

High Risk Neuroblastoma in the New Decade: Incorporating Targeted Therapies To Maximize Impact in Current Children's Oncology Group Trials

Presenters

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COG Educational Track at APHON 2020



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Disclosure

- Wendy Fitzgerald and Denise Mills have no industry relationships.
- Off label use of Eflorinithine (DFMO) and Crizotinib will be discussed.

COG Disclosure

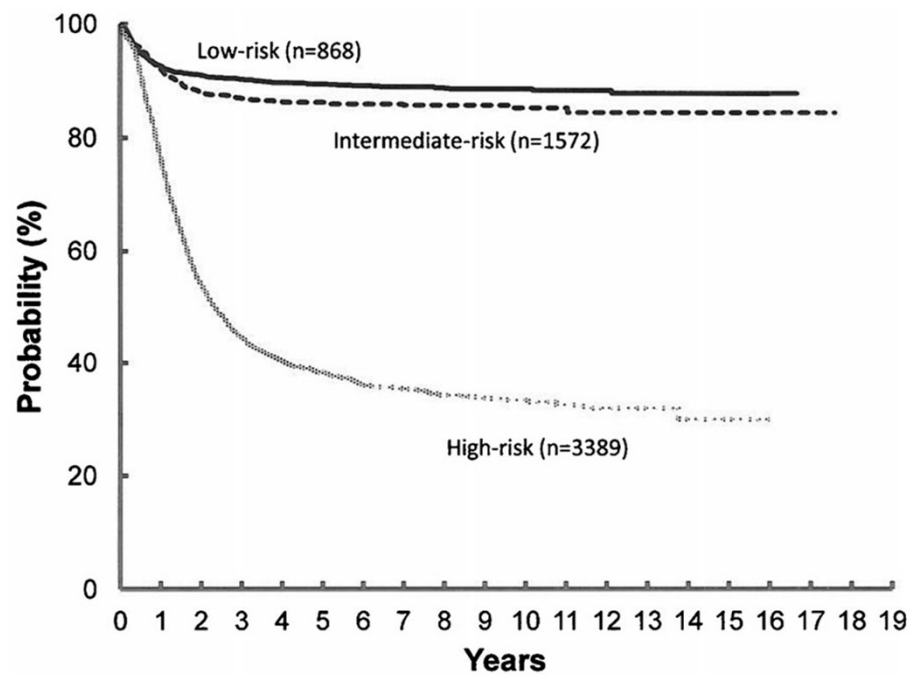
The information in this presentation is intended for educational purposes only and is solely for the use of the individual nurse learner. This information is not intended as the sole source of guidance in providing Children's Oncology Group (COG) protocol-directed nursing care, and current COG protocols should always be consulted prior to making patient care decisions for any patient enrolled on a COG protocol. Learners should also be aware that COG protocols are research plans designed to investigate particular study questions, that recommendations for treatment and dosing are made within the context of specific research aims, and that these recommendations are intended only for use within a structured research setting. Although every attempt has been made to assure that the informational content contained herein is as accurate and complete as possible as of the date of presentation, no warranty or representation, express or implied, is made as to the accuracy, reliability, completeness, relevance, or timeliness of this content. This information may not be copied or redistributed in any form, or used for any purpose other than nursing education.

Learning Objectives

■ The learner will

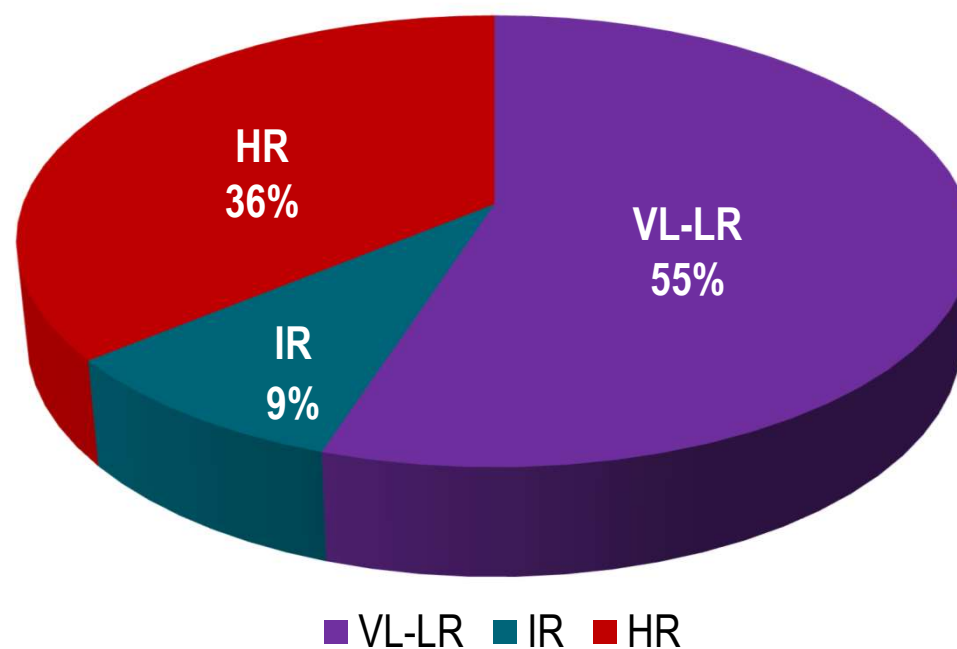
- ◆ identify the current standard of care for high risk neuroblastoma as established through COG trials.
- ◆ understand the mechanism of action for the agents being introduced into upfront and relapse trials in contemporary COG: eflornithine, ^{131}I -MIBG, crizotinib, busulfan in combination with melphalan for auto HCT and dinutuximab.
- ◆ appreciate nursing considerations surrounding administration of these agents, highlighting the unique toxicity profiles of dinutuximab and ^{131}I -MIBG in relation to toxicities.

Neuroblastoma (NBL): Risk Stratification and Prognosis



Risk Groups in NBL

- New classification within COG:
 - ◆ Non high risk > 90% survival
 - ◆ High risk < 50% survival
- At diagnosis stratified into prognostic categories with varying outcomes
- Risk group assigned based on:
 - ◆ Age
 - ◆ Stage
 - ◆ Biologic factors



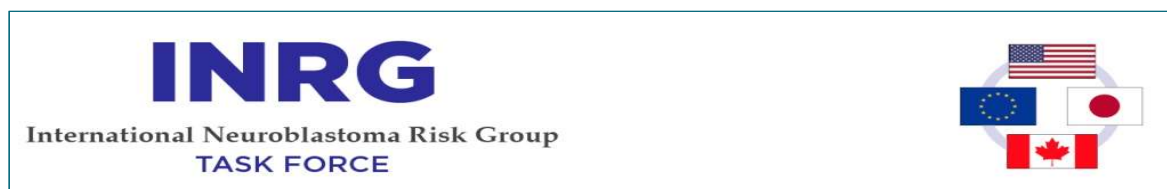
Neuroblastoma

- Tumor of neural crest cell precursors (primordial sympathetic nervous system)
- Most common solid tumor outside of CNS
- > 700 diagnosed/yr (US)
- Prevalence
 - ◆ 10% of pediatric cancer diagnoses
 - ◆ Median age of diagnosis 19 mos
 - ◆ Rare cases of familial inheritance
- Widely variable prognosis
 - ◆ African Americans and Native Americans more likely to have HR disease and fatal outcome



COG Risk Stratification

- Historically very complex
- Current goal
 - ◆ Simplify
 - ◆ Use INRG classification system (goal of less surgical intervention)
- Risk stratification by INRG classification system
 - ◆ Combination of clinical, pathologic, and genetic markers to determine prognosis
 - Defines risk as
 - VLR, LR, IMR, HR



INRG Classification



INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	MYCN	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS					No		C Very low
	< 18			NA	Yes		Q High
					Amp		

Neuroblastoma Staging is Complex!



Are you ready to learn more?

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COG Nursing Resources on VIMEO

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**The Landscape of Neuroblastoma in COG:
*Yesterday's, Today's &
Tomorrow's Therapies***

Joy Bartholomew, APRN
Wendy Fitzgerald RN MSN CPON® PPCNP-BC

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Current standard of care for High Risk Neuroblastoma: How did we get here?

