

**COG-ANBL1232: Utilizing Response- and Biology-Based Risk Factors to Guide Therapy
in Patients with Non-High-Risk Neuroblastoma**

FAST FACTS

Eligibility Reviewed and Verified By

MD/DO Date _____

RN 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. Prior to obtaining informed consent and enrolling a patient, a reservation must be made.
- ___2. Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system in OPEN. Prior to discussing protocol entry with the patient, site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available for the patient. Once a slot-reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.
- ___3. Enrollment on ANBL00B1 OR APEC14B1 is required for all newly diagnosed patients within 21 days of the definitive diagnostic procedure.
- ___4. Tissue procurement for ANBL00B1 OR APEC14B1 is **NOT** required for patients in Group A and those Group C patients detailed below:
 - **Group A:** Patients will not undergo tumor biopsy and will have the requirement for tissue submission on ANBL00B1 OR APEC14B1 waived.
 - **Group C:** Patients with Stage Ms disease, < 3 months of age with existing or evolving hepatomegaly and/or symptoms OR symptomatic patients 3 - 12 months of age deemed too ill to undergo an open diagnostic biopsy must enroll onto ANBL00B1 OR APEC14B1 but will not be required to submit tissue provided that exam and/or imaging studies are consistent with the diagnosis of neuroblastoma. Enrollment on ANBL00B1 OR APEC14B1, regardless of tissue submission, must occur prior to the start of chemotherapy.
- ___5. Tissue procurement for ANBL00B1 OR APEC14B1 is **MANDATORY** for all Group B patients and Group C patients not included in the description above. All patients with Stage Ms disease 12 - 18 months of age are required to undergo tumor biopsy and submit tissue as part of ANBL00B1 OR APEC14B1 requirements.
- ___6. See Section 3.1.8 for emergent treatment guidelines.
- ___7. **Disease evaluation (imaging studies and bone marrow aspirate/biopsy, if applicable) must be obtained within 3 weeks prior to start of protocol therapy (repeat if necessary).**
- ___8. **Timing - The institution will be notified of the definitive Treatment Group assignment, as determined by INPC, DNA ploidy, segmental chromosome CGH/SNP analysis, within 21 days of ANBL00B1 OR APEC14B1 specimen submission.**
- ___9. **Age** - Patients must be:
 - < 12 months (< 365 days) of age at diagnosis with INRG Stage L1; or
 - < 18 months (< 547 days) of age at diagnosis with INRG Stage L2 or Stage Ms neuroblastoma/ganglioneuroblastoma.
- ___10. **Diagnosis - Only patients with MYCN non-amplified tumors are eligible for this study.**
 - Group A
Patients < 12 months (< 365 days) of age with newly diagnosed **INRG Stage L1** neuroblastoma/ganglioneuroblastoma who meet the following criteria:
 - Greatest tumor diameter < 5 cm of adrenal or non-adrenal origin.
 - Patients with non-adrenal primaries are eligible, but must have positive uptake on MIBG scan or elevated catecholamine metabolites (urine or serum) to support the diagnosis of neuroblastoma.
 - No prior tumor resection or biopsy.Group A will be further split into two subsets, which are mutually exclusive, for statistical purposes.
 - Group A1:
 - > 6 months and < 12 months of age with an adrenal primary tumor < 5 cm in greatest diameter

