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ANBL2131

A Phase 3 Study of Dinutuximab Added to Intensive Multimodal Therapy for Children with Newly Diagnosed High-Risk Neuroblastoma
A COG Phase 3 Study

NCI Supplied Agent: Dinutuximab (NSC# 764038, IND# 168387)

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- This randomized study is evaluating whether chemo-immunoinduction (Arm B) is superior to ANBL0532 induction (Arm A).

- Those with a poor end of induction response will receive extended induction therapy with Irin/TMX/Din/GMCSF in an effort to convert a greater proportion of patients to a good end of induction response and thus increase the proportion of patients going to tandem transplant.

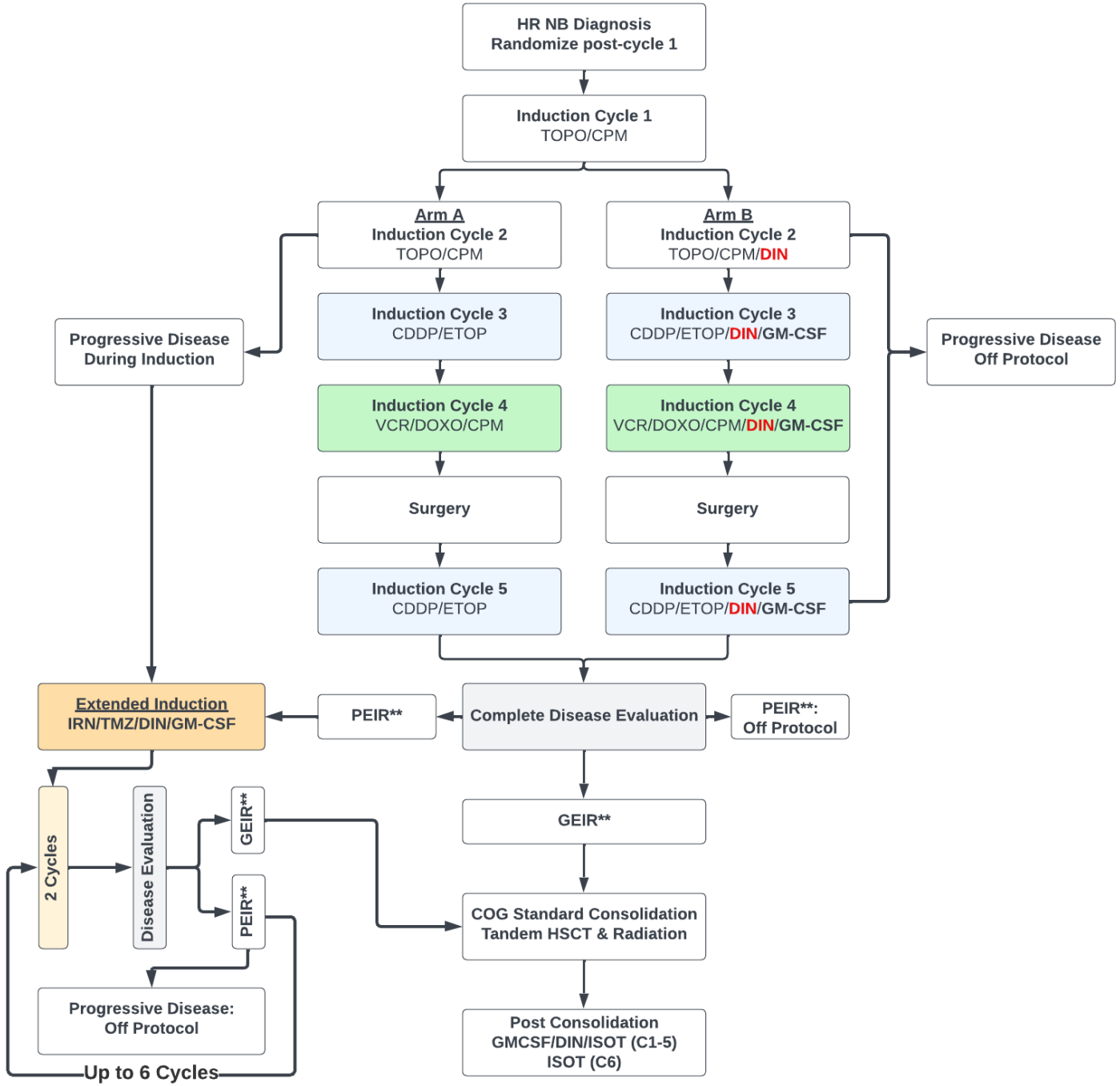
- Recent data suggests that subsets of HRNBL patients have equivalent local control with de-escalated local radiotherapy[1], as a result we will test a dose painting strategy in this multi-institutional phase 3 study.

- Finally, because MIBG persistence has been shown to be a marker of increased risk for metastatic site failure[2], varied response timing for selection of metastatic site radiotherapy will be evaluated in Arm A patients who convert from a PEIR to GEIR with extended induction.

[1]PMID: 30763661, PMID: 30496881
[2]PMID: 35345864

Trial Schema

- Patient randomization occurs after cycle 1.
- Surgery is recommended after cycle 4.
- A total of 5 cycles of induction will be given in Arm B, while Arm A patients with a PEIR may receive up to 11 cycles prior to transplant.
- TC/CEM conditioning with Tandem transplant is recommended for all GEIR patients.
- Radiotherapy will be delivered either at diagnosis for patients with threatened function (i.e., vision, paralysis) and/or following transplant.
- Additional post-consolidation immunotherapy and differentiation therapy is required for all patients following radiotherapy.



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Trial Response Evaluations

- Patients will undergo response assessment at multiple timepoints:
  - Post Cycle 5
  - +/- Post-transplant (for patients with >5 metastatic sites pre-ASCT)
  - After each 2-cycle block during extending induction in Arm A if a PEIR is obtained
- Response is split into:
  - Primary site
  - Soft Tissue & Bone Metastatic site
  - Bone marrow
- Various combinations of the above define the Overall Response category which defines status assignments on study (Good End of Induction Response or Poor End of Induction Response) (See adjacent from Appendix VI).