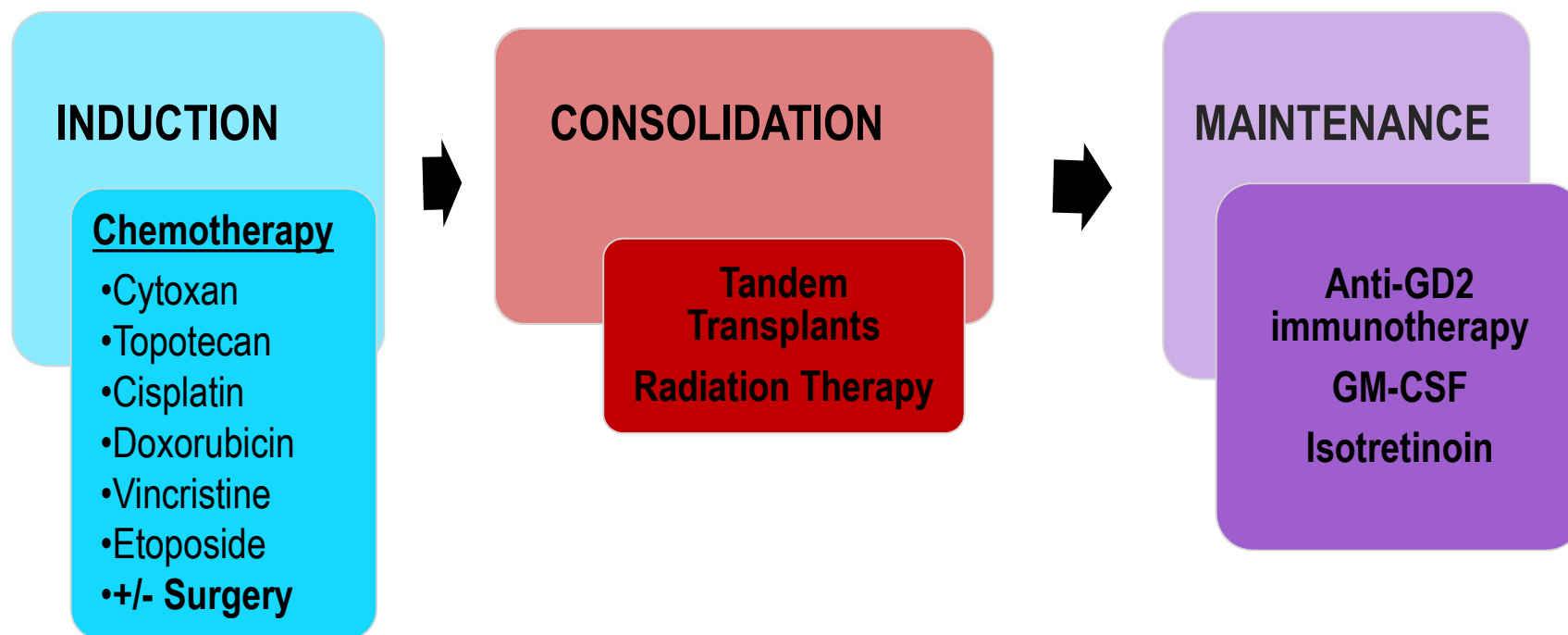


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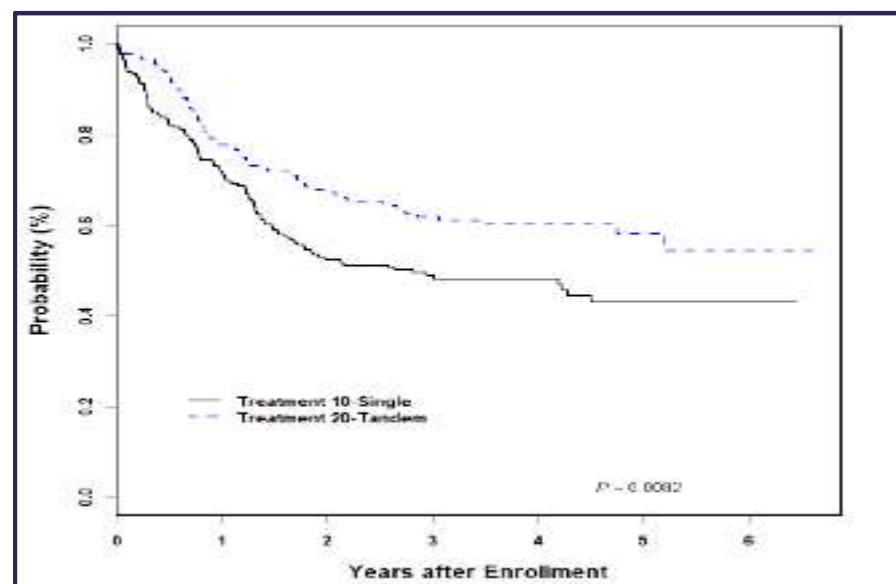
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High Risk Standard of Care (SOC) Treatment



ANBL0532 Consolidation Therapy Outcomes – Tandem Transplant

Tandem transplant 3 year EFS 74% compared to single transplant 55%



JAMA
The Journal of the American Medical Association

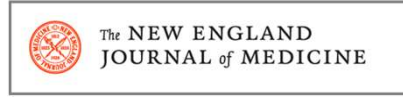
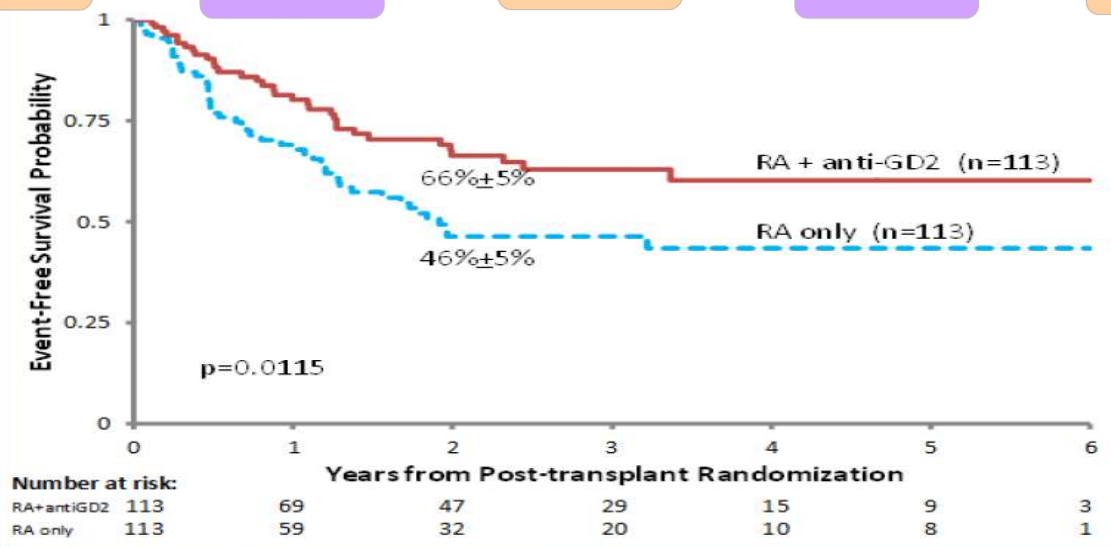
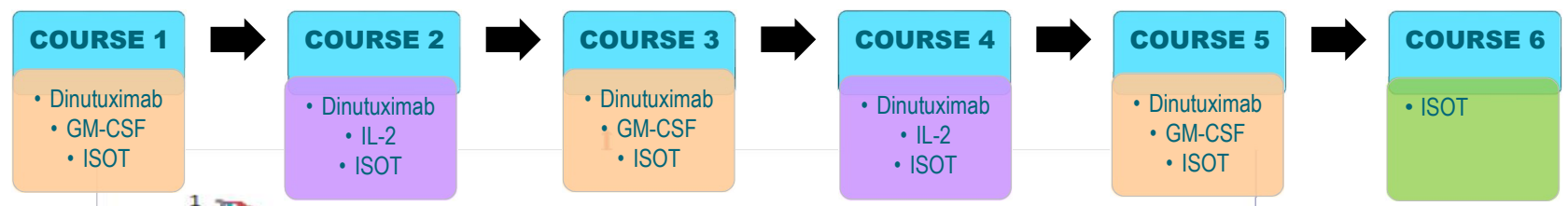
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Park JR, Kreissman SG, London WB, et al: Effect of Tandem Autologous Stem Cell Transplant vs Single Transplant on Event-Free Survival in Patients With High-Risk Neuroblastoma: A Randomized Clinical Trial. JAMA 322:746-755, 2019

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ANBL0032 Maintenance Therapy Outcomes



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Yu, A. L., Gilman, A. L., Ozkaynak, M. F., London, W. B., Kreissman, S. G., Chen, H. X., ... Sondel, P. M. (2010). Anti-GD2 Antibody with GM-CSF, Interleukin-2, and Isotretinoin for Neuroblastoma. *The New England Journal of Medicine*, 363(14), 1324–1334. <http://doi.org/10.1056/NEJMoa0911123>

Balancing the Toxicity

- How toxic is this therapy?
 - ◆ How can we still try to improve outcomes by adding more therapy but balancing toxicity?
- If we add more therapy, can anything be taken a way to make it tolerable/feasible?
- What is showing promise in early phase trials that is being studied now in current open trials?



Improving Outcomes: What can we take away?



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Interleukin-2 in Maintenance (Post-Consolidation)

SIOPEN

(randomized trial of dinutuximab beta vs. dinutuximab beta + IL-2)

- No difference in EFS or 5-yr OS
- IL-2 had higher rates of:
 - Pain, fever, allergic reaction, CLS
 - Hematologic, neurologic, GI toxicity
 - Inability to complete therapy due to toxicity

SIOPEN F/U Study

(randomized dinutuximab beta +/- **reduced** dose IL-2)

- IL-2 pts again with more pain and fever
- No significant difference between arms

SIOPEN Phase 2 Trial

(relapsed/refractory neuroblastoma)

- Showed similar EFS and OS for pts receiving dinutuximab **with or without** IL-2

COG Memo – August 2019

- Post-Consolidation cycles in ANBL1531 and ANBL17P1
 - ◆ Removes IL-2 from therapy (Cycles 2 and 4)
 - ◆ GM-CSF will be given during all 5 cycles



Improving outcomes: What else can we add?

