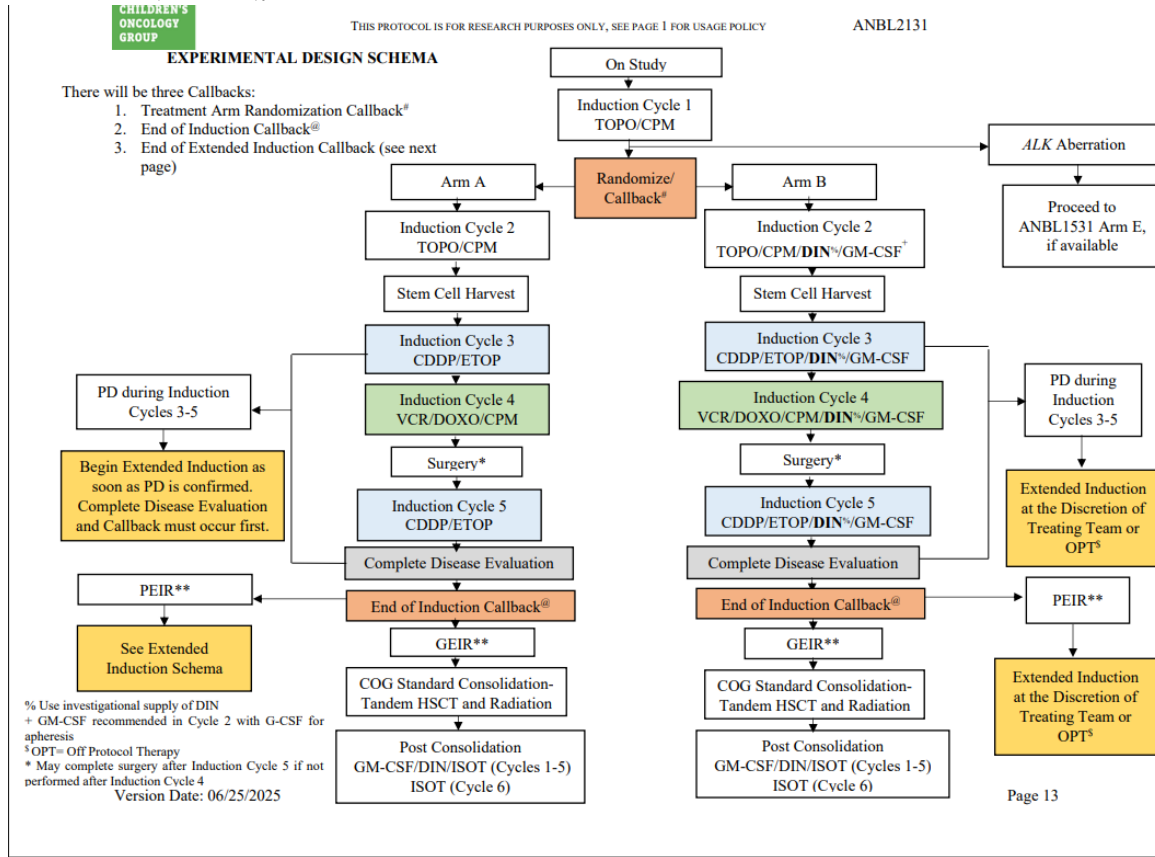
Required Observations - Cycle 1 for All Patients

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 14.1.2](#))
- k. Cross-sectional tumor imaging with CT or MRI (submit for central review; see [Section 16.6](#))
- l. ¹²³I-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 ^{125}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:



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 in addition to samples submitted as part of APEC14B1 unless otherwise specified.** Each of these correlative studies is **optional, but strongly encouraged**.

Correlative Studies: Induction

Every effort should be made to obtain samples from all timepoints, including the diagnosis time point. If the diagnostic timepoint needs to be collected after starting therapy for any reason, including blood volume constraints, contact the receiving laboratory to arrange a suitable timeframe for collection. Please add a comment to the specimen transmittal form if blood is collected after treatment starts. **However, if the diagnosis sample cannot be obtained, subsequent samples should still be collected as specified below. See collection prioritization list in [Section 15.2](#).**

The blood samples for circulating tumor cells ([Section 15.2.3](#)) and immune function profiling ([Section 15.2.4](#)) must be shipped **fresh** directly to the associated laboratory. Each sample should be shipped on the same day it is obtained, via overnight courier, and the laboratory should be notified. See specific details in Sections [15.2.3](#) and [15.2.4](#).

Time point	Sample Type	Total Volume	Quantity	Tube Type / Sample Prep	Notes	Destination lab	Section Number	
CORRELATIVE STUDIES: INDUCTION	Diagnosis	Tumor Tissue	-	7 slides	2 H&E stained slides AND 5 (5 µm) unstained sections on charged slides		BPC	15.2.5.4
			-	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	15.2.5.2	
		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	15.2.5.5	
		2.5 mL	1 tube	PAXgene RNA		BPC	15.2.5	

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