- Patients less than 6 months of age with an adrenal primary tumor > 3.1 and < 5 cm in greatest diameter **OR**
 - < 12 months of age with a non-adrenal primary site < 5 cm in greatest diameter.
 - Group A2: ≤ 6 months of age with an adrenal primary site and tumor ≤ 3.1 cm in greatest diameter.
 - Group B
Patients < 18 months (< 547 days) of age with newly diagnosed **INRG Stage L2** neuroblastoma/ganglioneuroblastoma who meet the following criteria:
 - No life threatening symptoms or no impending neurologic or other organ function compromise [e.g. epidural or intraspinal tumors with existing or impending neurologic impairment, periorbital or calvarial-based lesions with existing or impending cranial nerve impairment, anatomic or mechanical compromise of critical organ function by tumor (abdominal compartment syndrome, urinary obstruction, etc.)].
 - No prior tumor resection, tumor biopsy **ONLY**.**Only patients with both favorable histology and favorable genomic features will remain on study as part of Group B. The institution will be notified of histologic and genomic results within 3 weeks of specimen submission on ANBL00B1 OR APEC14B1.**
 - Group C
Patients < 18 months (< 547 days) of age with newly diagnosed **INRG Stage Ms** neuroblastoma/ganglioneuroblastoma.
- ___11. No prior radiotherapy or chemotherapy, with the exception of dexamethasone, which is allowed.

EXCLUSION CRITERIA:

- ___1. Patients with *MYCN* amplified tumors are not eligible.
- ___2. Group B and C patients who do not enroll on ANBL1232 within 4 weeks of definitive diagnostic procedure.
- ___3. Group A and C patients, not required to undergo tumor biopsy, who do not enroll on ANBL1232 within 4 weeks of confirmatory imaging study.

REQUIRED OBSERVATIONS:

Required Observations for Group A

STUDIES TO BE OBTAINED*

- History
- Physical Exam with VS
- Ht, Wt, BSA
- Tumor Imaging ¹
- Urine or Serum Catecholamines (HVA, VMA) ²
- MIBG scan ³

1. CT or MRI scan of the primary tumor is required at enrollment. MRI of the spine is required for patients with a paraspinal lesion.
2. If there is a > 50% increase in value of HVA/VMA decrease the time interval of subsequent studies to every 3 weeks. See Section 4.2 for full details.
3. Baseline MIBG imaging may be delayed for those patients with adrenal primary tumors and < 2 months of age or those weighing < 2.5 kg at diagnosis, but must be completed within 4 weeks of enrollment on ANBL1232 to confirm localized disease. If the patient has a non-adrenal primary tumor and MIBG imaging is required to confirm eligibility, the scan may not be delayed.

* Bone marrow aspirates and/or biopsies for staging are not required unless a patient has abnormalities on a complete blood count or demonstrates clinical symptoms concerning for bone marrow involvement.

Note: Biopsy is not required but tissue should be submitted per ANBL00B1 OR APEC14B1 guidelines if patient has progressive disease and undergoes tumor biopsy or surgical resection.

Required and Optional Observations for Group B: Observation only

STUDIES TO BE OBTAINED

- History
 - Physical Exam with VS
 - Ht, Wt, BSA
 - Performance Status ¹
 - CBC, differential, platelets
 - Urinalysis
 - Electrolytes including Ca⁺⁺ , PO₄, Mg⁺⁺
 - Serum creatinine
 - Total Bilirubin
 - ALT
 - Total protein/albumin
 - Ferritin
 - Urine or Serum Catecholamines (HVA, VMA)
 - Tumor Imaging ²
 - MIBG scan
 - MRI spine ³
 - Bilateral bone marrow aspirates/biopsies ⁴
 - Tumor Biopsy - Pathology review, Genomic analysis ⁵
1. Use Lansky for patients > 1 year of age; not required for patients ≤ 1 year
 2. CT or MRI of primary tumor required at baseline. US, CT scan or MRI of primary tumor will be obtained for subsequent imaging.
 3. Required for patients with paraspinal lesions.
 4. Required for patients with paraspinal lesions.
 5. Submit tissue for banking if disease progression and repeat biopsy obtained or if patient undergoes surgical resection. See [Section 13.1.3](#) for ANBL00B1 or APEC14B1 submission guidelines.

