

**COG ANBL0032: Phase III Randomized Study of Chimeric Anti-GD2 in High Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell Rescue**

***FAST FACTS***

**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 A3973 or ANBL00B1 is no longer an eligibility requirement for ANBL0032.
2. All patients must be diagnosed with neuroblastoma, and categorized as high risk at the time of diagnosis and must be  $\leq$  30.99 years of age at diagnosis.
3. If the patient was enrolled on A3973, then the patient must have completed frontline therapy followed by ASCT and radiotherapy as prescribed by A3973, **AND** have achieved CR, VGPR or PR at pre-ASCT evaluation to be eligible for ANBL0032.
4. If the patient was **not** enrolled on A3973, the patient will be eligible for ANBL0032 if the patient has achieved a CR, VGPR, or PR at pre-ASCT evaluation and after treatment with one of the following induction regimens of high-dose therapy and ASCT:
  - Following treatment per A3973 protocol
  - Following treatment per POG 9341/9342 protocol
  - Following treatment per CCG 3891
  - Following treatment on NANT 2001-02
  - Enrollment on or following treatment per ANBL02P1
  - Tandem transplant patients are eligible:
    - 1) Following enrollment and treatment on ANBL0532;
    - 2) Following treatment per POG 9640;
    - 3) Following treatment per COG ANBL00P1; or,
    - 4) Following treatment per CHP 594/DFCI 34-DAT.
  - Others: please call Study Chairs to discuss
5. No more than 9 months from the date of starting the first induction chemotherapy after diagnosis to the date of ASCT. For tandem ASCT patients, this will be the date of the FIRST stem cell infusion.
6. Prior to enrolling on ANBL0032, MRD assessment #2 (Tumor imaging studies including CT or MRI, bone scan, MIBG scan, bone marrow aspiration & biopsy, and blood and bone marrow samples for Dr. Seeger's lab) should be done preferably within 2 weeks (max. 4 weeks) before starting immunotherapy or RA. For those with residual disease before radiotherapy, re-evaluation of irradiated residual tumors should be performed at the earliest 5 days after completing radiotherapy. Patients who have biopsy proven residual disease after ASCT who are not enrolled on A3973 or ANBL0532 are NOT eligible for ANBL0032. Among patients with biopsy proven residual disease after ASCT, only those who are enrolled on A3973 or ANBL0532 will be non-randomly assigned to immunotherapy on stratum 07.
7. Patients must be enrolled and randomized between day 50 and day 77 (see 6.1 for special exemption) post final-ASCT procedure (second ASCT for tandem ASCT patients), when the total absolute phagocyte count (APC = neutrophils + monocytes) is at least 1000/ $\mu$  L (cytokine support allowed), and at least 7 days after completing radiotherapy, and patient has undergone tumor assessment. Informed consent should be obtained within 3 weeks pre-ACST up to the time of registration.
8. Patients must not have progressive disease.
9. Patients must have a Lansky or Karnofsky Performance Scale score of  $\geq$  50% (see Appendix II) and patients must have a life expectancy of  $\geq$  2 months.

10. Patients must have adequate organ functions at the time of registration:

- Renal

- Creatinine clearance or radioisotope GFR  $\geq 70\text{mL}/\text{min}/1.73\text{m}^2$  or
- A serum creatinine based on age/gender 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
$\geq 16$ 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.

- Hepatic- total bilirubin  $\leq 1.5$  x normal, and SGPT (ALT)  $\leq 5$  x normal. Veno-occlusive disease, if present, should be stable or improving.
- Cardiac- shortening fraction of  $\geq 30\%$  by echocardiogram, or if shortening fraction abnormal, ejection fraction of  $\geq 55\%$  by gated radionuclide study.
- Pulmonary- FEV1 and FVC  $> 60\%$  of predicted by pulmonary function test. For children who are unable to do PFTs, no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry  $> 94\%$  on room air.
- Central nervous system- Patients with seizure disorder may be enrolled if on anticonvulsants and wellcontrolled. CNS toxicity  $<$  grade 2.

