

**COG-ANBL1531: A Phase 3 Study of ¹³¹I-Metaiodobenzylguanidine (¹³¹I-MIBG) or
ALK Inhibitor Therapy Added to Intensive Therapy for Children with Newly Diagnosed High-Risk
Neuroblastoma (NBL) (IND# 134379)**

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 or ANBL00B1

Patients must be enrolled on APEC14B1 or ANBL00B1 prior to enrollment on ANBL1531.

- **It is strongly recommended that sites submit tissue on APEC14B1 or ANBL00B1 and commence the process of enrollment as soon as a diagnosis of high-risk neuroblastoma is suspected.**
- **Sites should receive notification of *MYCN* results within 7 days of receipt of adequate tumor specimens.**

___ 2. Mandatory *MYCN* testing for patients with localized disease and for patients 365-547 days of age with metastatic disease

To be eligible for ANBL1531, patients over 365 days of age with INRG L2 tumors and patients 365-547 days of age with metastatic disease must have *MYCN* amplified tumors (see Section 3.2.3). For patients whose eligibility for this trial depends upon *MYCN* status, every effort should be made to send specimens for *MYCN* testing as quickly as possible post-biopsy.

___ 3. Timing

Patients must be enrolled onto APEC14B1 or ANBL00B1 prior to the time of enrollment on ANBL1531. Once enrolled on APEC14B1 or ANBL00B1, biology results will be entered by the Neuroblastoma Reference Lab when available to be viewed by the institution. Shortly thereafter, the Neuroblastoma Tracking Center will perform the Risk Group Analysis based upon the age, stage, and biology results. Risk group assignment will then be made available to the institution. In emergency situations (or if in the opinion of the treating physician, it is in the patient's best interest) consent can be obtained and the patient can be enrolled on both APEC14B1 or ANBL00B1 and ANBL1531 on the same day if the patient is considered to have high risk neuroblastoma by virtue of BOTH stage (INRG Stage M) and age (>547 days) prior to submission of biology results by the Neuroblastoma Reference Lab.

___ 4. Treatment Assignment Overview and Callback Requirement

Non-random assignment to the ALK inhibitor therapy arm (Arm E) will take place as soon as documentation of an *ALK* aberration is available. Also see Section 3.1.7

___ 5. Staged Consent

An initial study consent will be obtained at study entry that provides details of the overall study design, but focuses on tumor testing for arm assignment and on the therapy to be delivered during up to 2 cycles of chemotherapy during Induction. Once *ALK* status and MIBG avidity status are known, patients will be offered participation in the following parts of the study based upon criteria in Section 4.1.1. Separate informed consent documents will be used.

- Non-random assignment to ALK inhibitor therapy arm for patients with *ALK* aberrant disease as defined in Section 3.1.7
- Non-random assignment to MIBG non-avid arm (see Section 3.1.7)
- Randomized portion of the study (patients with MIBG avid disease who do not meet criteria for assignment to the ALK inhibitor therapy arm or the MIBG non-avid arm)

Patients who qualify for a specific portion of the study, but decline participation in that portion of the study will be removed from protocol therapy. For example, a patient with tumors harboring a qualifying *ALK* aberration (see Section 3.1.7) and MIBG avid disease who declines participation in the ALK inhibitor therapy arm may **not** seek participation in the randomized portion of the study.

Patients may not proceed beyond Cycle 2 of Induction and remain on study without completing this second informed consent process.

6. Patient Eligibility Criteria

All clinical and 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 >7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: 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. Imaging studies and bone marrow aspirates/biopsies must be obtained within 2 weeks prior to start of protocol therapy (repeat if necessary). For patients who underwent an upfront resection of the primary tumor instead of biopsy and 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 3 weeks of the start of protocol therapy.

Note: The timing of baseline MIBG scans (and PET scans if the subject is found to have MIBG non-avid disease) is an exception to this rule. These scans must be performed within 14 days prior to or 14 days after the start of Cycle 1. Baseline audiogram or BAER must also be obtained before the end of Cycle 1.

7. Age - Patient must be ≥ 365 days and ≤ 30 years of age at diagnosis.

8. Diagnosis

Patients must have a diagnosis of neuroblastoma or ganglioneuroblastoma (nodular) verified by tumor pathology analysis or demonstration of clumps of tumor cells in bone marrow with elevated urinary catecholamine metabolites. The following disease groups are eligible:

- Patients with **INRG Stage M** disease are eligible if found to have either of the following features:
 - a) *MYCN* amplification (> 4-fold increase in *MYCN* signals as compared to reference signals), regardless of age or additional biologic features; OR
 - b) Age > 547 days regardless of biologic features;
 - Patients with **INRG Stage MS** disease with *MYCN* amplification
 - Patients with **INRG Stage L2** disease with *MYCN* amplification
 - Patients > 547 days of age initially diagnosed with INRG Stage L1, L2 or MS disease who progressed to Stage M without prior chemotherapy may enroll within 4 weeks of progression to Stage M.
 - Patients ≥ 365 days of age initially diagnosed with *MYCN* amplified INRG Stage L1 disease who progress to Stage^oM without systemic therapy may enroll within 4 weeks of progression to Stage M.
- See Appendix III for INRG Staging System.

