A Curative Approach for Neuroblastoma Metastatic to the CNS

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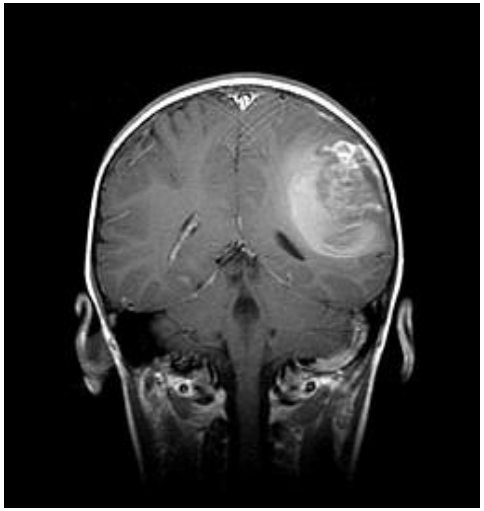
DISCLOSURE

- MSK has partnered with YmAbs Therapeutics, Inc to further develop Omburtamab (8H9).
- MSK and NKC have a financial interest in YmAbs Therapeutics, Inc.
- Some study investigators (KK, SM, NPT) are paid consultants for YmAbs Therapeutics, Inc.

Background

- The CNS is a sanctuary site for metastatic cancer.
- CNS metastases occur in 5% of pts with cancer, including 15% of patients with high risk NB.



- Despite treatment
  - surgical debulking
  - focal or whole brain RT
  - combination chemotherapy

-CNS NB is uniformly fatal; 5.5 mon median survival

(Kramer K et al J Clin Oncol 19: 2821, 2001)

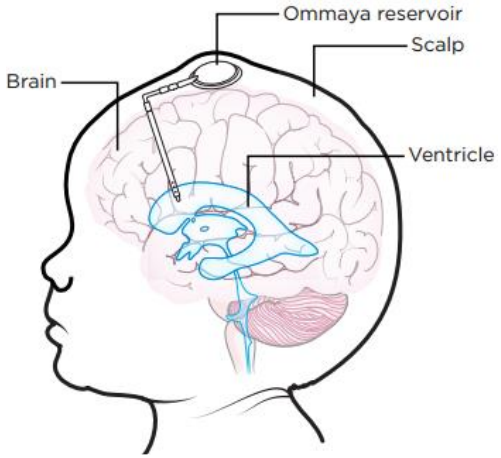
HYPOTHESIS

- Intraventricular compartmental radioimmunotherapy (cRIT)

  *radio-labeled tumor specific monoclonal antibodies

1) delivers a tumoricidal dose to the CSF

2) offers a therapeutic strategy



B7-H3

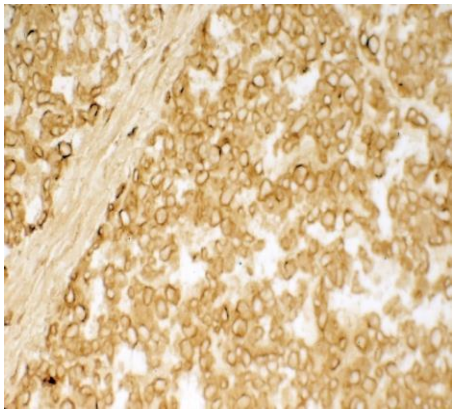
- Transmembrane protein homologous to other B7 members
- Immunomodulatory glycoprotein: possibly an inhibitory ligand for NK cells /T cells
- Over-expressed among many human solid tumors

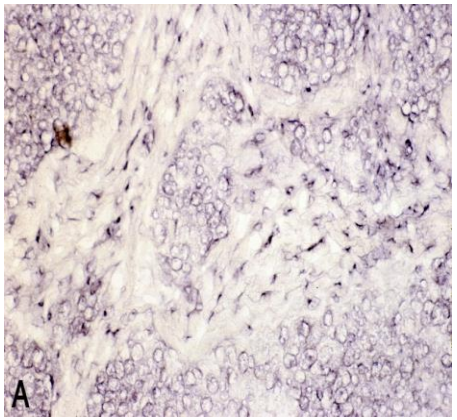
Modak S. Can Research 2001; 61: 4048)