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APPENDIX VI: OVERALL RESPONSE AND GEIR/PEIR CRITERIA

Primary Tumor	Soft Tissue and Bone Metastatic Disease (MIBG or ^{18}F-FDG-PET/CT or PET/MR)	Bone Marrow Metastatic Disease	Overall Response	End of Induction GEIR or PEIR
CR	CR	CR	CR	GEIR
CR for one response component with either CR or NI for other components			CR	GEIR
CR	CR	MD	PR	GEIR
CR	PR	CR	PR	GEIR
CR	PR	MD	PR	GEIR
CR	PR	NI	PR	GEIR
CR	NI	MD	PR	GEIR
PR	CR	CR	PR	GEIR
PR	CR	NI	PR	GEIR
PR	CR	MD	PR	GEIR
PR	PR	CR	PR	GEIR
PR	PR	NI	PR	GEIR
PR	PR	MD	PR	GEIR
PR	NI	CR	PR	GEIR
PR	NI	NI	PR	GEIR
PR	NI	MD	PR	GEIR
NI	CR	MD	PR	GEIR
NI	PR	CR	PR	GEIR
NI	PR	MD	PR	GEIR
NI	PR	PR	PR	GEIR
NI	PR	NI	PR	GEIR
CR	CR	SD	MR	PEIR
CR	PR	SD	MR	PEIR
CR	SD	CR	MR	PEIR
CR	SD	MD	MR	PEIR
CR	SD	SD	MR	PEIR
CR	SD	NI	MR	PEIR
CR	NI	SD	MR	PEIR
PR	CR	SD	MR	PEIR
PR	PR	SD	MR	PEIR
PR	SD	CR	MR	PEIR
PR	SD	MD	MR	PEIR
PR	SD	SD	MR	PEIR
PR	SD	NI	MR	PEIR
PR	NI	SD	MR	PEIR
SD	CR	CR	MR	GEIR
SD	CR	MD	MR	GEIR
SD	CR	SD	MR	PEIR
SD	CR	NI	MR	GEIR
SD	PR	CR	MR	GEIR
SD	PR	MD	MR	GEIR
SD	PR	SD	MR	PEIR
SD	PR	NI	MR	GEIR
SD	SD	CR	MR	PEIR
SD	NI	CR	MR	GEIR
NI	CR	SD	MR	PEIR
NI	PR	SD	MR	PEIR
NI	SD	CR	MR	PEIR
SD	SD	MD	SD	PEIR
NI	SD	MD	SD	PEIR
SD	NI	MD	SD	GEIR
NI	NI	MD	SD	GEIR
SD	SD	SD	SD	PEIR
SD	NI	SD	SD	PEIR
SD	SD	NI	SD	PEIR
SD	NI	NI	SD	GEIR
NI	SD	SD	SD	PEIR
NI	SD	NI	SD	PEIR
NI	NI	SD	SD	PEIR
Response of PD in any one of the 3 components			PD	PEIR
Response of NR for any one of the 3 components			*	ND
Response of ND in any one of the 3 components			ND	ND

CR: Complete Response; MD: Minimal Disease; PR: Partial Response; MR: Minor Response; SD: Stable Disease; PD: Progressive disease; NI: not involved; site not involved at study entry and remains not involved; GEIR: Good End Induction Response; PEIR: Poor End Induction Response;

Trial Response Criteria

- Adapted from INRC Criteria in Park et al. JCO 2017

Primary (soft tissue) Tumor Response*	
Resp	**Anatomic + MIBG/FDG-PET**
CR	<10 mm residual soft tissue at 1º site AND
	Complete resolution of MIBG/FDG-PET† uptake at 1º site
PR	≥ 30% decrease in longest diameter of 1º site AND
	MIBG/FDG-PET† uptake at 1º site stable, improved, or resolved
PD	> 20% increase in longest diameter (ref = smallest sum on study) AND
	Minimum absolute increase of 5 mm in longest dimension‡
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD at the 1º site
†Used for MIBG-non-avid tumors. ‡Mass that does not meet PD measurement criteria but has fluctuating MIBG avidity will not be considered PD.	

Bone Marrow Response	
Resp	**Anatomic + MIBG/FDG-PET**
CR	Bone marrow with no tumor infiltration on reassessment, independent of baseline tumor involvement
PR	Any of the following:
	Bone marrow without tumor infiltration that becomes > 5% tumor infiltration on reassessment OR
	Bone marrow with tumor infiltration that increases by > two-fold and has > 20% tumor infiltration on reassessment
MD	Any of the following: Bone marrow with ≤ 5% tumor infiltration and remains > 0 to ≤ 5% tumor infiltration on reassessment OR
	Bone marrow with no tumor infiltration that has ≤ 5% tumor infiltration on reassessment OR
	Bone marrow with > 20% tumor infiltration that has > 0 to ≤5% tumor infiltration on reassessment
SD	Bone marrow with tumor infiltration that remains positive with >5% tumor infiltration on reassessment but does not meet CR, MD, or PD criteria
See PMID: 28471719 for further details	

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Tumor Response at Metastatic Soft Tissue and Bone Sites	
Resp	**Anatomic + MIBG/FDG-PET**
CR	Resolution of all sites of disease, defined as: Non-1º target & nontarget lesions measure , <10 mm AND
	Lymph nodes identified as target lesions decrease to a short axis , <10 mm AND
	MIBG uptake or FDG-PET uptake (for MIBG-nonavid tumors) of non-1º lesions resolves completely
PR	≥30% decrease in sum of diameters† of non-1º target lesions compared with baseline AND all of the following:
	Nontarget lesions may be stable or smaller in size AND
	No new lesions AND
	≥50% reduction in MIBG absolute bone score (relative MIBG bone score ≥ 0.1 to ≤ 0.5) or ≥ 50% reduction in number of FDG-PET–avid bone lesions‡§
PD	Any of the following: Any new soft tissue lesion detected by CT/MRI that is also MIBG or FDG-PET avid
	Any new soft tissue lesion seen on anatomic imaging that is biopsied & confirmed to be neuroblastoma or Ganglioneuroblastoma
	Any new bone site that is MIBG avid
	A new bone site that is FDG-PET avid (for MIBG-nonavid tumors) AND has CT/MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or Ganglioneuroblastoma
	>20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions
	Relative MIBG score ≥ 1.2§
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD of non-1º lesions
See PMID: 28471719 for further details	

Indications for Radiotherapy

- A small subset of patients may present with functional compromise (respiratory, visual, neurologic) at diagnosis which may warrant emergent radiotherapy prior to initiation of protocol therapy.