Required and Optional Observations for Group B Patients Receiving First-Line Chemotherapy

STUDIES TO BE OBTAINED

- History
 - Physical Exam with VS
 - Ht, Wt, BSA
 - Performance Status ¹
 - CBC, differential, platelets
 - Urinalysis
 - Electrolytes including Ca⁺⁺ , PO₄, Mg⁺⁺
 - Serum creatinine ²
 - Total Bilirubin
 - ALT
 - Total protein/albumin
 - Ferritin
 - Urine or Serum Catecholamines (HVA, VMA)
 - Tumor Imaging ³
 - MIBG scan
 - Bilateral bone marrow aspirates/biopsies
 - Tumor Biopsy - Pathology review, Genomic analysis
 - Audiologic Evaluation ⁴
 - Echocardiogram ⁴
1. Use Lansky for patients > 1 year of age; not required for patients ≤ 1 year
 2. If elevated obtain calculated creatinine clearance or radioisotope GFR study.
 3. CT or MRI of primary tumor required at baseline. US, CT scan or MRI of primary tumor will be obtained for subsequent imaging.
 4. Can be obtained within 2 weeks of starting chemotherapy.

Required Observations for Group C: Observation only

STUDIES TO BE OBTAINED

- History
- Physical Exam with VS
- Ht, Wt, BSA
- Performance Status ¹
- CBC, differential, platelets
- Urinalysis
- Electrolytes including Ca⁺⁺ , PO₄, Mg⁺⁺
- Serum creatinine
- Total Bilirubin
- ALT
- Total protein/albumin
- Fibrinogen
- PTT
- Ferritin
- Urine or Serum Catecholamines (HVA, VMA)
- Tumor Imaging ²
- MIBG scan ³
- Bilateral bone marrow aspirates/biopsies ³
- Tumor Biopsy - Pathology review, Genomic analysis
- Objective Scoring System

1. Use Lansky for patients > 1 year of age; not required for patients ≤ 1 year
2. CT or MRI of primary tumor required at baseline. US, CT scan or MRI of primary tumor will be obtained for subsequent imaging.
3. Repeat only if disease progression noted clinically or on imaging. FDG-PET scan may be used for patients with MIBG non-avid disease.

Required and Optional Observations for Group C Patients Receiving First-Line Chemotherapy
STUDIES TO BE OBTAINED

- History
- Physical Exam with VS
- Ht, Wt, BSA
- Performance Status ¹
- CBC, differential, platelets
- Urinalysis
- Electrolytes including Ca⁺⁺, PO₄, Mg⁺⁺
- Serum creatinine ²
- Total Bilirubin
- ALT
- Total protein/albumin
- Fibrinogen
- PTT
- Ferritin
- Urine or Serum Catecholamines (HVA, VMA)
- Tumor Imaging ³
- MIBG scan ⁸
- Bilateral bone marrow aspirates/biopsies
- Tumor Biopsy - Pathology review, Genomic analysis ⁴
- Audiologic Evaluation ⁵
- Echocardiogram ⁵
- Objective Scoring System ⁶
- Optional PK Studies ⁷

1. Use Lansky for patients > 1 year of age; not required for patients ≤ 1 year
2. If elevated obtain a calculated creatinine clearance or radioisotope GFR study.
3. CT or MRI of primary tumor required at baseline. US, CT scan or MRI of primary tumor will be obtained for subsequent imaging.
4. Initial biopsy requirements waived for Group C patients < 3 months of age with existing or evolving hepatomegaly or symptomatic patients 3-12 months of age deemed too ill to undergo an open diagnostic biopsy. A biopsy must be performed once stable.
5. Can be obtained within 2 weeks of starting chemotherapy.
6. See Appendix VII for details.
7. See Section 14.2.1 for details of optional PK studies.
8. Baseline MIBG imaging may be delayed for patients < 3 months of age with existing or evolving hepatomegaly or symptomatic, patients requiring emergent therapy or patients < 2 months of age or those weighing < 2.5 kg at diagnosis, but must be completed within 4 weeks of enrollment on ANBL1232.

TREATMENT PLAN:**OVERVIEW OF GROUP AND TREATMENT ASSIGNMENTS**

NOTE: Patients not eligible for this study should receive best available therapy. Therapy can be initiated for Group C patients who are clinically symptomatic and/or at the discretion of the investigator prior to results of histology and genomic studies if it is considered to be in the patient's best interest. The first cycle of chemotherapy **must** be as per Cycle 1 of ANBL1232 (carboplatin-etoposide) to remain eligible for enrollment on ANBL1232.

