

ANBL1531

The current Phase III trial seeks to improve the event-free survival (EFS) for children with high-risk neuroblastoma through early integration of promising novel targeted therapies: Targeted radiopharmaceutical therapy with ^{131}I -MIBG or the ALK inhibitor, crizotinib.

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Study Chair: Rochelle Bagatell, MD
Prepared by: Paul Gibson and Christina McCauley

Background

Despite recent improvements in outcome for children with newly diagnosed high-risk neuroblastoma (NBL), cure rates remain unsatisfactory.

A substantial number of children with high-risk NBL still progress during induction therapy, show evidence of persistent metastatic disease, or relapse after completion of treatment.

Background

Current therapy treatments:

- Tandem autologous stem cell transplant during consolidation
- Immunotherapy (dinutuximab) during post-consolidation
- ^{131}I -MIBG for the treatment of patients with relapsed and refractory NBL

ANBL1531: Primary Aim

- Determine whether ^{131}I -MIBG improves EFS with acceptable long-term toxicity in patients with MIBG-avid tumours.
- Assess whether the addition of crizotinib to standard multi-modality therapy improves outcomes for newly diagnosed patients with tumours harbouring ALK aberrations.
- Estimate EFS and describe toxicities associated with ^{131}I -MIBG/BuMel transplant.
- Define the outcomes for patients with MIBG non-avid tumours.

^{131}I -MIBG Therapy

The integration of ^{131}I -MIBG earlier in therapy for the high-risk NBL population hopes to address the issue of early disease progression during induction therapy.