- All patients receive primary site radiotherapy

- Consolidative metastatic site radiotherapy to incompletely responding metastases should occur at the site time as the treatment of the primary site.

Changes in the Radiotherapy paradigm in ANBL2131

- Reduced dose (18 Gy) to the CTV when treating the primary site target volume is allowed in a subset of patients:
  - Good end of induction response
  - MYCN non-amplified
  - Primary Site CR (<10mm residual at the primary site following resection)

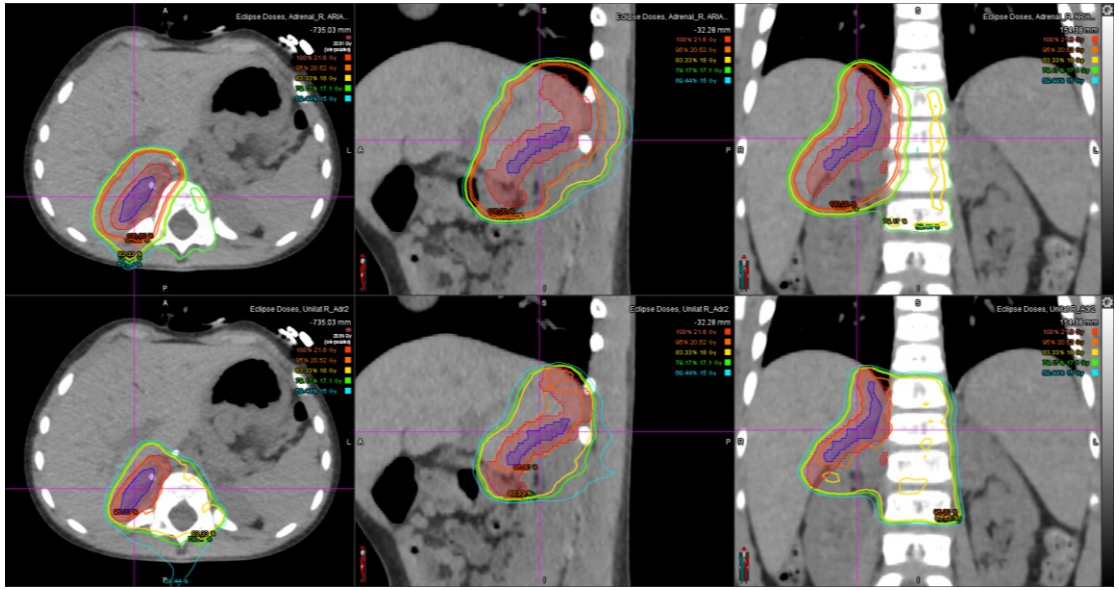
- Selection of metastatic sites for radiotherapy:
  - Those treated on Arm A will have metastatic sites chose based on the post-cycle 5 response evaluation.
  - Those treated on Arm B with a poor end of induction response will be selected based on extended induction response evaluations.

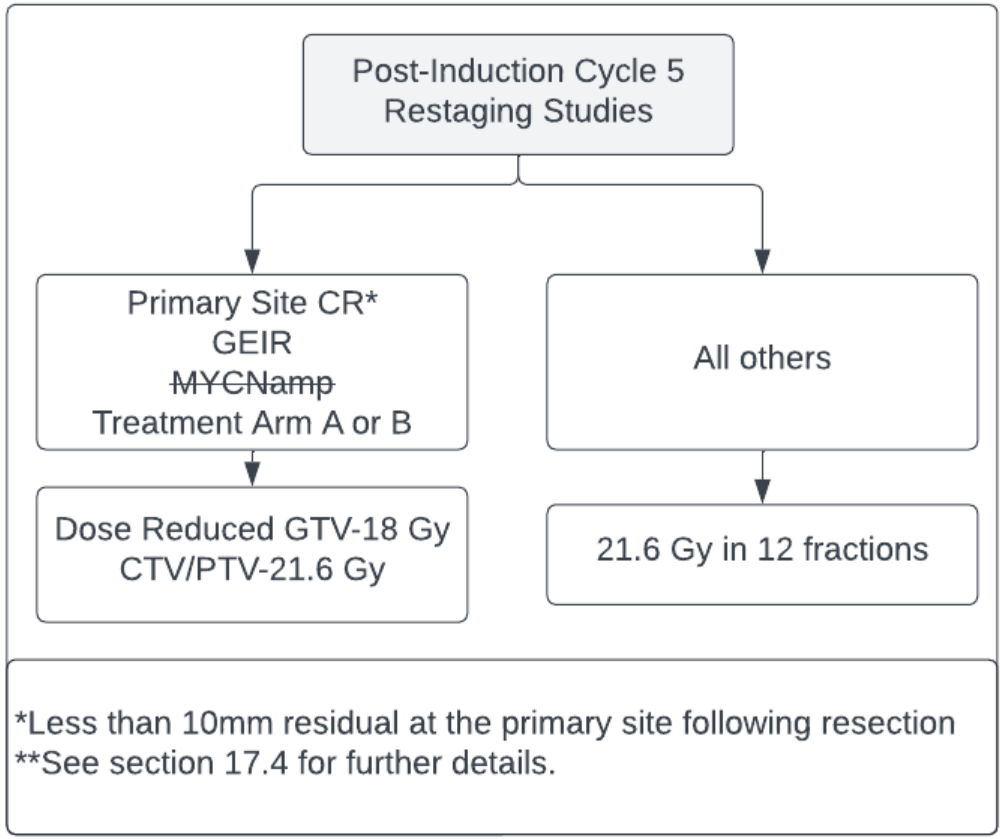
1º Site Dose Reduction

Dose Reduced Patients

-Dose reduction has been successful in single institution studies[1].

-This has the potential to limit renal, pancreatic, spleen and liver acute and late complications.