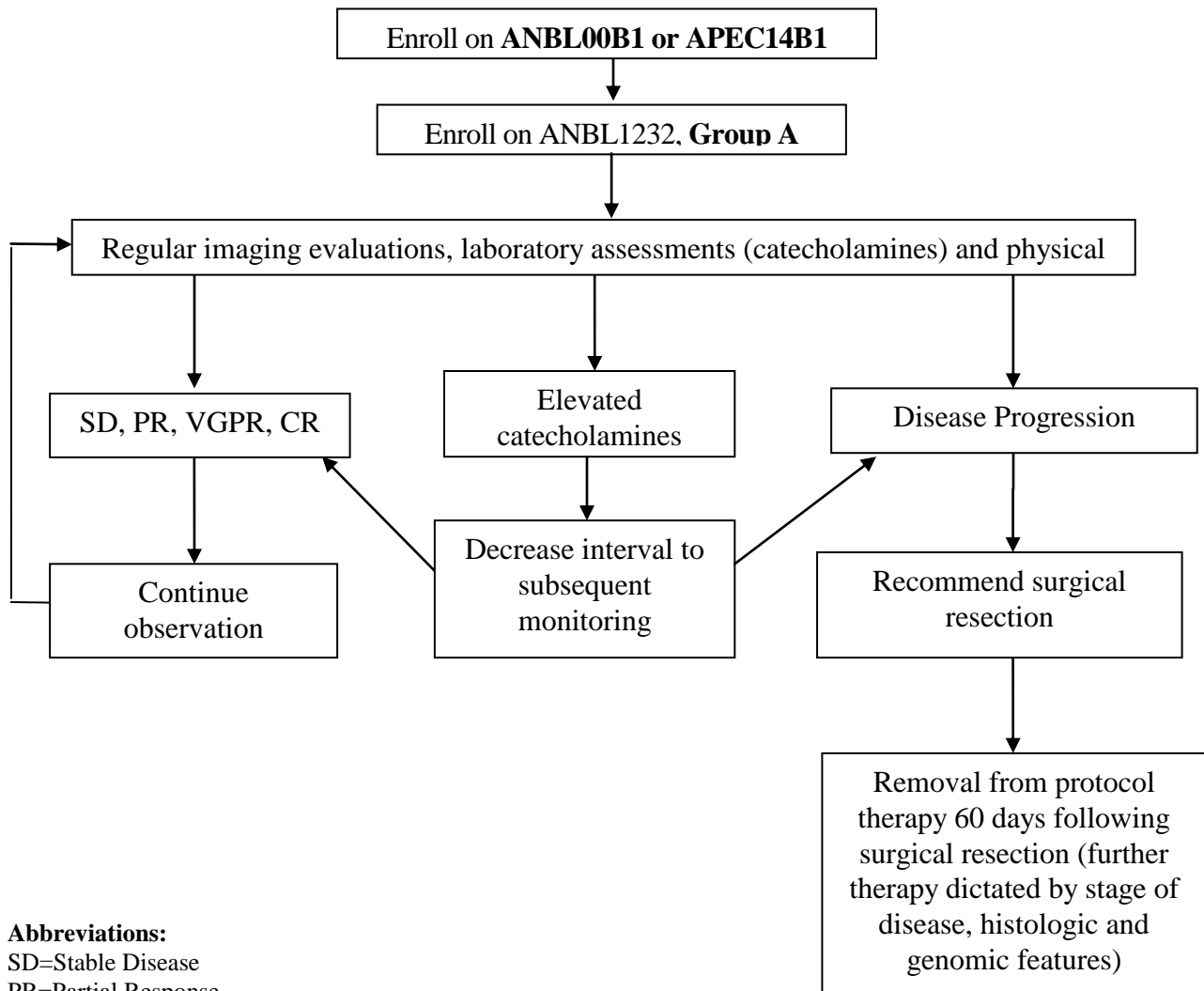
Group and Treatment Assignments

INRG Stage	Biology (Histology and Genomics)	Age	Other	Treatment	ANBL1232
L1		< 12 months	< 5 cm in diameter; Confirmatory study if non-adrenal	Observe on Study without biopsy	Study aim 1, Group A
		Any	Others	Not eligible for this study	
L2	Favorable Histology AND Genomics	< 18 months	Asymptomatic [^]	Observe on Study initially, may or may not involve treatment	Study aim 2, Group B
		≥ 18 months or <18 months and symptomatic		Not eligible for this study	
	Unfavorable Histology only	Any		Not eligible for this study	
	Unfavorable Genomics only	Any		Not eligible for this study	
	Unfavorable Histology AND Genomics	< 18 months		Not eligible for this study	
		≥ 18 months		Not eligible for this study (may be eligible for HR study)	
Any/Unknown	Any	Symptomatic	Not eligible for this study		
M	Favorable Histology AND Genomics	< 12 months		Not eligible for this study	
		12-18 months		Not eligible for this study	
	Unfavorable Histology AND/OR Genomics	< 12 months		Not eligible for this study	
		12-18 months		Not eligible for this study (may be eligible for HR study)	
	Unknown	< 18 months	Symptomatic	Not eligible for this study	
Ms	Any	< 3 months	Existing or evolving hepatomegaly or symptomatic	Immediate treatment, Response-based chemotherapy	Study aim 3, Group C
	Favorable	< 3 months	Asymptomatic [^] without existing or evolving hepatomegaly	Observe per Clinical Scoring system	
			Asymptomatic [^]	Observe per Clinical Scoring System	
	Favorable	3-18 months		Symptomatic	
			Unfavorable Histology OR Genomics OR Unknown	<18 months	

[^]Asymptomatic is defined as no life threatening symptoms or no impending neurologic or other organ function compromise [e.g. epidural or intraspinal tumors with existing or impending neurologic impairment, periorbital or calvarial-based lesions with existing or impending cranial nerve impairment, anatomic or mechanical compromise of critical organ function by tumor (abdominal compartment syndrome, urinary obstruction, etc.)] Horner Syndrome is not considered neurologic compromise.