9. Prior Therapy

Patients initially recognized to have high-risk disease must have had no prior systemic therapy (other than topotecan/cyclophosphamide initiated on an emergent basis and within allowed timing 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 (e.g., 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 will also be eligible. Patients who receive localized emergency radiation to sites of life-threatening or function-threatening disease prior to or immediately after establishment of the definitive diagnosis will be eligible.

10. Organ Function Requirements

- Adequate renal function defined as:
 - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m² or
 - A serum creatinine based on age/sex as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
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.

- Adequate liver function defined as:
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
 - SGPT (ALT) < 10 x ULN. For the purposes of this study, ULN for SGPT (ALT) is 45.
- Adequate cardiac function defined as:
 - Shortening fraction of $\geq 27\%$ by echocardiogram, or
 - Ejection fraction of $> 50\%$ by echocardiogram or radionuclide angiogram.
- Ability to tolerate 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.

EXCLUSION CRITERIA:

- ___ 1. Patients who have an INRG Stage L2 tumor without amplification of *MYCN* regardless of tumor histology (may meet criteria for may meet criteria for high risk classification but are not eligible for this trial).
- ___ 2. Patients with bone marrow failure syndromes
- ___ 3. Patients for whom targeted radiopharmaceutical therapy would be contraindicated due to underlying medical disorders.
- ___ 4. Pregnancy and Breast Feeding
 - 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.

REQUIRED OBSERVATIONS:

Required Observations in Induction Cycle 1

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

- Physical exam, height, weight
- CBC with differential and platelets
- Electrolytes, BUN, creatinine, magnesium, phosphorous
- ALT, AST, total bilirubin
- PT/INR
- Free T4, TSH
- Urinalysis
- Pregnancy test (obtain for females of childbearing potential)
- GFR or creatinine clearance (obtain if serum creatinine is above maximum for age/sex)
- ECG
- ECHO or MUGA
- Audiogram or BAER (may be obtained during Cycle 1 therapy)
- Cross sectional tumor imaging (MRI or CT) (for central review as soon as scan is obtained)
- MIBG scan – may be obtained during the first two weeks of Cycle 1 in the case of logistical constraints (submit for central review as soon as scan is obtained)
- Curie score profile (patients with MIBG avid disease; see Appendix IX for worksheet) (obtain and submit for central review)
- FDG-PET scan for patients with MIBG non-avid disease -- may be obtained during the first or second week of Cycle 1 in the case of logistical constraints. Submit for central review.
- Bilateral bone marrow aspirates and biopsies
- Specimens for correlative studies (see Appendix II for specimen requirements)
- Household Material Hardship survey (may be collected any time from enrollment until the start of Induction Cycle 2; See Section 15.3).

Please note: data regarding urinary catecholamine levels are not being collected for research purposes during this trial. Institutional guidelines regarding catecholamine monitoring should be followed