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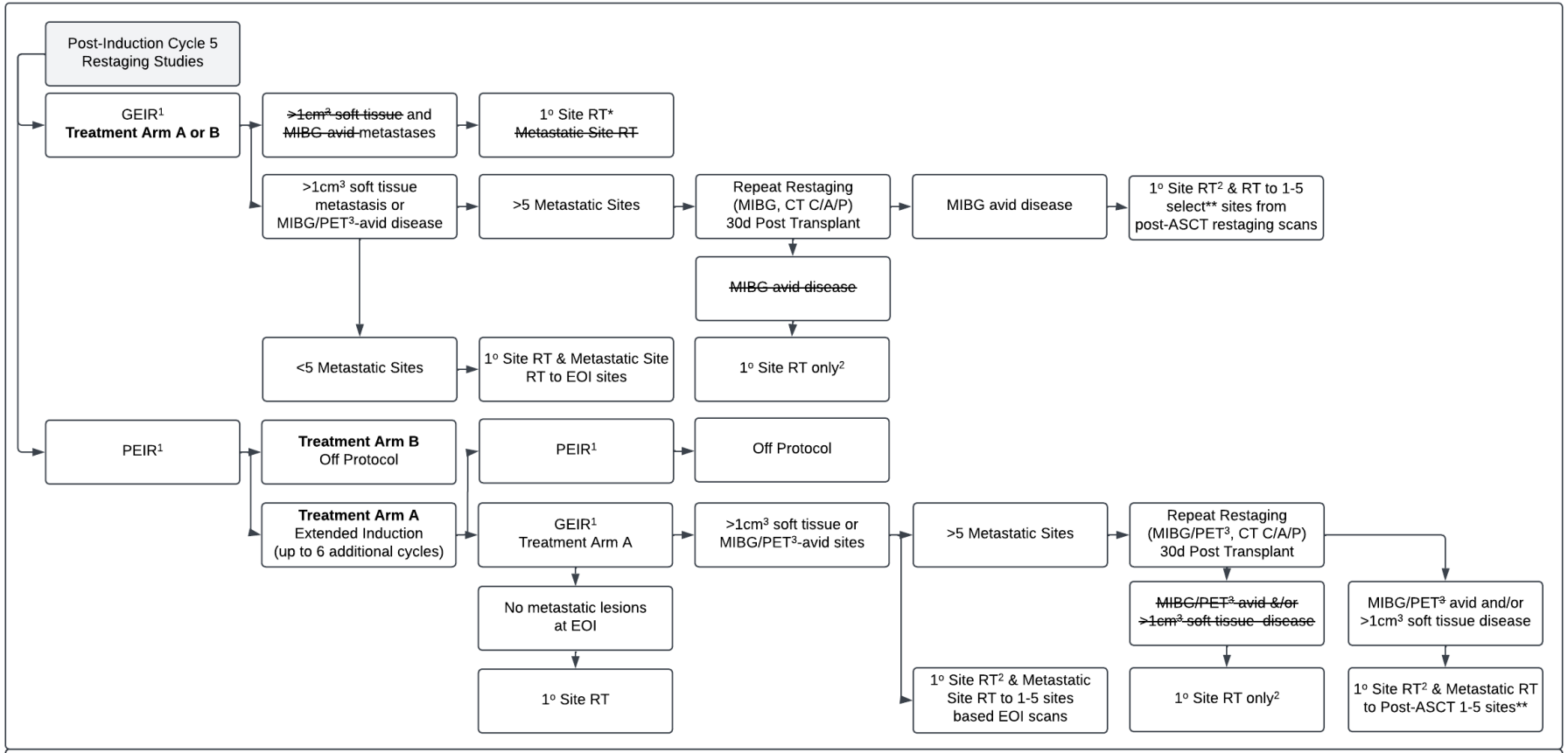
[1]PMID: 30763661

Altered Metastatic Site Selection in Arm A Patients

-Persistent MIBG avidity is associated with an increased risk of metastatic site relapse[1].
-PEIR patients in Arm A are re-evaluated every 2 cycles for up to 6 cycles.
-If a GEIR is obtained after extended induction, then the patient goes to ASCT.
-The immediate pre-ASCT response evaluation study will define the sites to be consolidated with RT.
-Arm B cases will be treated based on the post-cycle 5 response evaluation.



*Patients who have achieved GTR, and had a GEIR are eligible for dose reduction to 18 Gy - See section 17.9.2.4 Treatment Sites and Doses for details. EOI=End of Induction; GEIR=Good End of Induction Response; PEIR=Poor End of Induction Response; RT=Radiation Therapy; d=days; ASCT=Autologous stem cell transplant. [1]See section 10.3 for definitions of GEIR and PEIR, [2]See section 17.4 for further details, [3]PET scans will be used for patients with MIBG non-avid tumors.

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[1]PMID: 35345864

Radiotherapy Timing & Delay Criteria

- Radiation will be given after recovery from the ASCT.
- It is recommended that radiation therapy begin no sooner than Day +42 and no later than Day +80 following the second ASCT.
- Organ toxicity within the radiation field should have resolved.

Organ in Radiation Field	Considerations for Delay of Radiation Therapy
Bone Marrow^	Persistent cytopenias, including absolute neutrophil count (ANC) ≤ 500/μL (off G-CSF for ≥ 48 hours), and/or transfusion-refractory thrombocytopenia with platelet count < 40,000/ μL.
Liver	Active sinusoidal obstruction syndrome without signs of resolution*
Trachea	Grade 2 or higher airway edema that requires respiratory support
Abdomen	Refractory diarrhea, greater than CTCAE Grade 2
Kidneys**	Persistently elevated serum creatinine for age/sex (see Section 3.3.4) or 2 x the creatinine value obtained at the start of Consolidation therapy
Bladder	Persistent hematuria

^Volume of potential marrow radiation exceeding 10% of total marrow (see Table 3)
*Radiation involving the liver should be delayed for active sinusoidal obstruction syndrome (SOS) of any grade. Hepatomegaly and fluid accumulation may persist after SOS has begun to resolve, and radiation may be initiated provided that physiologic portal flow has returned, hyperbilirubinemia and pain are improving, and the patient has been stable on room air for five days. Consultation with anesthesiology should be pursued prior to initiation of sedated radiotherapy treatment.
**Please refer to Table 11 for discussion of renal scintigraphy if recommended kidney dose constraints are exceeded.