EXPERIMENTAL DESIGN SCHEMA FOR GROUP A

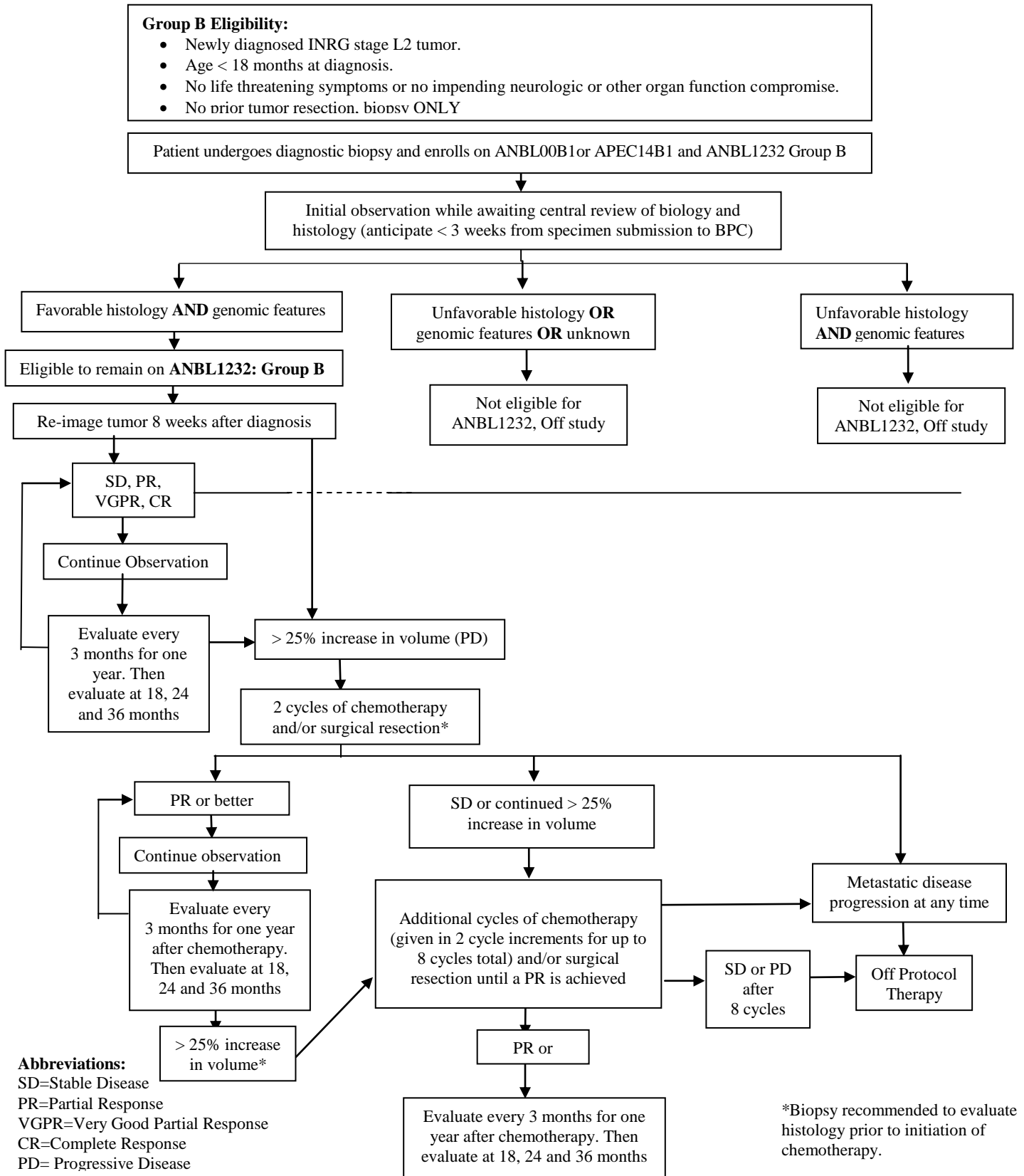
- Group A Eligibility:**
- Newly diagnosed INRG stage L1 tumor.
 - Age < 12 months at diagnosis.
 - Greatest tumor diameter < 5 cm.
 - Patients with non-adrenal primaries must have positive uptake on MIBG scan or elevated catecholamine metabolites.
 - No prior tumor resection or biopsy.
 - No prior systemic chemotherapy.