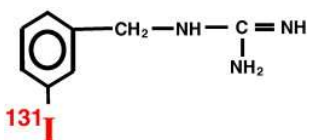


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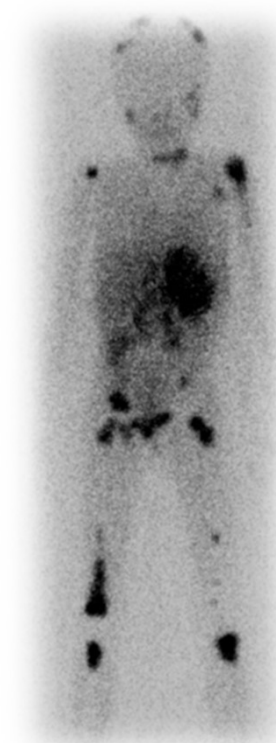
What about Metaiodobenzylguanidine (^{131}I -MIBG)?

- ^{131}I -MIBG
 - ◆ Concentrates selectively in sympathetic nervous tissue
 - ◆ Is taken up in 90% of neuroblastomas
 - ◆ Used for diagnostic scans in low dose
 - ◆ When conjugated with ^{131}I becomes targeted therapy
- Available since the 1980s
- Studied in relapse setting



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Matthay et al, JCO, 2007

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Indications for ^{131}I -MIBG Therapy

- ^{131}I -MIBG for the treatment of relapsed or refractory disease has been studied since the late 1980's
- Numerous clinical trials examining ^{131}I -MIBG as monotherapy or in combination with other agents have been conducted
- Large phase 2 multi-institution study demonstrated overall complete plus partial response rate of 36%
- ^{131}I -MIBG has been proven to be an effective treatment modality for relapsed or refractory neuroblastoma with minimal toxicities

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VOLUME 25 · NUMBER 9 · MARCH 20 2007

JOURNAL OF CLINICAL ONCOLOGY

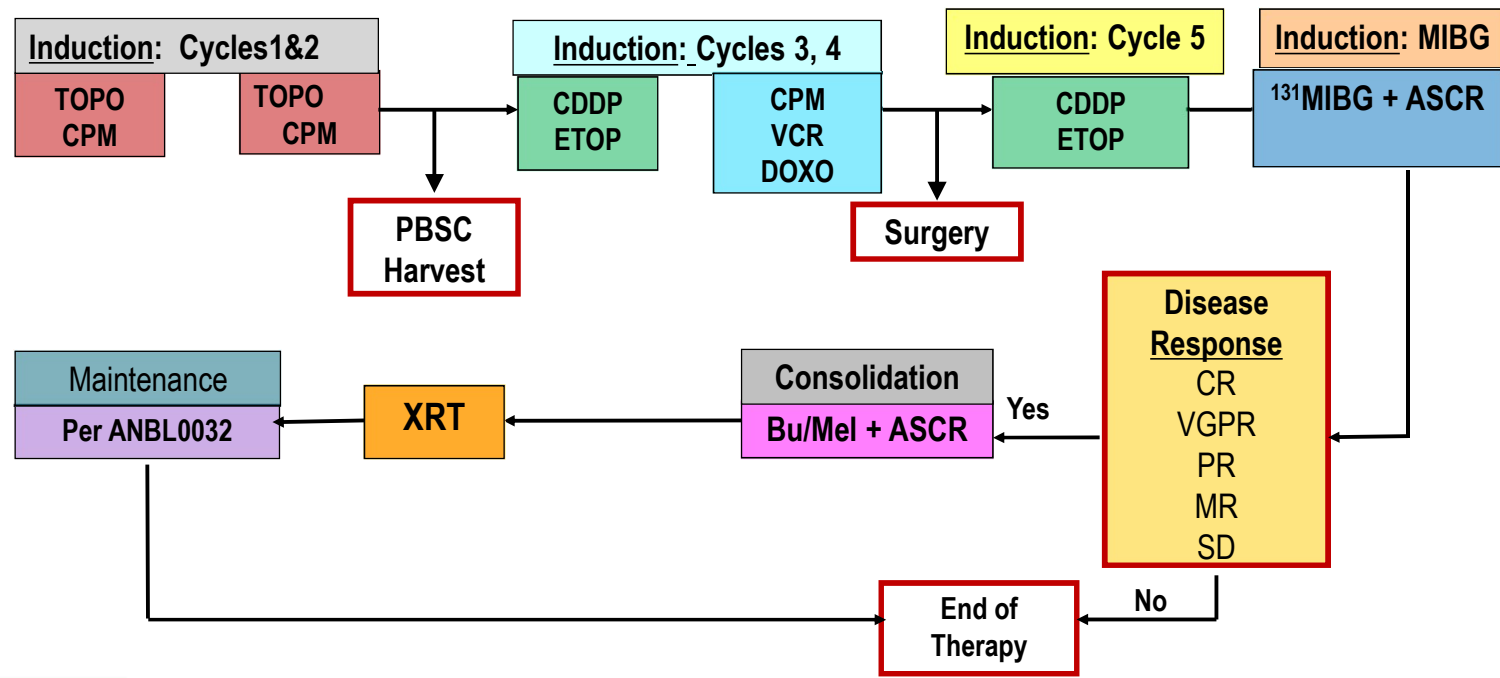
ORIGINAL REPORT

Phase II Study on the Effect of Disease Sites, Age, and Prior Therapy on Response to Iodine-131-Metaiodobenzylguanidine Therapy in Refractory Neuroblastoma

Katherine K. Matthay, Gregory Yanik, Julia Messina, Alekist Quach, John Huberty, Su-Chun Cheng, Janet Veatch, Robert Goldsby, Patricia Brophy, Leslie S. Kersun, Randall A. Hawkins, and John M. Maris

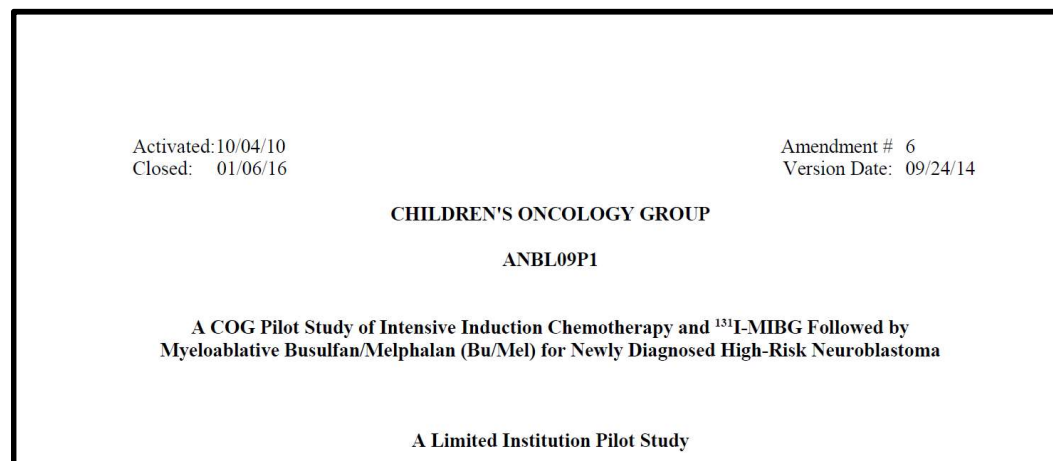
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ANBL09P1



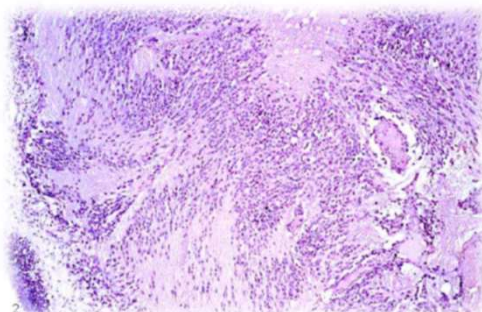
ANBL09P1 – findings

- Adding MIBG to front-line induction chemotherapy is financially/clinically feasible
- 3 patients developed SOS with BuMel auto HCT



ALK Inhibitors in High Risk Neuroblastoma

- ALK = Anaplastic Lymphoma Kinase –expressed in embryonal and neonatal brain
- Mutations or amplifications of ALK are “activating” and serve as oncogenes responsible for development and maintenance of tumors.
 - ◆ Seen in HR-NBL, NSCLC, ALCL
- 14% HR-NBL tumors with ALK mutation or amplification
- The presence of an ALK Aberration is associated with inferior EFS



Refractory Neuroblastoma

Crizotinib

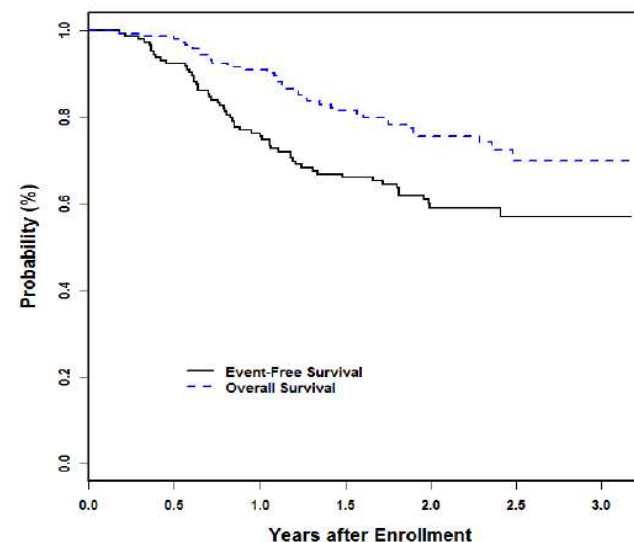
- In vitro studies show synergistic activity when combined with CPM/Topo
- Early studies in children
 - ◆ ADVL0912 – established tolerability and safety with ALCL
 - ◆ ANBL12P1:
 - Determination of ALK status in real time
- Studies in conjunction with chemotherapy in patients:
 - ◆ ANHL12P1 – added to cytotoxic chemotherapy – risk for thromboembolic events
 - Amended to require prophylactic anticoagulation
 - Continued cases → stopping rules met – arm suspended
 - ◆ ADVL1212 – Added to CPM/Topo or VCR/DOXO/DRZ for relapsed solid tumors and ALCL



Single transplant with Busulfan and Melphalan

Study	Results
SIOPEN HR-NBL-1 <i>Compared single CEM HCT with BuMel HCT</i>	Bu/Mel had improved survival 50% vs. 38% 3-yr EFS 54% vs. 41% OS ↓ toxicity EXCEPT for ↑ SOS
ANBL12p1 <i>Pilot Study Using Myeloablative BuMel Consolidation Following Induction Chemo For Pts. With Newly Diagnosed HR-NBL</i>	Hepatopulmonary toxicity of 9%

Figure 1. EFS and OS for ANBL12P1 (n=146).