Radiotherapy Prescriptions

GEIR AND Primary Site CR (<10mm residual)				
Site	**Target**	**Dose**	**Dose/ Fraction**	**Fractions**
Primary tumor site, initially involved lymph nodes, surgical bed	CTV	18 Gy/GyRBE	1.5 Gy/GyRBE	12
	GTV	21.6 Gy/GyRBE	1.8 Gy/GyRBE	12
Approximating Vertebral Bodies	OTV_VB	18 Gy/GyRBE	1.5 Gy/GyRBE	12

Primary Site: GEIR and < Primary Site CR (≥ 10mm residual)				
Site/Target	**Target**	**Dose**	**Dose/ Fraction**	**Fractions**
Primary tumor site, initially involved lymph nodes, surgical bed	CTV	21.6 Gy/GyRBE	1.8 Gy/GyRBE	12
Approximating Vertebral Bodies	OTV_VB	18 Gy/GyRBE	1.5 Gy/GyRBE	12

Metastatic Site Consolidation				
Site/Target	**Target***	**Dose**	**Dose/ Fraction**	**Fractions**
Metastatic disease after Induction or Extended Induction	mCTVx/ ITVx/ PTVx*	21.6 Gy/GyRBE	1.8 Gy/GyRBE	12
Hepatomegaly leading to respiratory distress	Partial Liver^	4.5 Gy	1.5 Gy	3
Visual Compromise at Diagnosis	Base of Skull^	5.4 Gy	1.8 Gy	3
Craniospinal Radiotherapy Dose**		21.6 Gy/GyRBE	1.8 Gy/GyRBE	12

*When proton therapy is used, the prescription target will be the CTV or ITV depending on whether target motion is present at the primary or metastatic site. When photon radiotherapy is used, the prescription target for coverage will be the PTV.

**If leptomeningeal disease is discovered during therapy, the study team should be contacted regarding optimal management as craniospinal radiotherapy may be required.

^Contoured Target Volumes are not required for emergency cases.

Organs at Risk

- OARs are categorized into 3 groups:
  - Required, Conditional, or Suggested

- Definitions:
  - Required: these should be delineated for all cases where that treatment site is treated with radiotherapy.

  - Conditional: these organs may or may not be present based on the patient's gender i.e., Vagina/Uterus are only contoured for girls.

  - Suggested: these organs are variably be at risk for subsequent treatment related injury depending on the specific site i.e., the lacrimal gland would only be relevant for disease volumes which approximate the orbit, parotid/submandibular gland volumes would only be appropriate for persistent soft tissue adenopathy in the high neck which might compromise late salivary function.

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Table 11. Required Organs at Risk According to Treatment Site

Site	TG263 Name	Required DVH	Status	Constraint
Cranium/ Head & Neck	Brain	Brain	R	NA[□]
	Cochlea_L	Left Cochlea	R	Dmean < 30 Gy
	Cochlea_R	Right Cochlea	R	
	Glnd_Lacrimal_L	Left Lacrimal Gland	S	Dmean < 26 Gy
	Glnd_Lacrimal_R	Right Lacrimal Gland	S	
	Glnd_Submand_L	Left Submandibular Gland	S	
	Glnd_Submand_R	Right Submandibular Gland	S	
	Lens_L	Left Lens	R	ALARA
	Lens_R	Right Lens	R	ALARA
	OpticNrv_L	Left Optic Nerve	R	NA[□] D50% < 5400 cGy D0.1cc < 5600 cGy
	OpticNrv_R	Right Optic Nerve	R	
	OpticChiasm	Optic Chiasm	R	
	Orbit_L	Left Orbit	R	NA[□]
	Orbit_R	Right Orbit	R	NA[□]
	Parotid_L	Left Parotid	S	Dmean < 26 Gy
	Parotid_R	Right Parotid	S	
	SpinalCord	Spinal Cord	R	NA[□]
	Retina_L	Left Retina	R	Dmean < 30 Gy[173]
	Retina_R	Right Retina	R	
	Thyroid	Thyroid	R	Dmax <10 Gy[174]
Abdomen/ Pelvis	A_LAD	Left Anterior Descending a.	S	Dmean < 5 Gy* [175]
	Heart	Heart[≈]	R	Dmean < 26 Gy
	Ventricle_L	Left Ventricle	S	Dmean < 5 Gy*[175]
	Bladder	Bladder	R	NA[□]
	Esophagus	Esophagus	R	NA[□]
	Kidney_L	Left Kidney	R	Contralateral[©] D25% < 18 Gy Ipsilateral[©] D75% < 18 Gy D100% < 14.4 Gy Dmean ≤ 18 Gy
	Kidney_R	Right Kidney	R	
	Kidneys	Kidneys	R	D50% < 24Gy
	Liver	Liver	R	Dmean < 15 Gy[®]
	Ovary_L	Left Ovary (Females Only)	C	ALARA
	Ovary_R	Right Ovary (Females Only)	C	
	Pancreas	Pancreas	R	ALARA[Ω]
	SpinalCord	Spinal Cord	R	NA[□]
	Testis_L	Left Testis (Males Only)	C	ALARA
	Testis_R	Right Testis (Males Only)	C	
	Uterus	Uterus (Females Only)	C	
	Vagina	Vagina (Females Only)	C	
Chest/ Paraspinal	A_LAD	Left Anterior Descending a.	S	Dmean < 5 Gy* [175]
	Breast_L	Left Breast (Females Only)	C	ALARA
	Breast_R	Right Breast (Females Only)	C	ALARA
	Esophagus	Esophagus	R	NA[□]
	Heart	Heart[≈]	R	Dmean < 26 Gy
	Lung_L	Left Lung	R	Ipsilateral V20 < 30% Contralateral V20 <10%
	Lung_R	Right Lung	R	
	Lungs	Lungs	R	V20 < 30%
	SpinalCord	Spinal Cord	R	NA[□]
	Thyroid	Thyroid	R	Dmax <10 Gy^ [174]
	Ventricle_L	Left Ventricle	S	Dmean < 5 Gy* [175]

Required = R, Conditional = C, Suggested = S, ALARA = As Low As Reasonably Achievable, NA[□] = Dose constraints are not expected to be exceeded for this organ but reporting of the DVH may be relevant for late effects surveillance and as such has been included, [©] = If kidney dose exceeds the constraints outlined, renal scintigraphy is recommended to ensure that both kidneys are functioning prior to beginning radiotherapy. [®] = If liver constraints are exceeded due to need to radiate a liver lesion, extra concern should be exercised for patients who are recovering from SOS. [Ω] = The pancreas frequently approximates the primary site target and as such, limited potential exists for sparing; however, this remains a source of late morbidity (Glucose Intolerance/Diabetes Mellitus) in childhood cancer patients [91]. As such, attempts should be made to limit dose to the pancreatic tail when possible[90]. [≈] = Risk of Pericarditis. * = Risk of Coronary Artery Disease. ^ = Risk of Hypothyroidism, a. = artery.

