COG-ANBL1531: A Phase 3 Study of ^{131}I-Metaiodobenzylguanidine (^{131}I-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:

<u>Important note</u>: 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. <u>Enrollment on APEC14B1 -MCI</u>

Patients must be enrolled on APEC14B1-MCI prior to enrollment on ANBL1531.

- **It is strongly recommended that sites submit tissue on APEC14B1 and commence the process of enrollment <u>as soon as a diagnosis of high-risk neuroblastoma is suspected</u>.**

___2. Mandatory *MYCN* testing for patients with localized disease and for patients <547 days of age with metastatic disease

___3. Specimen Submission

See the APEC14B1 Manual of Procedures for a full list of detailed instructions for submitting required materials and for shipping details.

Additional samples to support correlative biology work on ANBL1531 are outlined in Section 15 and Appendix II

For patients transferring from ANBL2131 to ANBL1531 Arm E after one cycle of therapy on ANBL2131, additional samples for molecular testing are not required at time of transfer to ANBL1531 Arm E. Instead, baseline tissue submission and ALK testing will have been performed in the context of APEC14B1/ANBL2131. Other testing indicating the presence of a qualifying ALK aberration will not be accepted.

Mandatory MYCN testing for patients with localized disease and for patients <547 days of age with metastatic disease. For patients originally enrolled to ANBL2131, MYCN testing that qualified a patient as having high-risk disease for enrollment to that trial will be acceptable for the purposes of transferring to Arm E of ANBL1531.

___4. <u>Timing</u> for patients enrolling onto ANBL 1531 without prior ANBL2131 enrollment.

Patients must be enrolled onto APEC14B1 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.

___5. <u>Timing for Patients Transferring to ANBL1531 Arm E from ANBL2131</u>

Patients transferring to ANBL1531 Arm E from ANBL2131 may enroll after no more than one cycle of therapy on ANBL2131 and prior to randomization on ANBL2131. Centralized ALK testing will have been completed prior to transfer to ANBL1531 Arm E. Patients who have completed the randomization process on ANBL2131 are not eligible to transfer to ANBL1531 Arm E even if a qualifying ALK aberration is subsequently reported post-randomization.

___6. 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. For patients transferring from ANBL2131 to ANBL1531 Arm E, the transfer will take place after no more than one cycle of therapy on ANBL2131.

Definition of an ALK aberration conferring eligibility for assignment to Arm E is as follows:

1. **ALK mutation**: Pathogenic or likely pathogenic activating ALK tyrosine kinase domain mutation with VAF ≥ 5%. If the reference lab identifies an ALK variant of unclear significance, the data will be reviewed by an expert panel (includes a structural biochemist and chemical bioengineering experts with extensive experience modeling new variants in known oncogenes) in real-time to determine the functional consequences of the variant. If the aberration is deemed likely pathogenic, it will be designated as a variant that qualifies the patient for assignment to Arm E.

OR

2. **ALK amplification:** a. Pre-Amendment 13C: >10 copies of the ALK gene detected by central FISH testing performed as part of ANBL1531 b. Amendment 13C and later: ALK amplification as detected by the Molecular Characterization Initiative's tumor normal whole exome sequencing approach at the Institute for Genomic Medicine performed for patients enrolled initially to APEC14B1 and ANBL2131

For patients whose tumors lack the findings listed above and for those in whom ALKtesting cannot be performed, non-random assignment to the MIBG non-avid arm (Arm D) will be made once the baseline 123I-MIBG scan has been centrally reviewed and designated as MIBG non-avid.

For patients enrolled initially to ANBL1531, nonrandom assignment will take place via the callback form in OPEN. For patients enrolled initially to ANBL2131 and transferring to ANBL1531 Arm E, nonrandom assignment to Arm E will take place directly upon enrollment to ANBL1531.

Randomization for patients who do not meet criteria for assignment to Arm D or Arm E is intended to take place by the end of Induction Cycle 1 and prior to the beginning of Induction Cycle 2. If determination of ALK status is delayed, randomization will be delayed until ALK status is finalized. Treatment randomization for these patients will be accomplished by completing the Randomization Callback form in OPEN. **Patients may not proceed beyond Cycle 2 of Induction until the Randomization Callback form has been completed and appropriate consent has been obtained (see below)**.