Improve early response = Improve overall outcomes

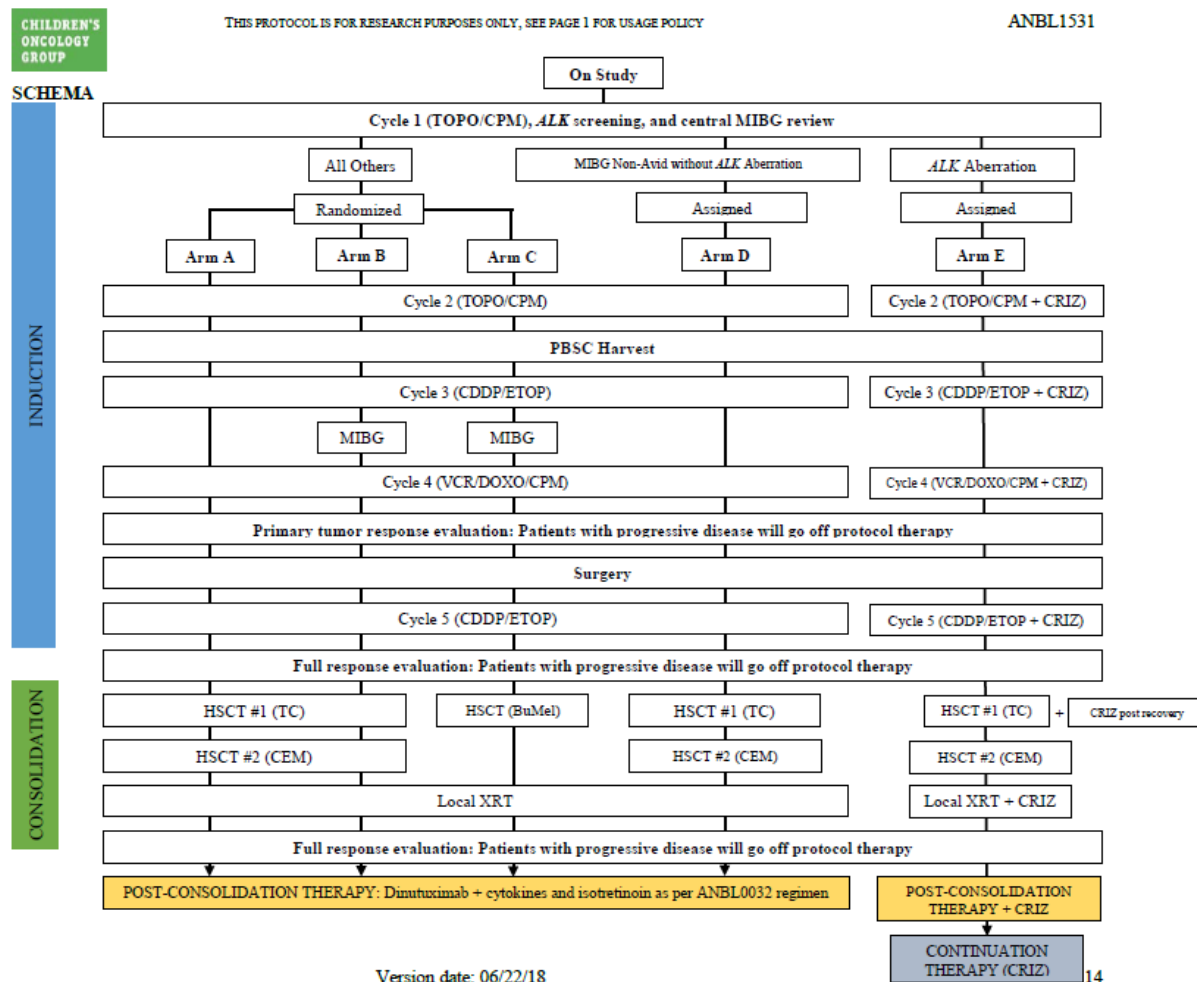
ASCT – Tandem vs. Single

Tandem ASCT is the current COG-recommended consolidation regimen for patients with high-risk neuroblastoma.

Which one's better?

In this study, both the toxicity and EFS associated with single ASCT – Bu/Mel vs. Tandem ASCT – TC/CEM during consolidation will be evaluated.

Study Schema



Induction Therapy:

- Five cycles of induction chemotherapy
- Surgery
- ^{131}I -MIBG Therapy (Arms B & C only)

Consolidation Therapy:

- Two transplants + Local radiation
- One transplant (Arm C only)

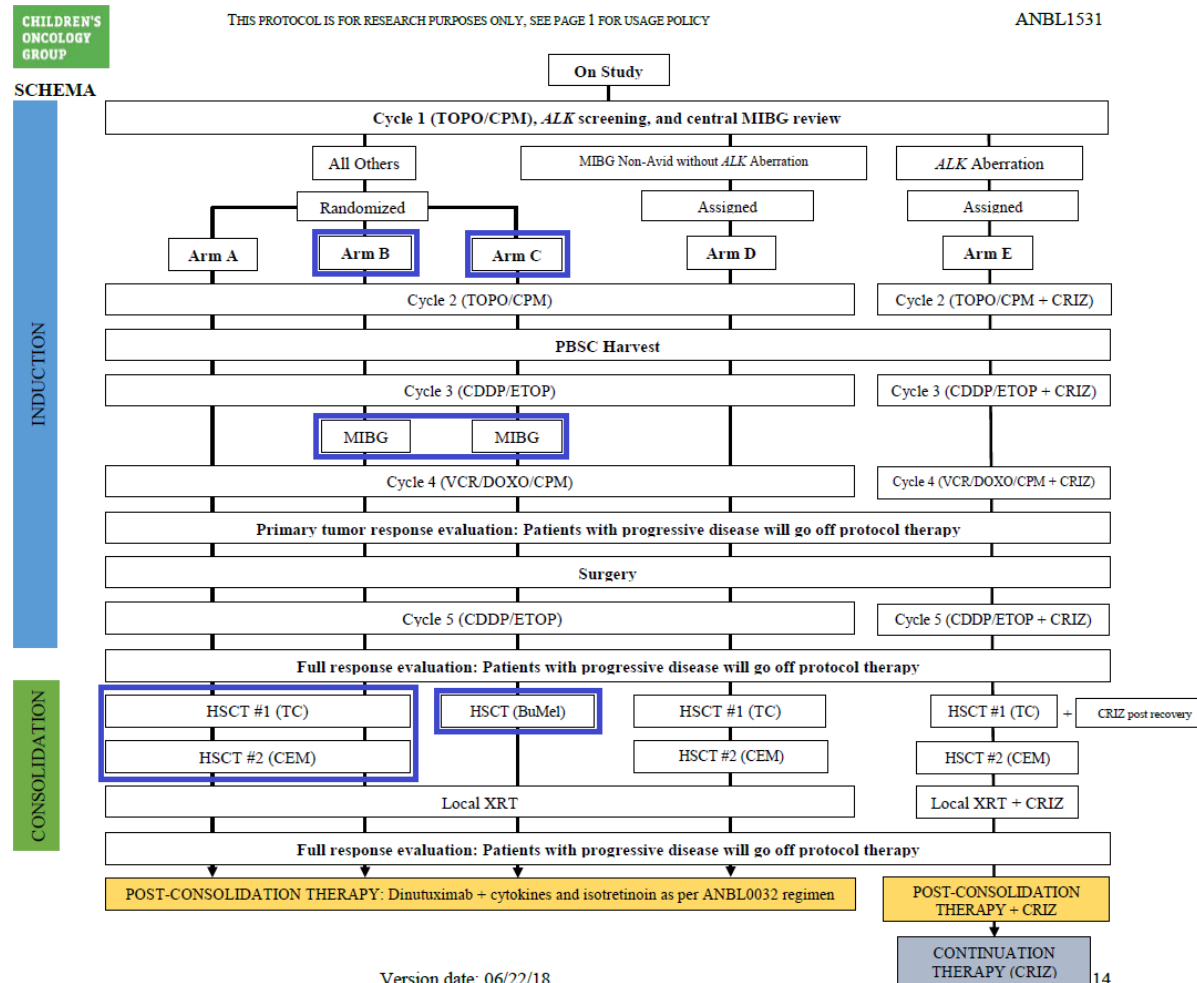
Post-Consolidation Therapy:

- Dinutuximab + cytokines and Isotretinoin

Continuation Therapy:

- Crizotinib (Arm E only)

Arm B vs. Arm C



Both Arms receive ^{131}I -MIBG after the third cycle of Induction.

Arm B receives **tandem ASCT** (TC + CEM)

Arm C receives **single ASCT** (BuMel)

– ASCT and ^{131}I -MIBG will be done in the tertiary centres

¹³¹I-MIBG Induction Therapy

		Ht	cm	Wt	kg	BSA	m ²					
Date Due	Date Given	Day	¹³¹ I-MIBG _____mCi	KI LD _____mg MD _____mg				Myeloid growth factor used: Calc. dose _____		Studies		
			Enter calculated dose above and actual dose administered below						Start Date	Stop Date		
		1	_____mCi	LD _____mg	MD _____mg	_____mg	_____mg	_____mg			a-h	
		2		MD _____mg	_____mg	_____mg	_____mg	_____mg				
		3		MD _____mg	_____mg	_____mg	_____mg	_____mg				
		4		MD _____mg	_____mg	_____mg	_____mg	_____mg			g, h, i	
		5		MD _____mg	_____mg	_____mg	_____mg	_____mg				
		6		MD _____mg	_____mg	_____mg	_____mg	_____mg				
		7		MD _____mg	_____mg	_____mg	_____mg	_____mg				
		8		MD _____mg	_____mg Daily						b-d	
		13	PBSCs to be given on Day 13 ± 3 days. See Section 4.15.3.2								b-d	
		15									b-d	
		22									b-d	
		29									b-d	
		35	Start Cycle 4 once criteria in Section 4.15.4 are met; continue KI through Day 45									a-d
		45										

- ¹³¹I-MIBG will be delivered at an approved centre after the third cycle of induction.
- Weekly CBC/Lytes post-MIBG and PBSC can be done at the Satellite Clinic.

Things to Consider

A patient is radioactive once ^{131}I -MIBG Therapy has been administered.