Contouring Process

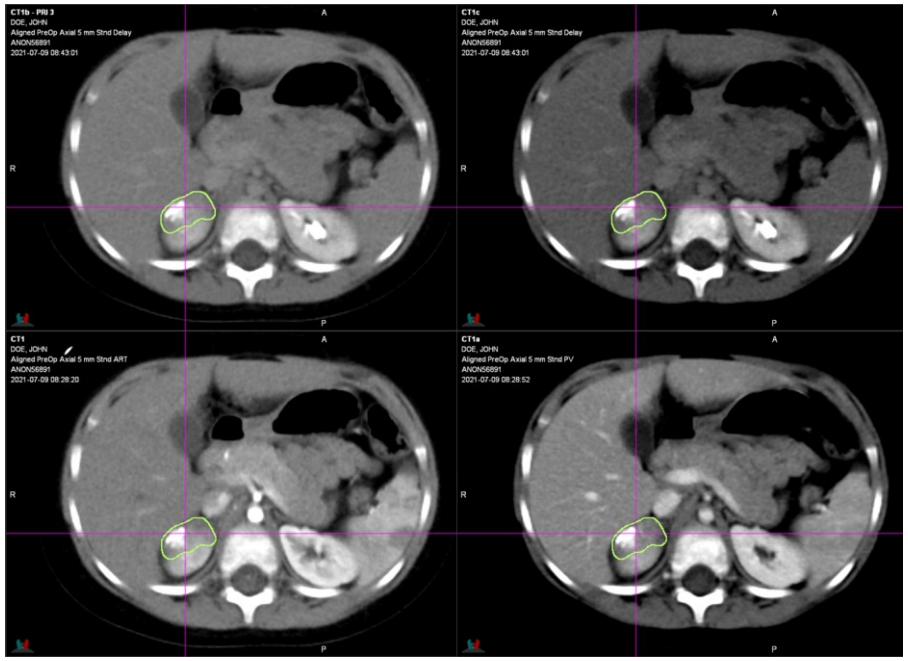
The following steps are suggested for primary site volume delineation.

1) Delineate all required OARs, & patient and site specific conditional and suggested OARs.
2) Co-register the post-induction Cycle 4, pre-surgery scans with the simulation CT scan.

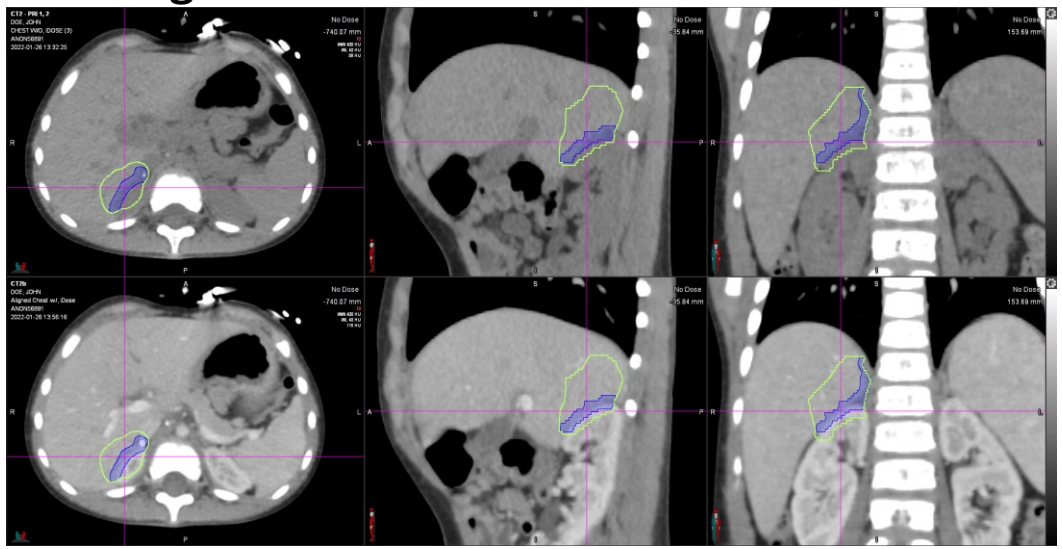
   (See Aligned PreOp scans for ANBL2131 Case 1)

3) Delineate the GTV_Preop (see green volume)
4) Copy the GTV_Preop and adjust for inclusion of clips, operative boundaries, pathologic findings & exclusion of pushing/non-infiltrated boundaries.
5) Rename the adjusted contour GTV (blue volume)

Post-C4 Induction, Preoperative Scans



Planning Scans



Contouring Process

6) Expand the GTV by 1cm to derive the CTV

7) Adjust the CTV such that uninvolved/non-infiltrated tissues only have a rim of 3-5mm extending into the adjacent organ, while ensuring that proximal infiltrated organs/tissues and the entirety of the operative bed are within the CTV.

8) Use accompanying scans to estimate organ motion (i.e., 4DCT or derived series [MIP])

9) Expand the CTV to ITV to reflect motion in all 3 planes.