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___7. Staged Consent
Patients Enrolling onto ANBL1531 without Prior ANBL2131 Enrollment 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
• 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.

Patient Eligibility Criteria for Patients transferring to ANBL1531 Arm E from ANBL2131 9effectived with Amendment 13C(see section 3.3.

___**8. Patient Eligibility Criteria for Patients Enrolling on to ANBL1531 without prior ANBL2131 enrollment**
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.

___9. Age - Patient must be ≥ 365 days and ≤ 30 years of age at diagnosis.

___10. 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°M without systemic therapy may enroll within 4 weeks of progression to Stage M.
  See Appendix III for INRG Staging System.

___11. 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.

___12. Organ Function Requirements

- Adequate renal function defined as:
  – Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 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 ≥ 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:

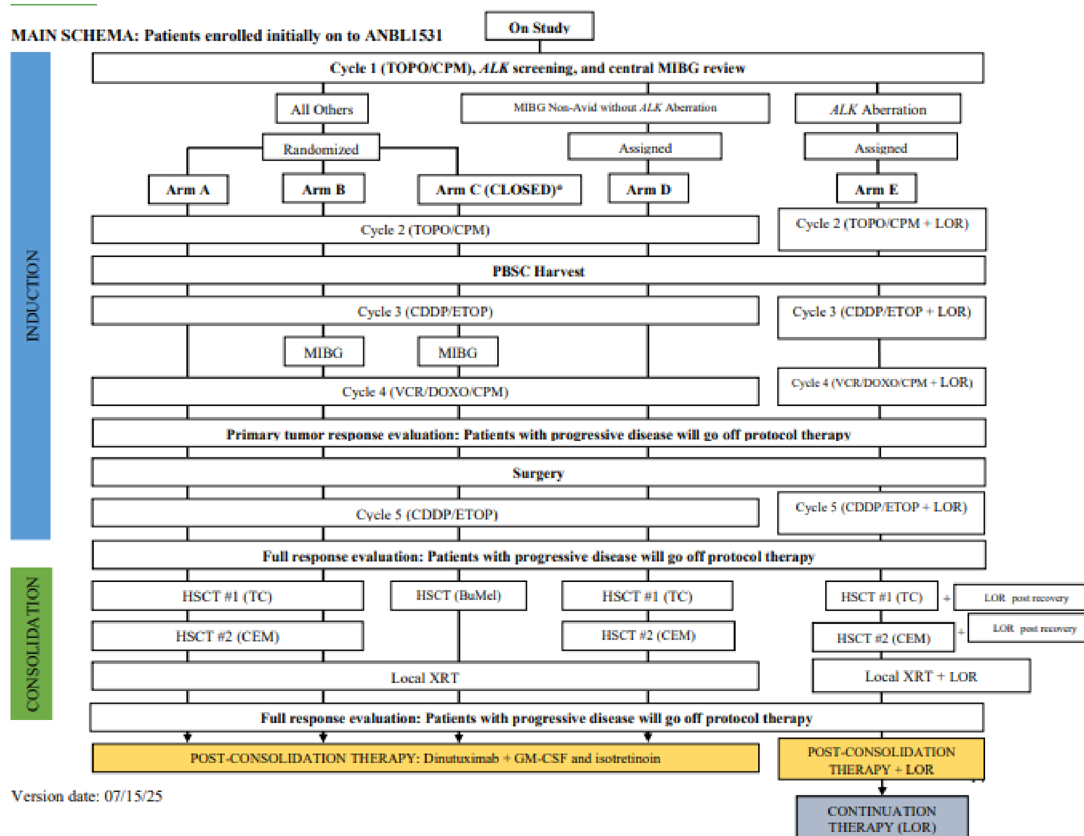
Required Observations in Induction Cycle 1

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:



TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5

SPECIMEN REQUIREMENTS: See APEC14B1 MOP
Specimen Submission
The following specimens are projected to be submitted within 14 days of the definitive diagnostic procedure as per APEC14B1.

Additional samples to support correlative biology work on ANBL1531 are outlined in Section 15 and Appendix II.

BIOLOGY REQUIREMENTS:
See Appendix II