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Ladenstein, 2017, Desai, 2016, Granger 2016 27



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Current Phase 3 ANBL1531 Upfront COG study for HR-NBL: Incorporating what we have learned!

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ANBL1531

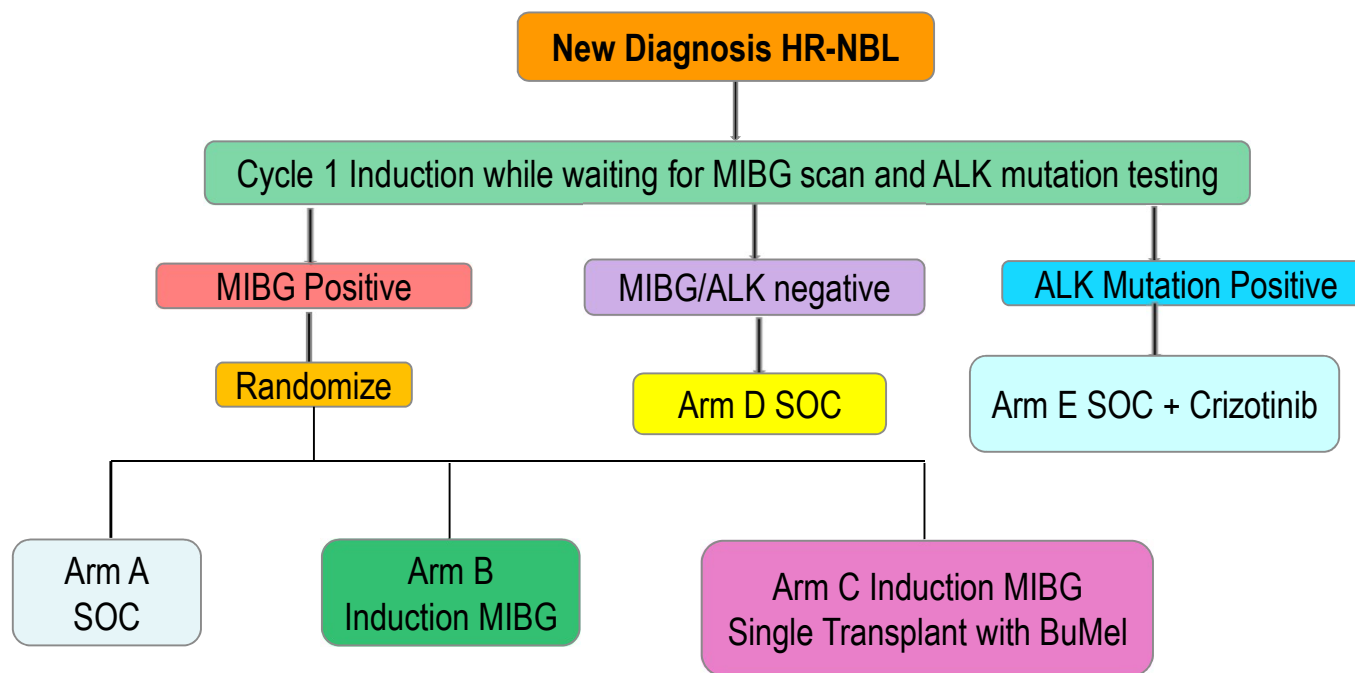
A Phase 3 Study of ^{131}I -Metaiodobenzylguanidine (^{131}I -MIBG) or Crizotinib Added to Intensive Therapy for Children with Newly Diagnosed High-Risk Neuroblastoma (NBL) (IND# 134379)

A COG Groupwide Phase 3 Study



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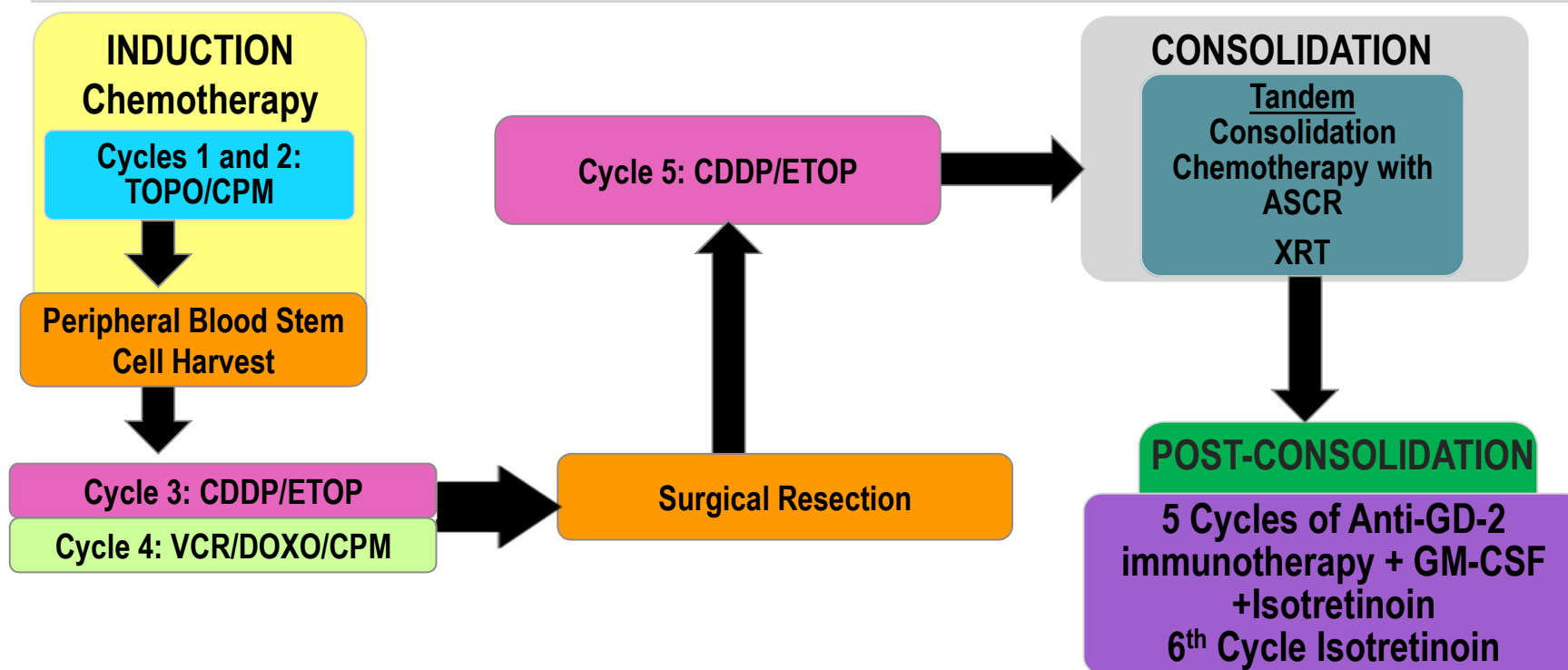
ANBL1531: 5 arm study