11. Written informed consent in accordance with institutional and FDA guidelines must be obtained from parent or legal guardian.

**REQUIRED OBSERVATIONS:**

Before Myeloablative Therapy (2 weeks prior to Consolidation):

All patients on A 3973 and ANBL0532 must have the following tests done, which are required by both A 3973 and ANBL0532:

- Tumor measurement (CT, MRI, MIBG\*, bone scan etc.);
- Bone marrow aspirates/biopsies (from two sites):  
**3-5** cc heparinized marrow from each site plus 10 cc heparinized peripheral blood to Dr. Seeger's lab.

**(MIBG scan, bone marrow and blood for MRD assessment, 1st time point (MRD#1) are mandatory for A3973 and ANBL0532 patients and strongly encouraged for other patients who are only enrolled on ANBL00B1.) For sending pre-enrollment specimens (MRD#1) to Dr. Seeger, please use the ANBL00B1 Biology Data Sheet and Specimen Shipping Form only if patient is enrolled on ANBL00B1.**

- See MIBG scan guidelines in appendix III. Copies of MIBG scans are required to be sent for central review. MIBG scans are to be sent from time of entry into ANBL0032. (Not from diagnosis, since A3973 would have requested for MIBG). For non-A3973 patients, MIBG scans at diagnosis and pre-ASCT should also be sent, if done. QARC is able to accept electronic imaging data in lieu of films when digital output is in DiCom format. The digital images can be burned to a CD and mailed to QARC. Please submit only one patient's studies per CD. Alternatively, where institutional information systems allow, the images can be e-mailed to QARC to COG@QARC.org. Institutions with PACS systems can contact QARC regarding installation of the COG DiCommunicator software that manages e-mailing studies to QARC. Contact this e-mail address if further assistance is needed

- Please send copy of all MIBG scans from study entry on to the following address:  
Quality Assurance Review Center (QARC)  
272 West Exchange Street. 101  
Providence, RI 02903-1025  
Tel: (401) 454-4301  
Fax: (401) 454-4683

#### After ASCT and Radiotherapy

#### **MRD assessment, 2nd time point: mandatory tests (Please note that this assessment replaces day 100 evaluation and is mandatory for both A3973 and non-A3973 patients)**

- Tumor measurement (CT, MRI, MIBG\*, bone scan etc.);
- MIBG scan\*
- Bone marrow aspirates / biopsy from two sites (biopsy may be omitted if negative prior to ASCT)

**3-5 cc** heparinized marrow from each site must be obtained plus 10 cc heparinized peripheral blood to Dr. Seeger's lab. (also see Section 5.61)

The above studies should be done preferably within 2 weeks (max. 4 weeks) before starting immunotherapy or RA. For those with residual disease before radiotherapy, re-evaluation of irradiated residual tumors should be performed at the earliest 5 days after completing radiotherapy.

\*See MIBG scan guidelines in appendix III. Copies of MIBG scans are required to be sent for central review (Send copy of all MIBG scans from diagnosis on).

For sending BM and blood specimens to Dr. Seeger, please print out the ANBL0032 Specimen Shipping form, complete it and send with the specimen. Please note that consent must be obtained prior to sending the specimen for MRD #2.

Physical Exam (including weight, height, vital signs, and performance status [see Appendix II]), CBC and differential with APC, chemistry survey (electrolytes, calcium, BUN, creatinine, albumin, AST, ALT, triglycerides, total bilirubin, LDH), and urinary VMA and HVA within 1 week before starting immunotherapy or RA.

#### Special Studies

Dr. Yu's lab for ADCC (also see Section 5.62) for **all patients** before starting immunotherapy or RA:

15 cc blood in preservative-free heparin or green-top tube obtained within 1 week before starting RA or the first GM-CSF injection for ch14.18 therapy (on a Monday through Thursday, to avoid Friday shipment). Freshly obtained samples should be sent at room temperature by overnight carrier to Dr. Yu's lab. For regimen B patients, plasma samples will be processed by Dr. Yu's lab and sent in batches to Dr. Sondel's lab for analysis of HACA and ch14.18 levels.