10) Expand the ITV to PTV using an immobilization & image-guidance appropriate amount

Primary Site	Non-CBCT	CBCT
Head and Neck	5 mm	3 mm
Upper Paraspinal	5 mm	3-5 mm
Intra-thoracic	5 mm	5 mm
Abdomen	5-8 mm	3-5 mm
Lower Paraspinal/Pelvic	5 mm	3-5 mm

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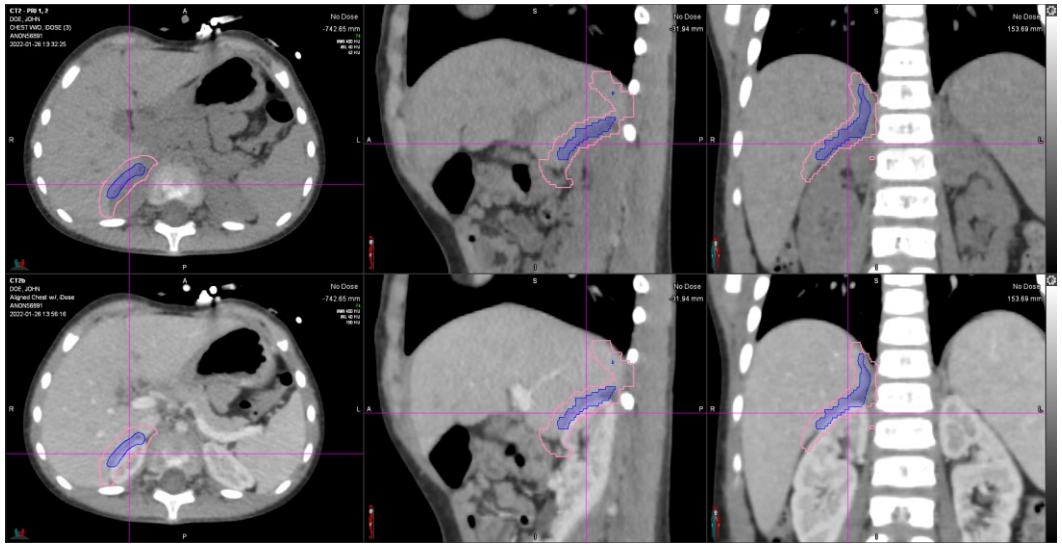
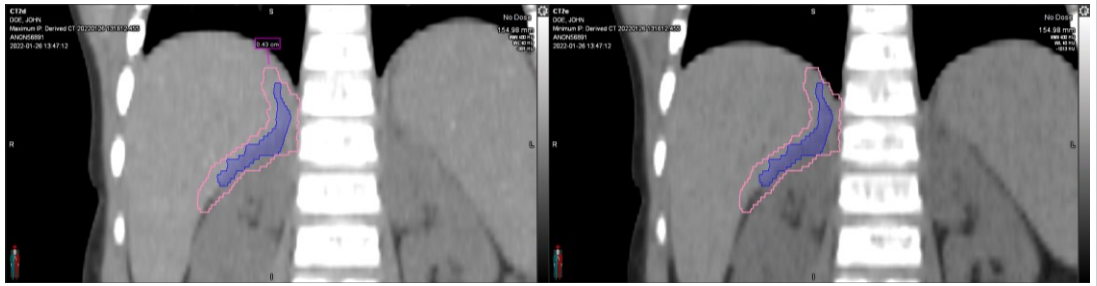
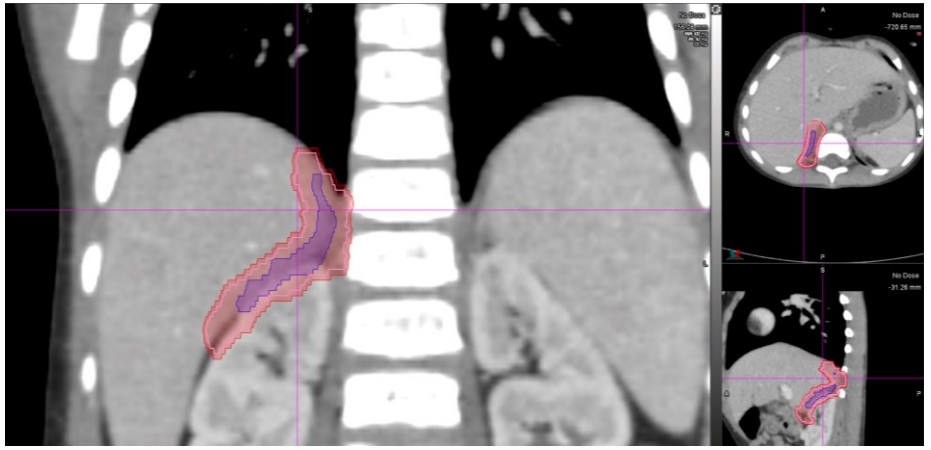
Planning Scans – CTV delineation



4D Evaluation scans – Min IP & MaxIP



Planning Scans – ITV delineation



Metastatic Site Naming

- If metastatic sites are consolidated, they should be named according to the Curie Scoring system region.

  i.e., A left sided extremity metastasis would be named mGTV7_L.
- Additional site-specific modifications to the metastatic target CTV are discussed in Section 17, Table 9.

Region	Site	Curie score
1	Head / Neck	
2	Cervico-Thoracic spine	
3	Ribs / Sternum / Clavicles/ Chest	
4	Lumbar / Sacral spine	
5	Abdomen/Pelvis	
6	Upper Extremity (Proximal)	
7	Upper Extremity (Distal)	
8	Lower Extremity (Proximal)	
9	Lower Extremity (Distal)	
10	Soft Tissue	
TOTAL	Total scores from Regions 1 - 10	