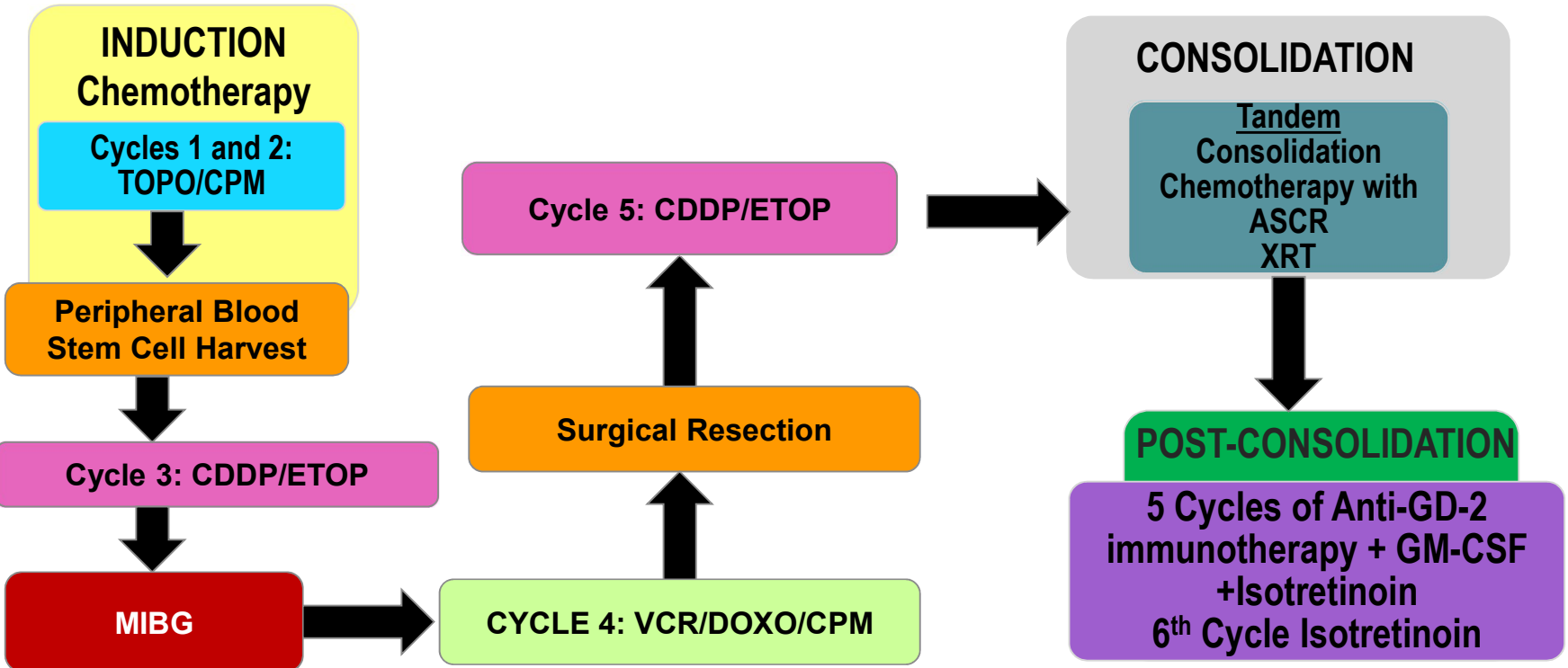
ANBL1531 Overview

- **Study Goal:** to improve outcomes by integrating targeted therapy (^{131}I -MIBG, ALK inhibition) early on in the treatment of children with HR-NBL. This protocol builds on the goals of past protocols to:
 - ◆ Determine whether ^{131}I -MIBG improves EFS with acceptable long-term toxicity in patients with MIBG-avid tumors.
 - ◆ Assess whether the addition of crizotinib to standard multi-modality therapy improves outcomes for newly diagnosed patients with tumors harboring ALK aberrations.
 - ◆ Estimate EFS and describe toxicities with ^{131}I -MIBG/ BuMel transplant.
 - ◆ Define the outcomes for patients with MIBG non-avid tumors.

Arms A (Randomized) and D (MIBG negative): Standard of Care



Arm B: Induction MIBG



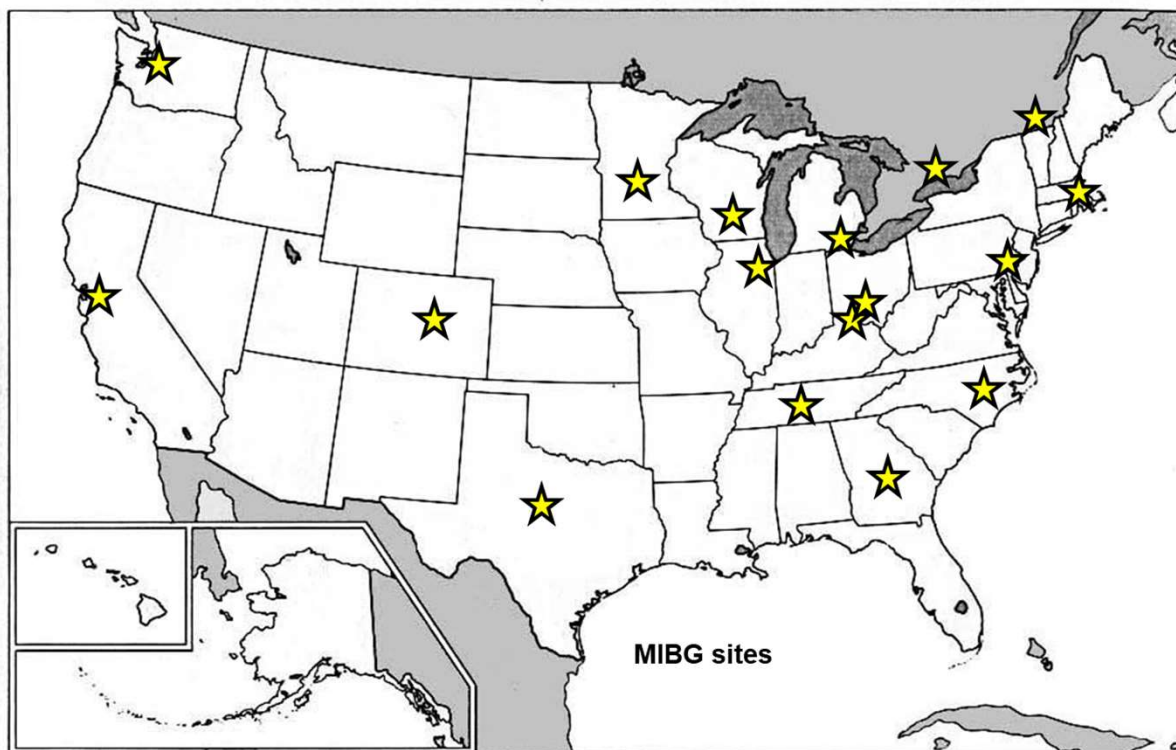
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¹³¹I-MIBG Therapy

- MIBG IV
 - ◆ Limited to certain hospitals
- Whole body dosimetry
- Side effects based upon radiation effect to bone marrow – ASCR and growth factor
- Uptake by thyroid -SSKI



17 Approved MIBG Therapy Centers: USA and Canada



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Planning for MIBG Therapy in ANBL1531?

- Once a patient is enrolled on ANBL1531, non-MIBG sites should identify two preferred MIBG centers for the patient
 - ◆ MIBG therapy can only be given at COG approved MIBG centers
 - ◆ Enrolling centers that are not transplant centers can send patient to any COG-approved transplant center as long as that center has ANBL1531 open
- To avoid delays in care, the insurance process for MIBG therapy should be started during Cycle 1 for all patients with MIBG-avid disease

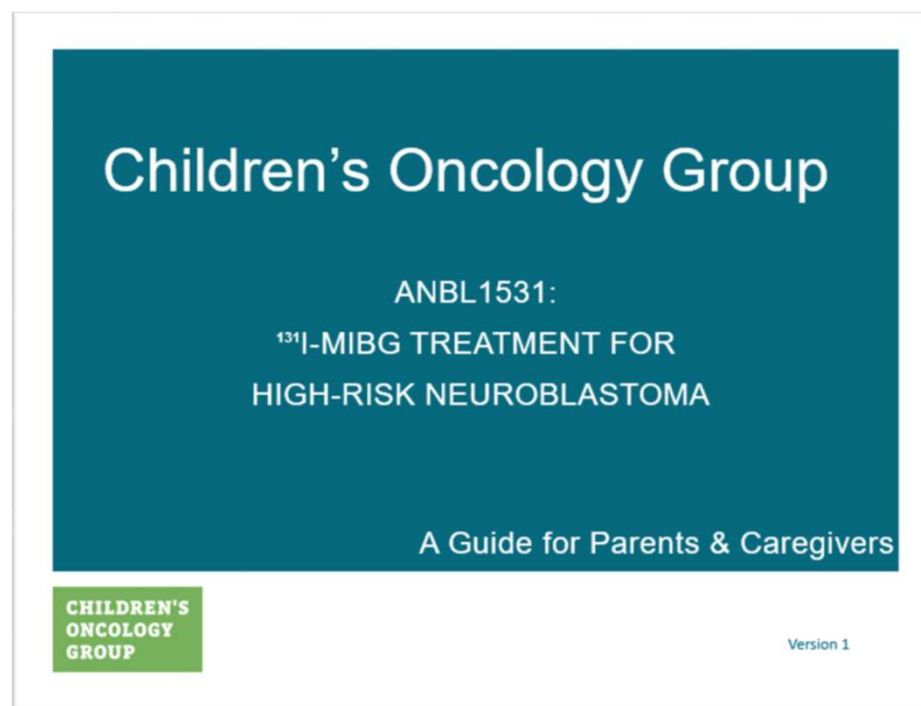


ANBL1531 – MIBG Planning Continued

- MIBG coordinator on the study to assist with communication between sites and determine which site is feasible for treatment
- Template insurance letter on protocol website
- Optional Household Material Hardship (HMH) study to be administered by primary site before cycle 2 induction



ANBL1531 – MIBG Guide for Caregivers



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¹³¹I-MIBG Side Effects

- GI
 - ◆ N&V: usually within the first 24-48 hrs post the infusion
 - ◆ Temporary loss of appetite
 - ◆ Parotid pain and/or dry mouth
- GU
 - ◆ Discomfort from the urinary catheter
- Hematopoietic
 - ◆ Low blood counts requiring stem cell support