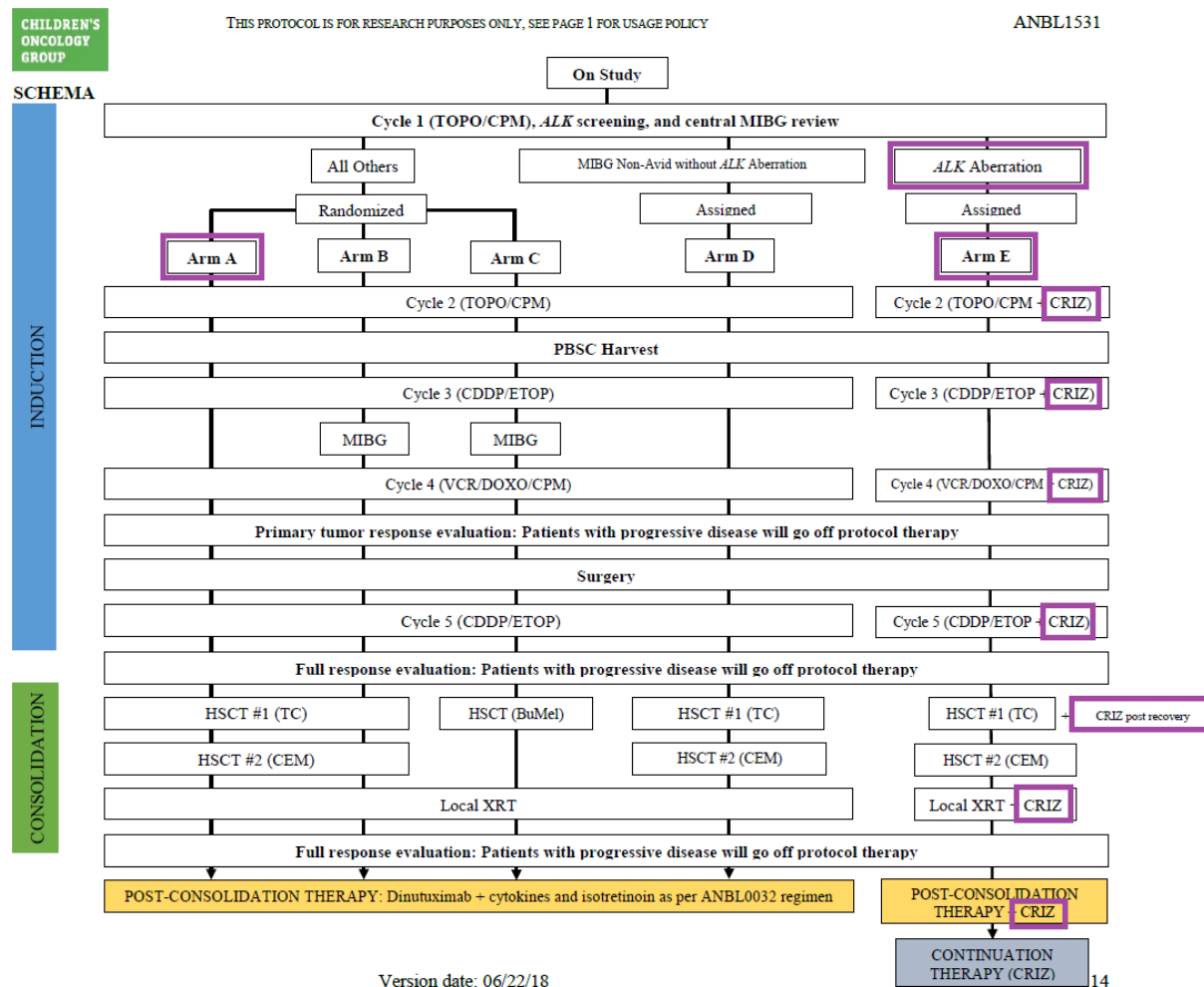
Upon discharge from the tertiary hospital, most of the radioactivity is eliminated; however, small amounts will continue to be eliminated in the urine and feces.

Basic principles for radiation safety should be followed for approximately **14 days** post-discharge. Patients may be seen in your Satellite Clinics during this time.

Radiation Safety Principles

- **Distance** – The greater the distance from others, the less radiation they will receive. Therefore, maximize your distance from the patient whenever possible.
- **Time** – Radiation exposure to others depends on how long you remain close to them. Try to minimize the time spent in close contact with the patient.
- **Hygiene** – Good hygiene reduces the possibility that other people will be contaminated with the radioactivity as it leaves the body, particularly good toilet hygiene (i.e. flush toilet twice after each use).