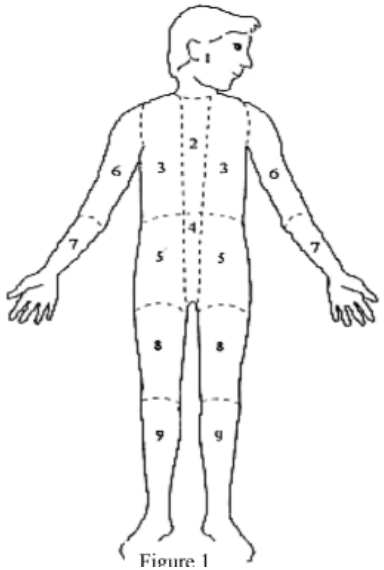


Figure 1

Table 9. Suggestions for Metastatic Site CTV Modifications

Treatment Site(s)	Methods to anatomically confine CTV
Calvarium	Adjust CTV to avoid extension into the cerebral cortex unless the lesion extends through the skull with suspected dural involvement. In cases where the entire calvarium needs to be treated, a brain sparing approach such as that used by Wolden et al[163] should be used.
Base of Skull	Adjust CTV to avoid extension beyond bony structures unless there is radiographic evidence of extension into brain tissue. T2-weighted imaging can be useful in delineating the target.
Limb	Adjust CTV to avoid circumferential limb treatment, growth plates & joint spaces (unless involved).[62, 164-166]
Spine	Adjust CTV to facilitate uniform dose to the entire vertebrae including the transverse and spinous process, vertebral body, and pedicles (regardless of if non-uniformly involved by disease) to minimize the risk of scoliosis.[167-169] The entire vertebral body should receive >18 Gy if treatment is required.
Rib	The CTV should be adjusted such that CTV does not extend into the lung parenchyma unless there is strong evidence of parietal pleura involvement. Pleural space involvement is rare in neuroblastoma.
Lung/ Pleural Space	Lung involvement at diagnosis is rare, but when encountered is considered a risk factor for distant metastatic site failure and an overall adverse prognostic factor.[170, 171] Only focal consolidative radiotherapy approaches will be employed on this protocol for incompletely responding lung disease.
Craniospinal	Leptomeningeal disease at diagnosis is rare in neuroblastoma, and craniospinal irradiation (CSI) should be avoided as it could potentially compromise the marrow reserve and limit the potential for Post-Consolidation therapy.[172]

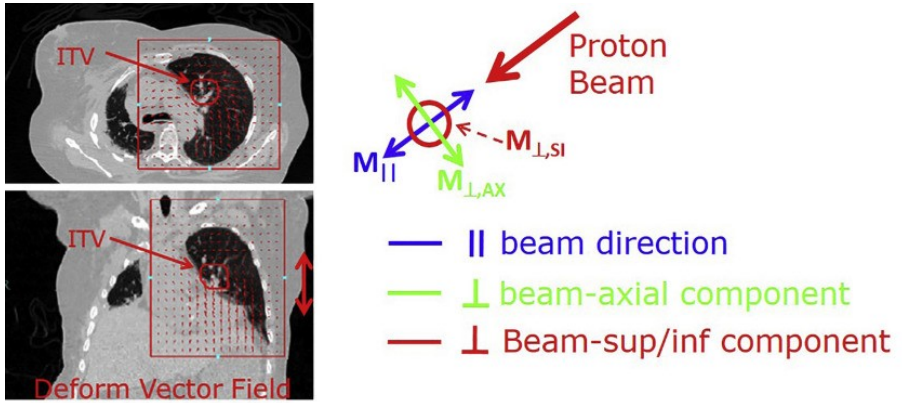
Treatment Planning

Planning Objectives

1. >95% IDL covers 100% PTV
2. >93% IDL covers 100% PTV
3. <10% PTV receives < 110% of the Rx dose
4. Meet renal dose constraints (if 1^{o} abdomen case)
5. Meet required OAR constraints (Sec. 17, Table 11)
6. Coverage of OTV_VB with Dmean 18 Gy (if encroaches on adjacent spine).

Motion Evaluation

1. If significant motion is noted at the time of 4D/motion evaluation, consider beam angles with minimal change in amplitude (**M⊥,AX**).



2. Proton plans should have beam angles chosen which minimize the water equivalent thickness.
3. Photon cases are generally robust to motion, although accounting for motion during contouring and planning remains essential.

Protocol Deviation Criteria

- Protocol deviations are subclassified according to the following:
  - Dose, Uniformity, Volume Delineation, OAR Tolerances, and Timing.
  - Some variations are considered acceptable while others have the potential to either cause harm, compromise protocol objectives, and/or disease control.
- If a potential deviation is anticipated, its encouraged that the treating physician reach out for guidance regarding the case prior to initiation of radiotherapy.

	DEVIATION	
	Variation Acceptable	Deviation Unacceptable
Prescription Dose		
Primary or Metastasis	Difference in prescribed or computed dose is 6-10% of protocol specified dose	**Difference in prescribed or computed dose is > 10% of protocol specified dose**
Dose Uniformity		
Primary or Metastasis	>10% PTV* received > 110% of the prescription dose or <93% isodose covers 100% of PTV*	**<90% isodose covers 100% of PTV***
Target Volume		
Primary Site	CTV or PTV margins are less than the protocol specified margins in the absence of anatomic barriers to tumor invasion (CTV) or without written justification (PTV)	**GTV does not encompass the dimensions defined by the GTV_Preop or Motion not accounted with the use of proton therapy**
Metastasis	mCTV or mPTV margins are less than the protocol specified margins in the absence of anatomic barriers to tumor invasion (CTV) or without written justification (PTV)	**mGTV does not encompass the dimensions of the residual soft tissue metastatic disease or the dimensions of the area defined by persistent MIBG/PET avidity.**
Vertebral Body	Corpus only contoured in the setting of challenging renal constraints	**Omission of OTV_VB when the treated region approximates the vertebral column.**
Organs at Risk		
Kidney	The OTV_VB may be reduced to corpus only to facilitate meeting renal dose constraints.	**Exceeding renal dose constraints and corpus only OTV_VB.**
All Other OARs	OAR deviations will be assessed at the time of final review.	**OAR deviations will be assessed at the time of final review.**
Radiotherapy Timing		
Timing	Radiation started more than 80 days after the 2nd ASCT	**Radiation started more than 120 days after the 2nd ASCT or Radiation started during active SOS, ANC ≤ 500/µL, and/or platelet count < 40,000/ µL.**

* = While the target structure used for planning depending on treatment planning technique, motion management and modality, a PTV is generated for all patients and as such coverage, and uniformity will be assessed using the generated PTV. When robust optimization is used during proton planning, variation/ deviation will not be assigned based on PTV coverage, but instead based on CTV/ ITV coverage.

Protocol Data Submission

- Please submit the following forms within 1 week following RT:
  - RT1/Proton Dosimetry Summary Form
  - RT-2 Radiotherapy Total Dose Record Form
  - Diagnostic imaging data CT, MRI, MIBG scans performed prior to surgery as well as operative and pathology reports.
  - Digital Radiotherapy Planning Data including:
    - DICOM Planning CT, RT structure, RT dose, and RT plan files.
  - Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
  - Any written explanations for why there were deviations from the specified protocol therapy.
  - Smearing radius of compensator used for proton therapy (if applicable) as well as the setup and PTV margin used for each beam with an accompanying rationale.
  - Motion Management reporting form (if applicable)

ANBL2131 Case Downloads

- Example Cases are available for download at:

  https://www.qarc.org/cog_protocol_resources.htm

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