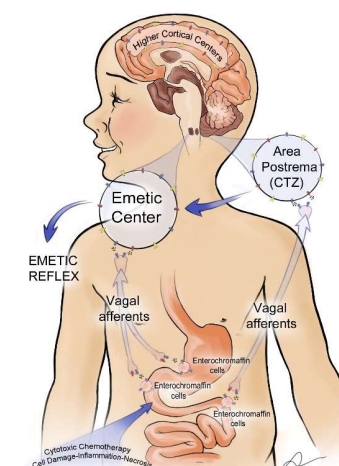
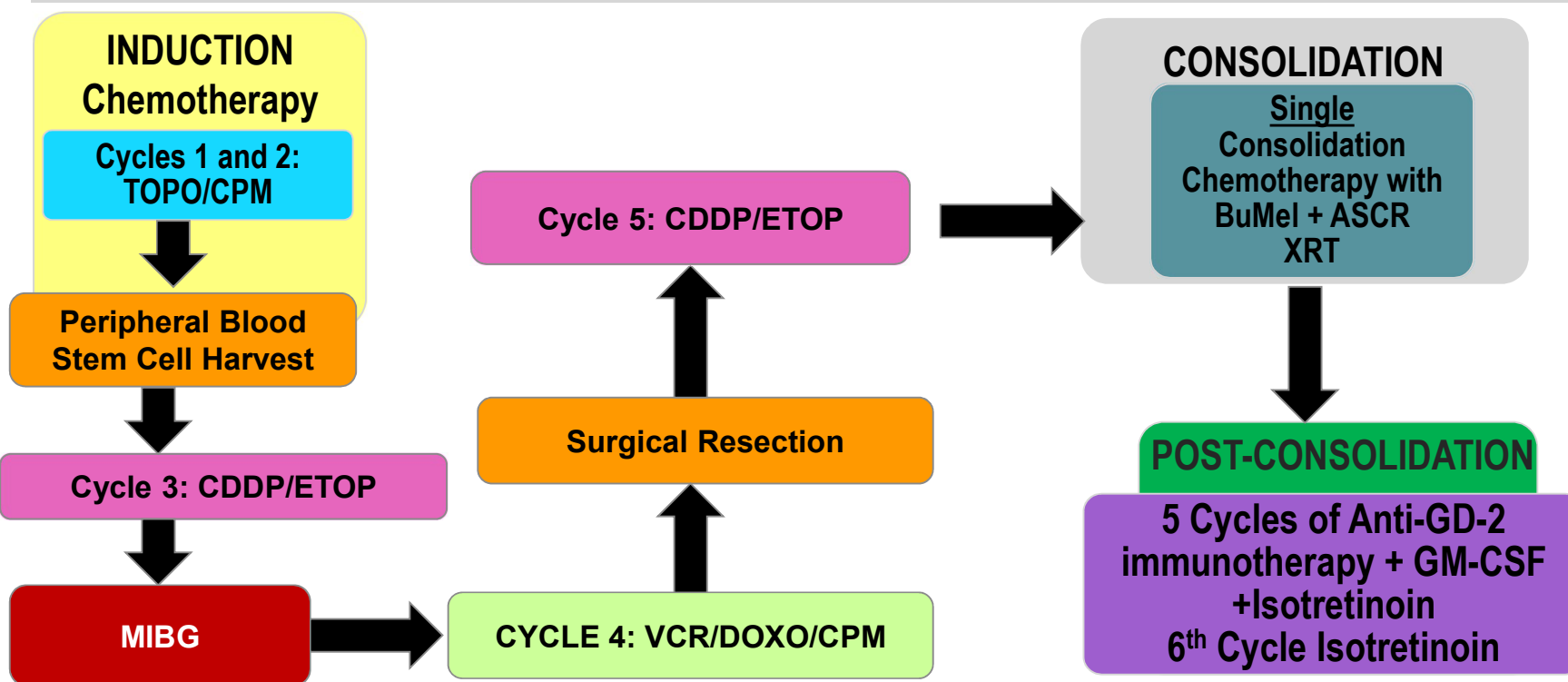


Illustration by Alice Yang, 2012

BOREDOM from having to stay in bed!

The common length of admission is 5 days but may be longer depending on travel.

Arm C: Induction MIBG



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BuMel Transplant – Nursing Considerations

- Anti-seizure prophylaxis mandatory
- Observe for signs/symptoms of SOS
 - ◆ Anti-SOS prophylaxis with ursodiol recommended
- Busulfan PK studies **REQUIRED** for pts on ARM C
 - ◆ Often sent to Seattle Cancer Care Alliance Pharmacokinetics Laboratory
 - Requisition form to accompany samples



Sinusoidal Obstruction Syndrome (SOS)

■ Baltimore Criteria:

- ◆ Serum total bilirubin > 2mg/dL within 21 days of HCT
- ◆ 2 of the following:
 - Hepatomegaly
 - > 5% weight gain
 - Ascites

■ Modified Seattle Criteria:

- ◆ Serum total bilirubin > 2mg/dL within 20 days of HSCT
- ◆ Hepatomegaly with RUQ pain
- ◆ > 2% weight gain from baseline

■ European Society for Blood and Marrow Transplantation (EBMT)

- ◆ Adds unexplained transfusion refractory thrombocytopenia

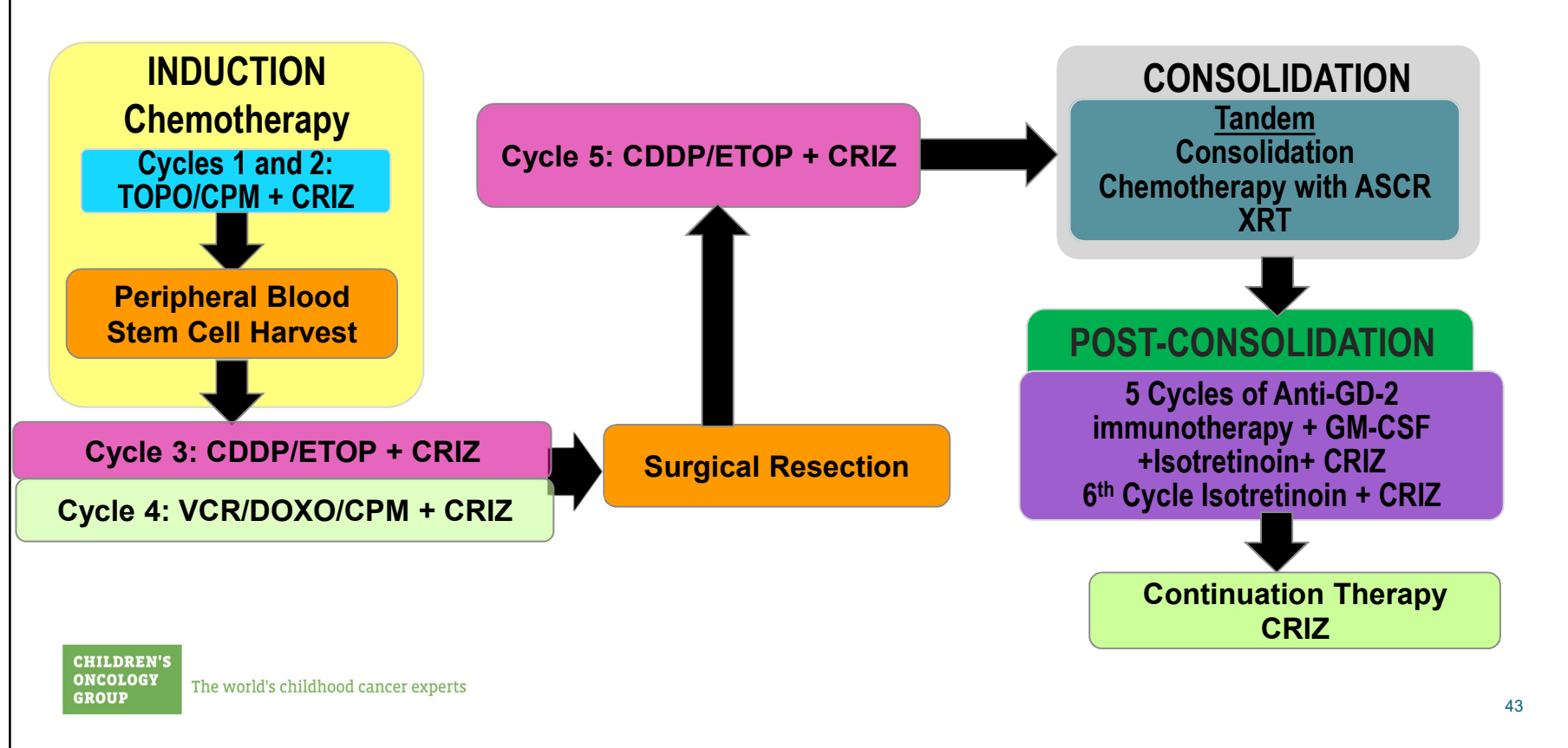


SOS Management

- Significant mortality with SOS + multi-organ system failure
 - ◆ Diuretics
 - ◆ Defibrotide
 - Side effect – bleeding
 - Thrombocytopenia – transfuse to maintain platelets > 50,000/microliter



Arm E: ALK Inhibition - Crizotinib



Crizotinib – Nursing Considerations

- Investigational product supplied by manufacturer
- Available as liquid or capsule formulation
- Appendix XII of protocol – liquid dosing education for parents:
 - ◆ Keep drug in refrigerator
 - ◆ OK to use in feeding tube
 - Flushing with water per Appendix XII based on size
 - ◆ Do **not** repeat dose if vomited
- Testing to Factor V Leiden and prothrombin gene mutations recommended for patients with a first degree relative with h/o TE event prior to age 40 yrs
 - ◆ Recommend Anticoagulation ppx if mutation associated with significant risk identified
- **Discourage** dexamethasone as antiemetic for less emetogenic cycles
- QTc prolonging agents and CYP3A active discouraged



Crizotinib (Arm E) – Nursing Considerations

- Crizotinib should start by cycle 2 or 3 at the latest
- Crizotinib timing:
 - ◆ Hold 48 hours prior to PBSC collection. Continue to hold during the collection
 - ◆ Hold on admission for HCT #1 and HCT#2
 - Restart post-HCT once ANC >750, PLT >50K and stable organ function
 - ◆ Continue Crizotinib during XRT and during Immunotherapy for 18 month course post HCT #2.
- Patient Safety: Wallet Card

Crizotinib Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial and will receive the experimental study drug, **Crizotinib**. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Crizotinib interacts with certain specific enzyme(s) in the liver*, and can alter the heart's electrical activity (QTc prolongation).