#### **TREATMENT PLAN:**

##### **Overall Treatment Outlines:**

Eligible patients would have completed frontline therapy as prescribed by A3973, or other frontline therapeutic regimens as described in section 4.3 and evaluated for pre-ASCT responses. Patients will be enrolled and randomized into regimen A or B on day 50 post-ASCT, up to day 77 (see special exemption below) post-ASCT when 1) total absolute phagocyte count (APC) is at least 1000/ $\mu$  L 2) organ functions have met the eligibility criteria, and, 3) tumor assessment has been completed following the end of radiotherapy at least 5 days before. Although informed consent for ANBL0032 can be obtained up to the time of registration, it is **strongly encouraged** that those who are eligible for ASCT sign the informed consent within 3 weeks before ASCT, so as to prevent attrition from the study after transplantation.

Randomization will be stratified by pre-ASCT CR versus VGPR versus PR and by purging vs. nonpurging of the stem cells for ASCT. Regimen A consists of oral intake of isotretinoin (13-cis-retinoic acid, or RA) starting day 67 post-ASCT at 80 mg/m<sup>2</sup>/dose twice a day for 14 days every 28 days, for 6 courses. Please avoid Sunday or Monday as start date for the first course of therapy so that day 14 blood sample for 13-cis-RA pharmacokinetics will not fall on weekend. For regimen B, patients will receive oral isotretinoin (13-cis-retinoic acid, or RA) as in regimen A. In addition, patients will receive 5 courses of ch14.18 + cytokines, with ch14.18 + GM-CSF administered in courses 1, 3, and 5, and ch14.18 + aldesleukin (IL-2) given in courses 2 and 4. The intervals between antibody administrations are 28 days for all courses.

At the post ASCT / radiotherapy evaluation, if persistent active disease is documented by biopsy, patients will be non-randomly assigned to regimen B (immunotherapy). Criteria for biopsy includes persistent soft tissue density by CT or MRI, new or worsening lesion on bone scan, new or persistent lesion on MIBG scan. Findings of MIBG scan can be used to guide biopsy but not as a criteria for proven active disease. Those who do not undergo biopsy will be randomized as all other patients. The criteria for active disease in the bone marrow is based on morphological examination, regardless of the results of immunocytology and PCR analysis, since one of the study objectives of this protocol is to assess the value of the latter two parameters in detecting MRD. Among patients with biopsy proven residual disease after ASCT, only those who are enrolled on A3973 or ANBL0532 will be non-randomly assigned to immunotherapy on stratum 07. Prior to starting immunotherapy or isotretinoin (13-cis-retinoic acid, or RA), patients must have completed post-ASCT radiotherapy, preferably as prescribed by A3973 at least 7 days before, and they must be medically stable and have APC  $\geq$  1000/ $\mu$  L. The first dose of GM-CSF will ideally begin on day 56, preferably on a Friday and first dose of RA on day 67, preferably on a Tuesday so that day 14 blood sample for 13-cis-RA pharmacokinetics will fall on a Monday during the first course of therapy, but it may be delayed up to day 77 post-ASCT for justified clinical reasons. Treatment with ch14.18 + GMCSF (1st, 3rd and 5th courses) consists of ch14.18 at 25 mg/m<sup>2</sup>/day x 4 days from Day 3 to 6, Day 59 to 62 and Day 115-118 of immunotherapy calendar, and GM-CSF at 250  $\mu$  g/m<sup>2</sup>/d subcutaneous injection daily from Day 0 to 13, Day 56 to 69 and Day 112 to 125 (daily with the infusion of ch14.18 and for 3 days before and 7 days afterward). The 2nd and 4th courses of immunotherapy will consist of continuous infusion of 3 MIU/m<sup>2</sup>/day (Chiron, Adesleukin (IL-2)) for 4 days during the first week of each course given on Days 0 – 3 and 4.5 MIU/m<sup>2</sup>/day (Chiron, Adesleukin (IL-2)) for 4 days during the second week of each course given on Days 7 - 10 (with the infusion of ch14.18). Treatment should be stopped if progressive disease is detected.