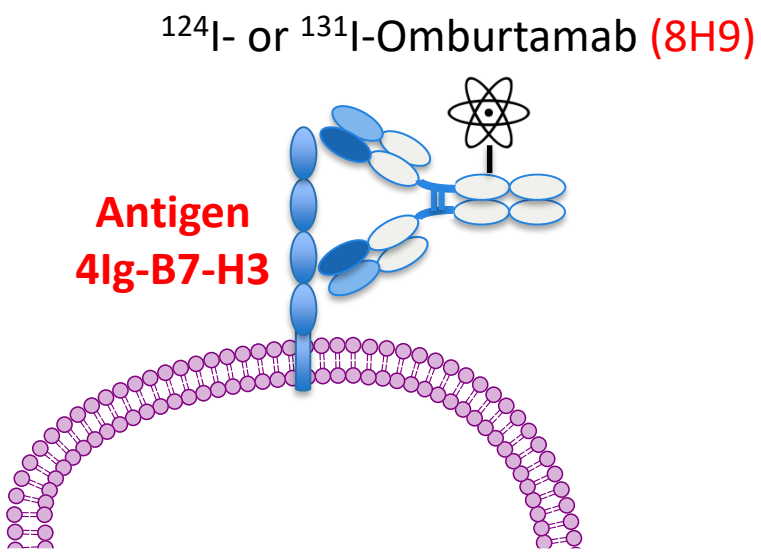
- Limited expression in normal tissues
- Tumor B7-H3 expression, prognostic marker:
  - prostate ca
  - clear cell renal ca
  - urothelial cell ca
  - ovarian ca
  - pancreatic ca
  - glioblastoma

Monoclonal Antibody 8H9 (Omburtamab)

- Murine monoclonal antibody 8H9 (Omburtamab) is specific for 4Ig-B7-H3.
- 131 and ^{124}I-8H9 retains its immunoreactive properties.







Objectives

PRIMARY:

- To define the *clinical toxicities (DLTs, MTD)* of cRIT ^{131}I-8H9 (Omburtamab) for patients with CNS NB

SECONDARY:

- To assess the *dosimetry*
- To assess *efficacy*: OS

Eligibility

- Recurrent CNS or LM NB

  (Other B7-H3 diseases –SIOP Poster 19-1597)

- >50K platelets; >1000 ANC
- Adequate CSF flow, ^{111}In-DTPA CSF flow through an indwelling intraventricular access device

Excluded

- pre-existing grade 3 or 4 major organ toxicity
- acutely deteriorating neurologic condition
- communicating or obstructive hydrocephalus

TREATMENT PLAN

Surgical resection of CNS lesion(s)

↓

XRT (CSI up to 18-21 Gy with focal boost 30 Gy)