*The enzyme(s) in question are: CYP3A4 and CYP3A5. Crizotinib is broken down by these enzymes. Some drugs may increase the activity of these enzymes resulting in Crizotinib being less

Crizotinib Side Effects

- GI
 - ◆ Increase in transaminases
 - ◆ N&V/diarrhea/constipation
 - ◆ Decreased appetite/taste disturbance
- CNS
 - ◆ Visual changes (shadows, streaking)
 - ◆ Dizziness
 - ◆ Neuropathy
- Neutropenia
- Rare – Thromboembolic event
- Dose modifications outlined in protocol

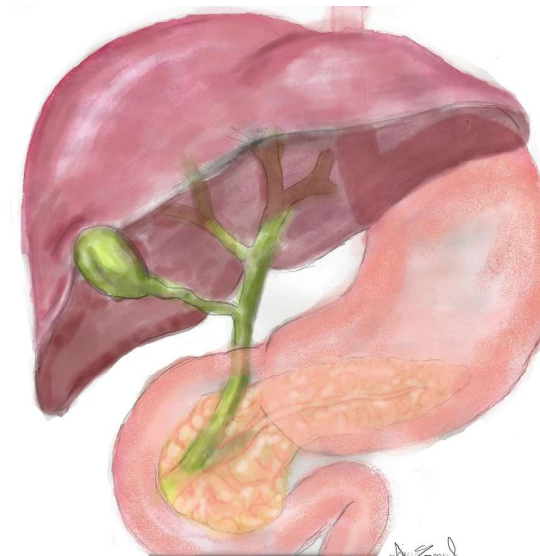


Illustration by Aimee Ermel, 2013

ANBL1531 Clinical Trial Summary for Families



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ANBL1531: A Phase 3 Study of 131I-Metaiodobenzylguanidine (131I-MIBG) or Crizotinib Added to Standard Therapy for Children with Newly Diagnosed High-Risk Neuroblastoma

Introduction



This clinical trial summary is about the Children's Oncology Group study **ANBL1531**. It tells who is eligible and gives basic information about the study. More details about the study are in the consent form. You can get this from your oncologist.

ANBL1531 is a Phase 3 clinical trial. A trial is another word for a study. This study (clinical trial) is a therapeutic clinical trial. The purpose of a Phase III trial is to learn if a drug or therapy known to work in treating a certain type of cancer is better than the standard treatment. For example: better cure rates, longer control of disease, fewer or less serious side effects, or fewer days in the hospital.



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**The Landscape of Neuroblastoma in COG:
*Yesterday's, Today's &
Tomorrow's Therapies***

Joy Bartholomew, APRN
Wendy Fitzgerald RN MSN CPON® PPCNP-BC



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Improving Outcomes: A Glimpse at the Future



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Eflornithine (DFMO)

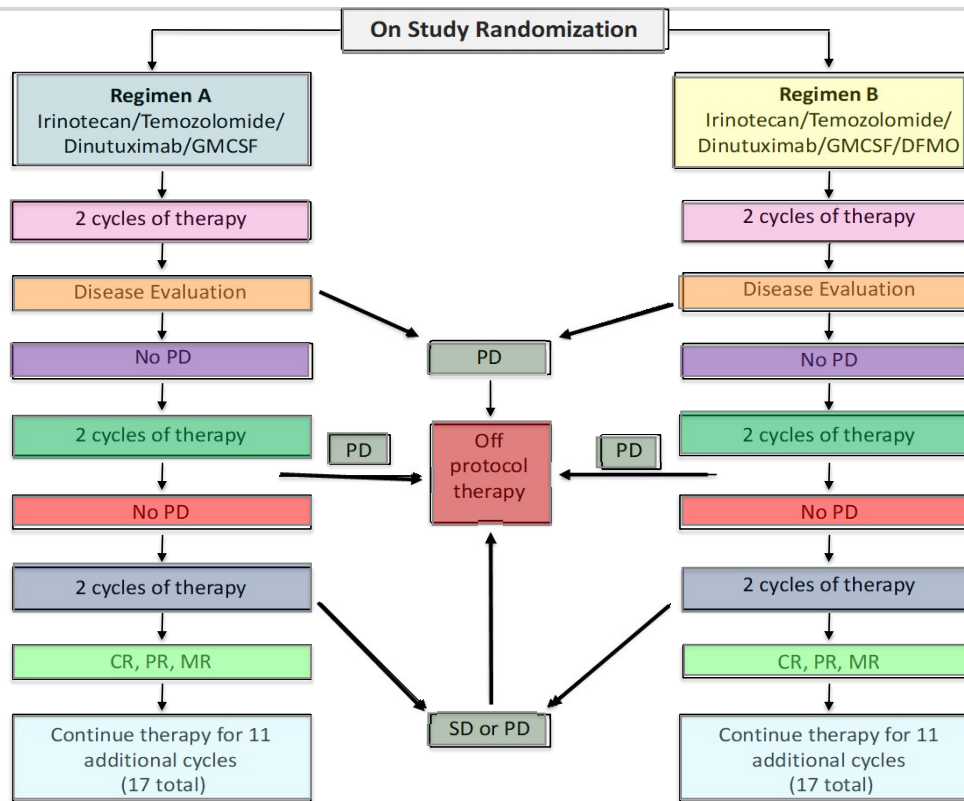
- Inhibitor of ODC1 protein which is a transcriptional target gene of MYCN
- Patients without MYCN amplification have hyperactive MYC signaling.
- FDA approved for Trypanosomiasis “sleeping sickness” encephalitis in Africa
- Well tolerated in pediatric trials
 - ◆ Phase 1 trial as a single agent
 - ◆ NANT 1201 with celecoxib, CPM and Topo
 - ◆ Multi-institution study adding as maintenance
- Oral medication
 - ◆ Few adverse events
 - ◆ Mild transaminitis
- Monitor for ototoxicity



ANBL1821 Goal

To determine if adding difluoromethylornithine (DFMO), Eflornithine) to a chemo-immunotherapy backbone (dinutuximab, irinotecan and temozolomide) has improved response rate compared to dinutuximab, irinotecan and temozolomide in patients with relapsed or refractory neuroblastoma and therefore is a therapeutic regimen worthy of further testing in patients with newly diagnosed high-risk neuroblastoma.

ANBL1821



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Eflorinine (DFMO) – Nursing Implications

- Supplied as powdered drug
- Parents to dissolve in sterile water based in drug dose (see table in Appendix XII)
 - ◆ Use gloves
 - ◆ Pregnant women should not prepare
 - ◆ Must be administered within 30 minutes of being dissolved
- May add juice for flavor.
 - ◆ **Avoid** grapefruit, orange and tomato juice
 - ◆ **Prefer** lemonade, apple, cranberry and grape juice



ANBL1821 – Nursing Implications


- Concomitant Therapy
 - ◆ The use of dexamethasone as an antiemetic therapy is **not** permitted
- Patients **must** receive pneumocystis prophylaxis during study therapy
- Cefixime should be started 2 days prior to the first dose of irinotecan and continued for a total of 10 days in each cycle



Dinutuximab in combination with chemotherapy

- ANBL1221

- ◆ Relapse patients randomized to 1 of 2 arms:
 - Irinotecan-temozolomide-temsirolimus or
 - Irinotecan-temozolomide-dinutuximab



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ANBL1221

Activated: 02/04/13
 Closed: 11/20/17

Version Date: 05/18/2017
 Amendment: #6

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ANBL1221

A Phase II Randomized Trial of Irinotecan/Temozolomide with Temsirolimus (NSC# 683864, IND# 61010) or Chimeric 14.18 Antibody (ch14.18) (NSC# 764038, IND# 4308) in Children with Refractory, Relapsed or Progressive Neuroblastoma