#### **REGISTRATION AND RANDOMIZATION:**

After completion of ASCT, local radiation, and tumor assessment between Day 50 and day 77 post-ASCT, the institution must again contact the C.O.G. on-line registration system to have the patient registered and randomized. Three questions that the institution should be prepared to answer are:

- a) During the ASCT, did the patient receive purged or unpurged stem cells?
- b) What was the clinical assessment of the patient's response prior to ASCT?
- c) What was the clinical assessment of the patient's response after ASCT and radiotherapy? If not CR, did patient undergo biopsy? If biopsied, was there evidence of active residual disease?

#### **TOXICITIES AND DOSAGE MODIFICATIONS:**

See Section 6.4

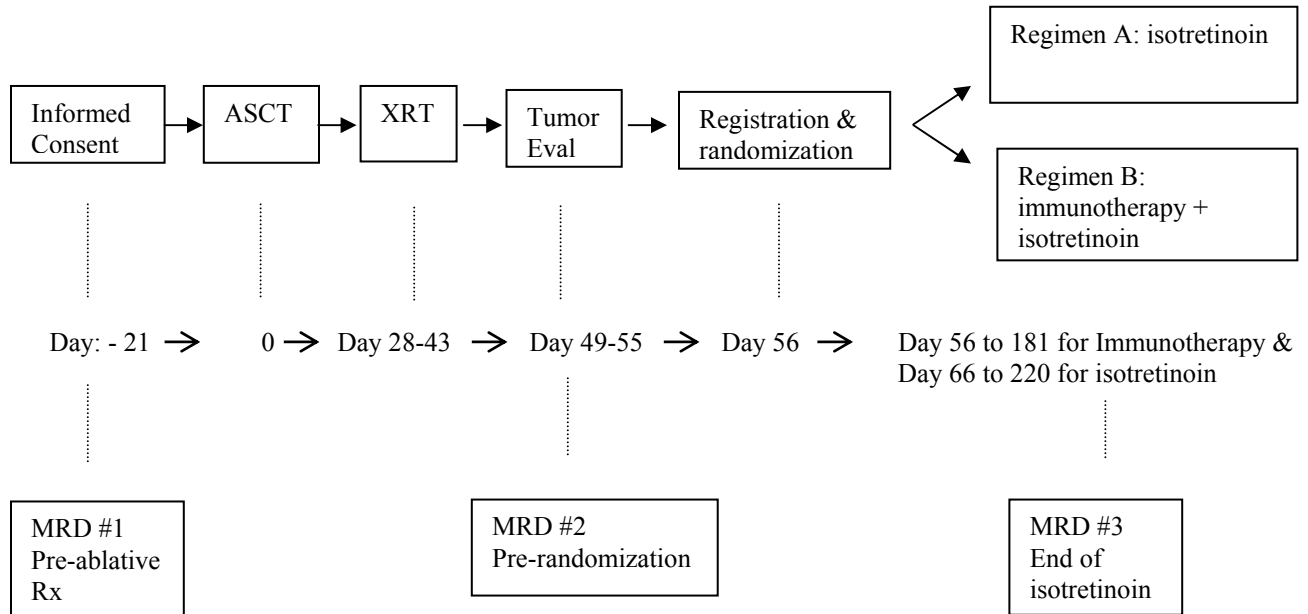
#### **SPECIMEN REQUIREMENTS:**

Please notify the COG research nurses so that arrangements can be made with pathology.

#### **CONCOMITANT THERAPY:**

See Section 6.5.

**Overall Schema**



\*MRD assessment:

Bone marrow for immunocytology & RT-PCR, MIBG scan and other radiographical studies.

\*\*In the rare cases with persistent tumor post ASCT/radiotherapy (time point #2), biopsy is required. Those with biopsy proven active disease will be non-randomly assigned to regimen B (immunotherapy). Those who do not undergo biopsy will be randomized as all other patients.

**For more information on this protocol, contact GRCOP at 616.391.1230**