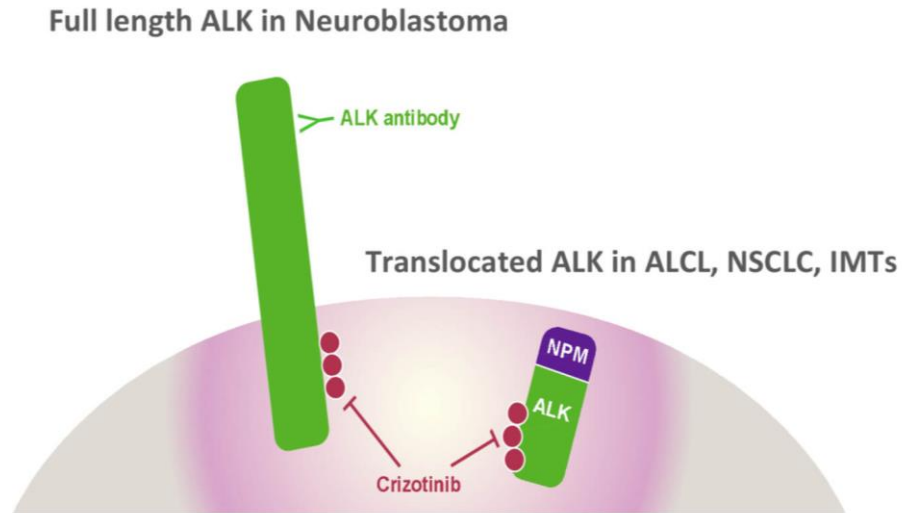
Study Schema



Arm A vs. Arm E: Compares the current COG-recommended regimen with the addition of Crizotinib.

Crizotinib

- Crizotinib is an oral small molecule inhibitor that targets and binds to the ALK tyrosine kinase, inhibiting its tumourgenesis activity.
- First approved in lung cancer, it's shown very promising results in ALK-mutated neuroblastoma.



Source: Mano H. Proc Jpn Acad
Ser B Phys Biol Sci. May 2015

Why Crizotinib?

Approximately 14% of children with high-risk NBL have tumours that harbor ALK aberrations (mutation or amplification).

Pre-clinical studies have shown synergistic activity in NBL cell lines harbouring the most common ALK mutations when crizotinib is used in combination with topotecan/cyclophosphamide.

Crizotinib Toxicities

Common (>20% of Patients)	Occasional (4-20% of Patients)	Rare
<ul style="list-style-type: none"> • Constipation • Diarrhea • Nausea • Vomiting • Appetite decreased • Edema • Vision disorders* • Fatigue • Neuropathy • Dizziness • Dysgeusia (taste) • Alanine aminotransferase increased • Aspartate aminotransferase increased • Neutrophil count decreased 	<ul style="list-style-type: none"> • Anemia • White blood cell count decreased • Bradycardia • Dyspepsia • Oral mucositis • Infection • Alkaline phosphatase increased • Lymphocyte count decreased • Abdominal pain • Serum creatinine increased • Electrocardiogram QT corrected interval prolonged • Headache • Rash 	<ul style="list-style-type: none"> • Heart failure • Blood bilirubin increased • Interstitial lung disease/pneumonitis/pneumonia • Renal cyst • Hepatic failure • Testosterone decreased • Esophagitis • Gastrointestinal perforation • Syndrome • Thromboembolic event

Crizotinib: When to Administer

- Crizotinib will be administered Days 1-21 during induction cycles (families should have their study supply with them)
- It should NOT be held for routine F&N admissions
- If cycles are delayed beyond 35 days, dose MAY be modified as per tertiary centre
- When in doubt, contact the tertiary hospital!

Summary

After enrollment, patients will receive one cycle of Induction chemotherapy. Subsequent therapy will be based upon MIBG avidity and ALK status.

The majority of treatment in this study will be provided in the tertiary centres – ^{131}I -MIBG Therapy, Induction cycles 3-5, HSCT, and radiation.

Satellite Clinic involvement will primarily be to provide supportive care, collect bloodwork, and administer chemotherapy in Induction cycles 1 & 2.

All adverse events should be documented and reported to the tertiary hospital.

Certificate of Completion

This certificate is awarded to

name

for the completion of the POGO ANBL1531 educational training module



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