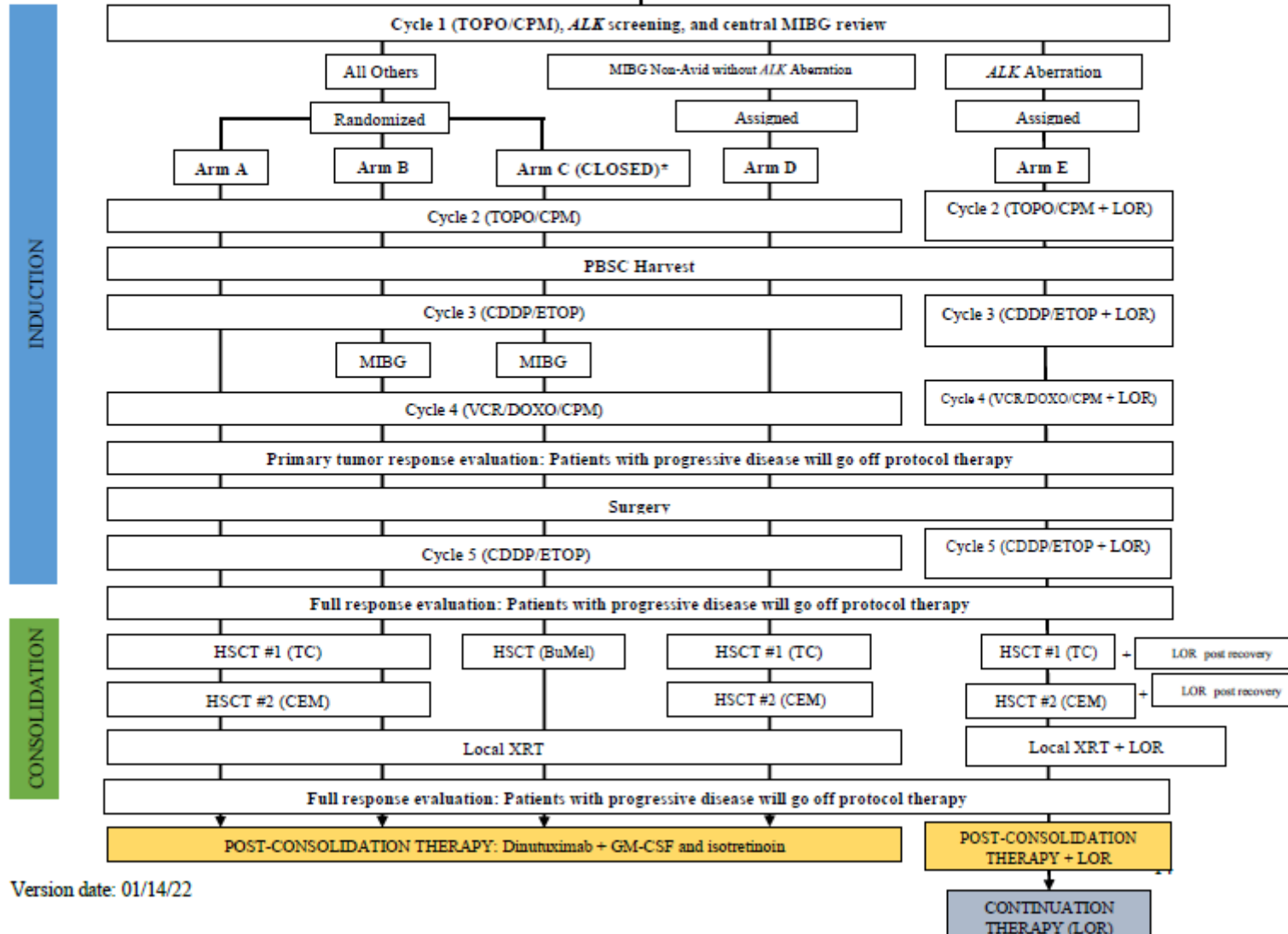
TREATMENT PLAN:



THIS PROTOCOL IS FOR RESEARCH PURPOSES ONLY, SEE PAGE 1 FOR USAGE POLICY

ANBL1531

SCHEMA



Version date: 01/14/22

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

SPECIMEN REQUIREMENTS:

Specimen Submission

The following specimens are projected to be submitted within 14 days of the definitive diagnostic procedure as per APEC14B1 or ANBL00B1.

Required Testing Performed using Materials Submitted on APEC14B1 or ANBL00B1 (see biology protocol for complete instructions)

Sample	Study	Ship To
<ul style="list-style-type: none"> • 2 H&E stained slides of tumor from each block • 10 unstained slides • Optional: additional paraffin embedded blocks 	Pathology Review	Neuroblastoma Reference Laboratory
Snap frozen tumor tissue (See biology protocol for guidance regarding rare cases in which no frozen tumor is available)	<i>MYCN, ALK</i>	Neuroblastoma Reference Laboratory
Block or scrolls and H&E stained slide (with biology study chair permission in rare cases in which frozen tumor is not available)	<i>MYCN</i>	Neuroblastoma Reference Laboratory
Involved bone marrow (relevant to this study only if frozen tumor is unavailable and marrow involvement is extensive). Samples with low tumor content may be indeterminate for this testing	<i>MYCN, ALK</i>	Neuroblastoma Reference Laboratory

Note that these materials are the minimum required for pre-enrollment eligibility screening. *ALK* testing required for arm assignment on this study will be performed using tumor submitted for APEC14B1/ANBL00B1 if these specimens are adequate. Submission of frozen tumor tissue is strongly encouraged to facilitate *ALK* testing and arm assignment; use of an alternative source of tumor material for such testing is expected to be a rare occurrence. **Additional samples to support correlative biology work on ANBL1531 are outlined in Section 15 and Appendix II.**

BIOLOGY REQUIREMENTS:

See Appendix II