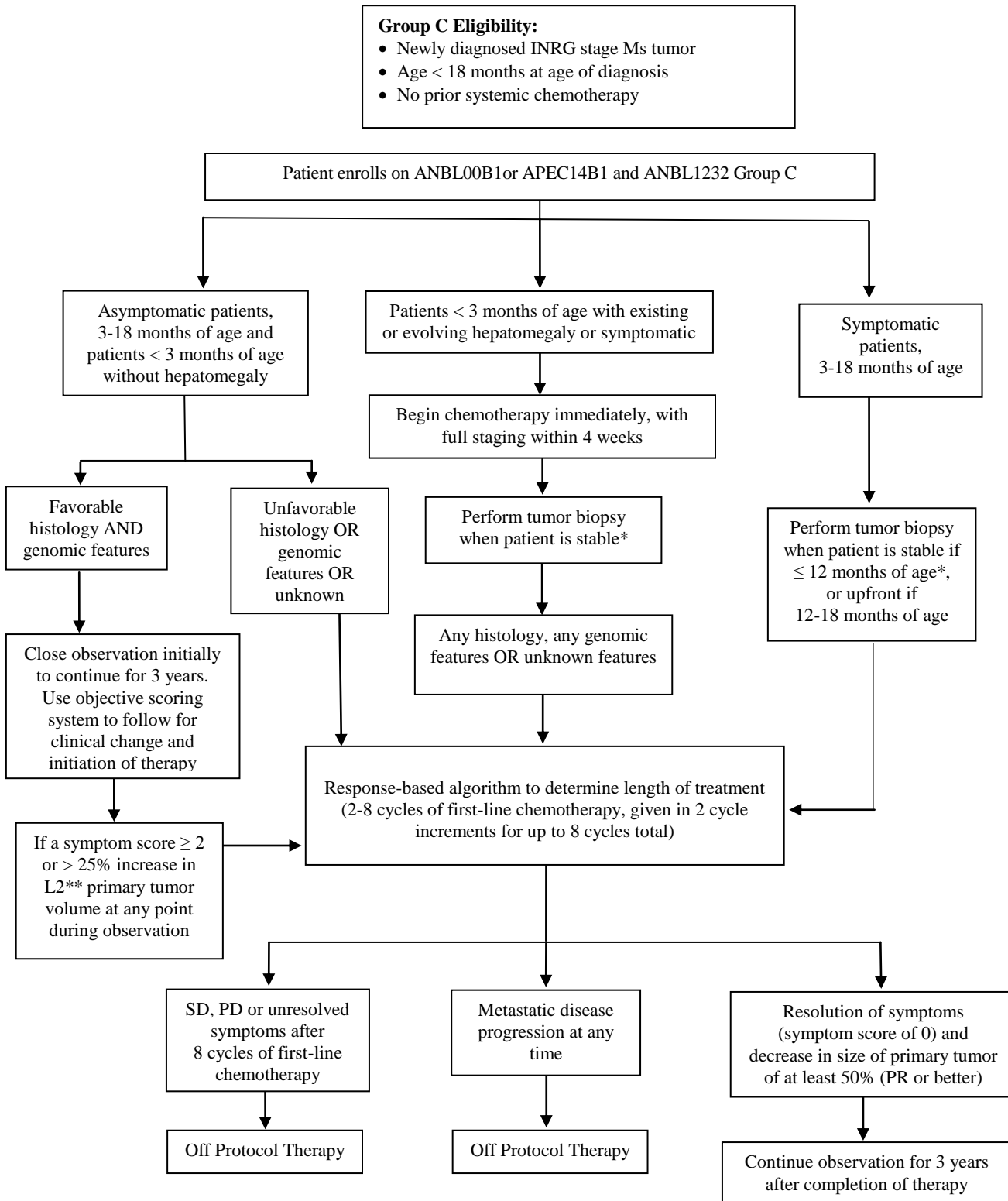
Abbreviations:

- SD=Stable Disease
- PR=Partial Response
- VGPR=Very Good Partial Response
- CR=Complete Response

EXPERIMENTAL DESIGN SCHEMA FOR GROUP B



EXPERIMENTAL DESIGN SCHEMA FOR GROUP C



Abbreviations:

SD=Stable Disease
 PR=Partial Response
 VGPR=Very Good Partial Response
 CR=Complete Response

*An open biopsy is recommended.

**If > 25% increase in L1 primary tumor volume the decision to initiate chemotherapy, offer surgical resection, or continue observation would be based on clinical status and at the discretion of the treating physician.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0

SPECIMEN REQUIREMENTS:

Submission of Blood Sample on ANBL00B1 OR APEC14B1

ANBL1232 will utilize a CGH/SNP microarray to determine the tumor genomic profile and assign subjects to treatment groups. In some cases, matched blood DNA will be helpful in interpreting the CGH/SNP array data. Therefore, **submission of the EDTA blood sample listed in ANBL00B1 OR APEC14B1 is STRONGLY ENCOURAGED in order for the patient to be eligible for therapy modification in Group B.**

A peripheral blood and serum sample is the only specimen REQUIRED to be submitted on ANBL00B1 OR APEC14B1 for Group A patients and Group C patients who do not undergo biopsy as defined in Section 3.1.4.

BIOLOGY REQUIREMENTS:

Optional biology studies for Group C. See Section 14.2.1