↓

Temodar/CPT11

↓

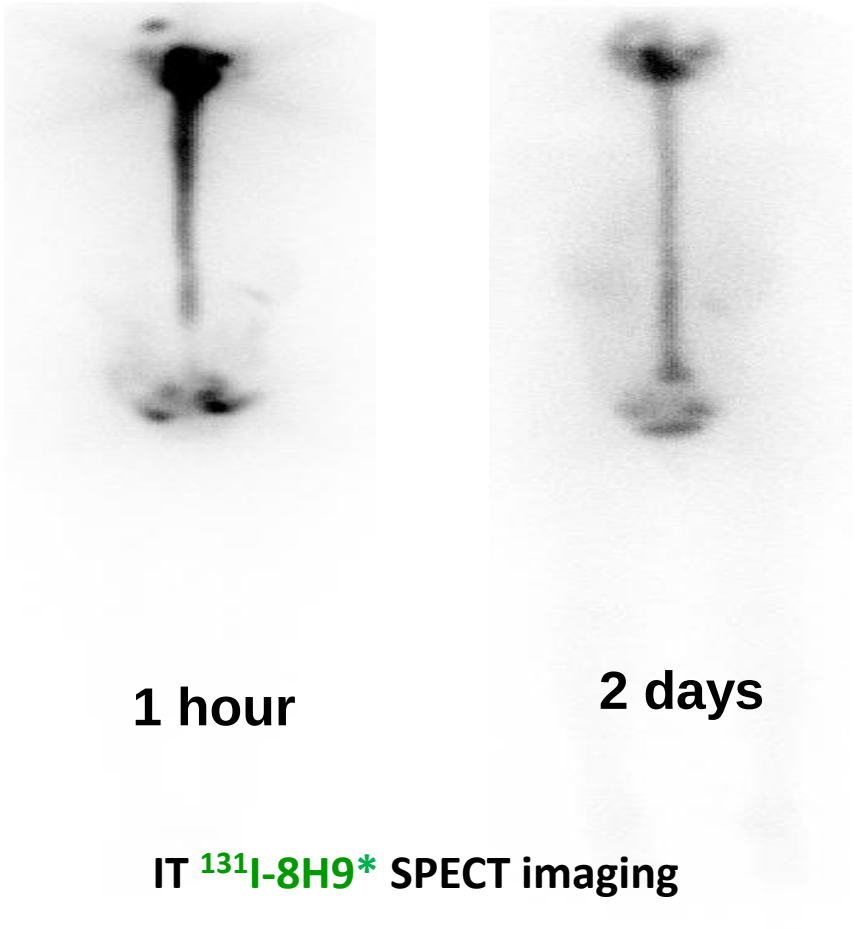
cRIT ^{131}I-8H9* (Omb)

↓

3F8 + GM-CSF

↓

Temodar
Accutane



IT ^{131}I-8H9* SPECT imaging

METHODS

Phase I/II : ^{131}I-Omburtamab (8H9)

- **Phase 1 dosing: 10-80 mCi ^{131}I-8H9/injection x 2**
  DLT myelosuppression for pts w/prior CSI
- **Phase 2 dosing: 50 mCi per injection x 2**

Baseline exam, MR brain/spine, CSF cytology
0-3 weeks prior

Wk 1

- **Dosimetry dose**
  2 mCi
- **Serial CSF/blood**
- **Serial PET scans**

Wk 2

Therapy dose
50 mCi

- Toxicity : CTCAE v.3.0 over 5 weeks
- Repeat clinical, radiographic eval at 5 weeks;
- Repeat therapy dose if no SAE and no PD

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^{131}I-Omburtamab (Oct 13, 2004-June 30, 2019)

DIAGNOSIS	No. patients	No. Injections
Neuroblastoma	109*	340
Other	68	172
Total	177	512