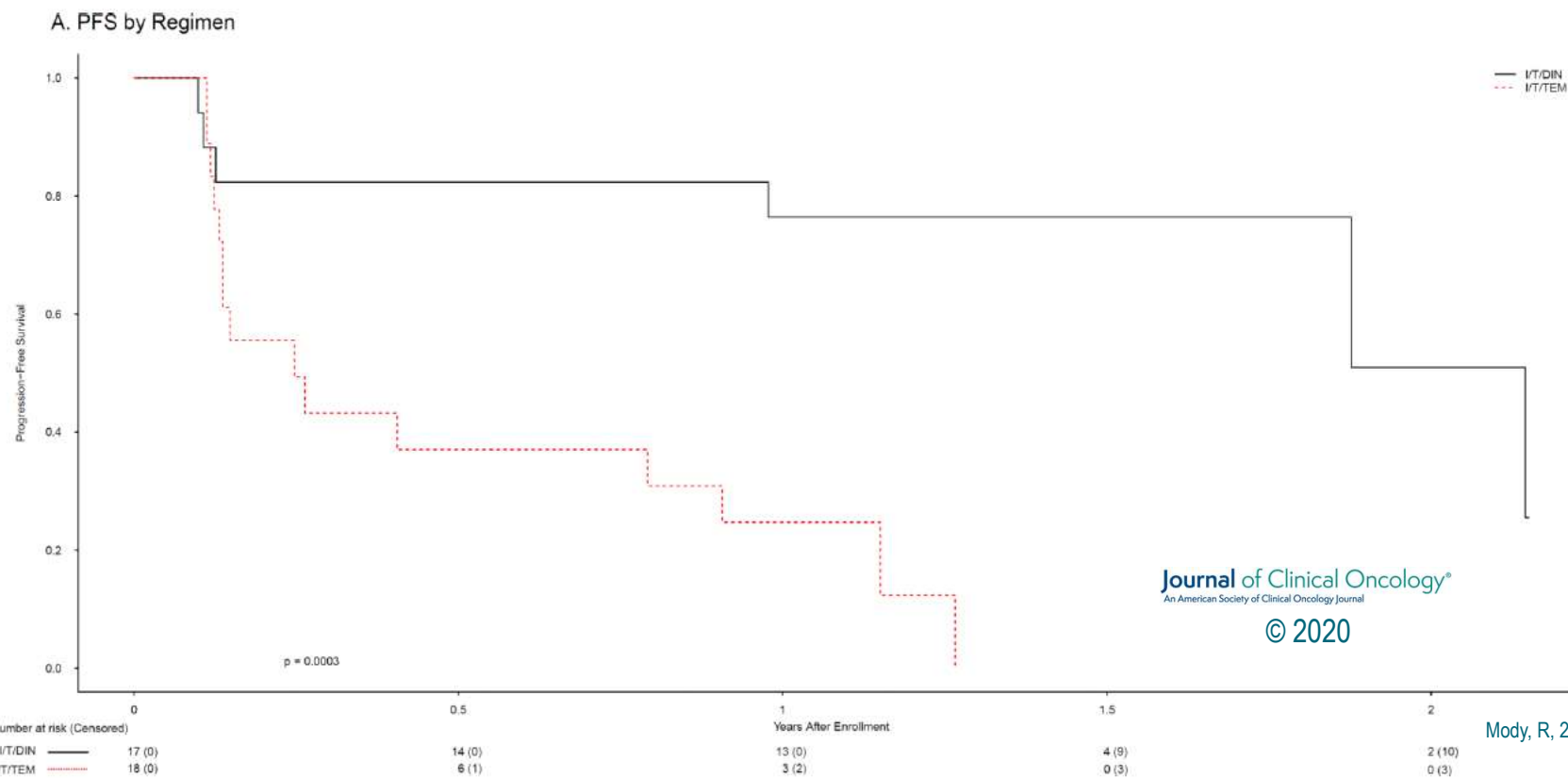
A Groupwide Phase II Study

RESULTS 

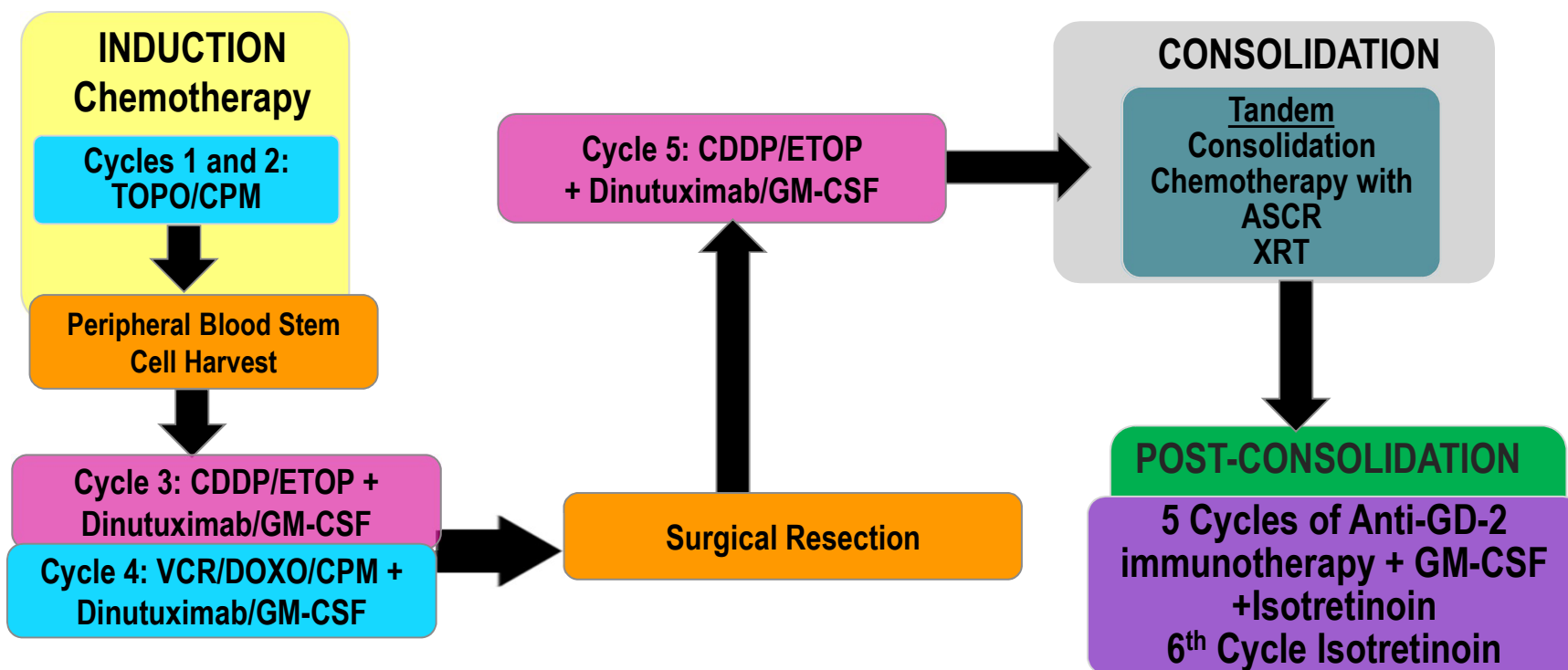


The world's childhood cancer experts

Dinutuximab Arm Superior



ANBL17P1 – Now Complete



ANBL17P1 – Nursing Implications

- What is the challenge of administering dinutuximab in conjunction with supportive hydration for chemotherapy?
- Furosemide discouraged except for respiratory compromise
- Monitor fluid status very carefully (BID weights)
- Close observations and physical exams
- Daily serum electrolytes
- Strict I&O



Summary

- High risk neuroblastoma continues to be a challenge to cure
- State of the art therapy for high risk neuroblastoma is lengthy and toxic
- New therapies entering up-front neuroblastoma trials include targeted agents including ALK inhibitors, anti-GD2 antibodies and ^{131}I -MIBG.
- Future considerations for therapy include DFMO



Abbreviations

FULL TERM	ABBREVIATION
¹³¹ Iodine	¹³¹ I
Anaplastic large cell lymphoma	ALCL
Anaplastic lymphoma kinase	ALK
Association Pediatric Hematology Oncology Nurses	APHON
Autologous	auto
Autologous Stem Cell Rescue	ASCR
Busulfan	BU
Busulfan/Melphalan	Bu/Mel
Capillary Leak Syndrome	CLS
Central nervous system	CNS
Children's Oncology Group	COG
Cisplatin	CDDP

Abbreviations

FULL TERM	ABBREVIATION
Complete remission	CR
Crizotinib	Criz
Cyclophosphamide	CPM
Cyclophosphamide/Etoposide/Melphalan	CEM
Dexrazoxane	DRZ
Difluoromethylornithine	DFMO
Disialoganglioside	GD2
Doxorubicin	DOXO
Etoposide	ETOP or VP
European Bone Marrow Transplant	EBMT
Event free survival	EFS

Abbreviations

FULL TERM	ABBREVIATION
Federal Drug Agency	FDA
Gastrointestinal	GI
Genitourinary	GU
Granulocyte macrophage- colony stimulating factor	GMCSF or GM-CSF
Hematocrit	HCT
High risk	HR
High Risk-Neuroblastoma	HR-NBL
Hours	hrs
Household Material Hardship	HMH
Intake and output	I&O
Interleukin-2	IL-2

Abbreviations

FULL TERM	ABBREVIATION
Intermediate risk	IMR
International Neuroblastoma Group	INRG
International Society of Paediatric Oncology European Neuroblastoma	SIOPEN
Intravenous	IV
Isotretinoin	ISOT
Low risk	LR
Medium Response	MR
Melphalan	Melph
Metaiodobenzylguanidine	¹³¹ I-MIBG
Month(s)	mo(s)
Nausea and vomiting	N&V or N/V

Abbreviations

FULL TERM	ABBREVIATION
Neuroblastoma	NBL
New Advances in Neuroblastoma Therapy	NANT
Overall survival	OS
Partial remission or response	PR
Peripheral blood stem cell	PBSCT
Pharmacokinetics	PK
Prophylaxis	ppx
Radiation therapy	XRT
Right upper quadrant	RUQ
Sinusoidal obstruction syndrome	SOS
Stable disease	SD

Abbreviations

FULL TERM	ABBREVIATION
Standard of care	SOC
Super Saturated Potassium Iodide	SSKI
Thromboembolytic	TE
Topotecan	TOPO
Two times/day	BID
United States of America	USA or US
Versus	vs.
Very good partial remission	VGPR
Very Low-Low Risk	VL-LR
Vincristine	VCR
Week(s)	wk(s)
Year(s)	yr(s)

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