*6 patients enrolled but were not treated; 2 with NB

TOXICITY PROFILE

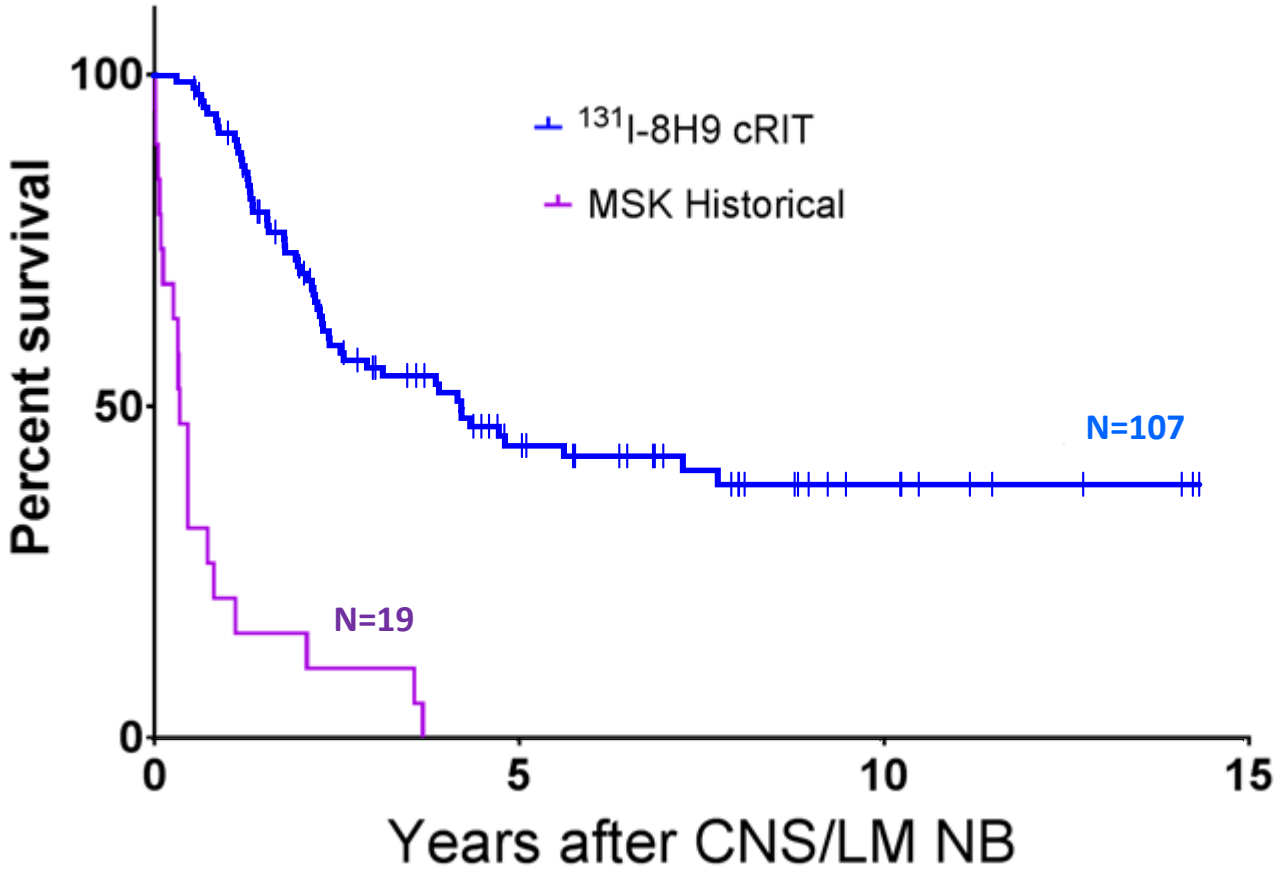
- Rare grade 1 pr 2 transient headache, fever, vomiting
  - self-limited, manageable with acetaminophen, anti-emetics
- Grade 3 or 4 myelosuppression
  - pts with poor BM reserve (≥1 ABMT, CSI)
  - <100K at Rx
  - no non-myelosuppressive DLT observed

DOSIMETRY

- High mean CSF: blood absorbed dose (ratio) achieved
  - 104.9 : 2.6 cGy/mCi
  - Average CSF Clearance T ½: 6.69 hours

Neuroblastoma	No.	Acute Adverse Event (CTC 3.0) Possibly/Probably/Definite	No (%)
	107	Gr 3 or 4 myelosuppression (ANC, hgb, platelets*)	88(82%)
		Gr 4 Hypersensitivity reaction	1 (<1%)
		Gr 3 ALT/AST	5 (4.6%)
		Gr 3 Chemical Meningitis	3 (2.8%)
		Gr 3 Headache	1 (<1%)
TOTAL	107	340 injections	

OS, Time from CNS relapse, N=107



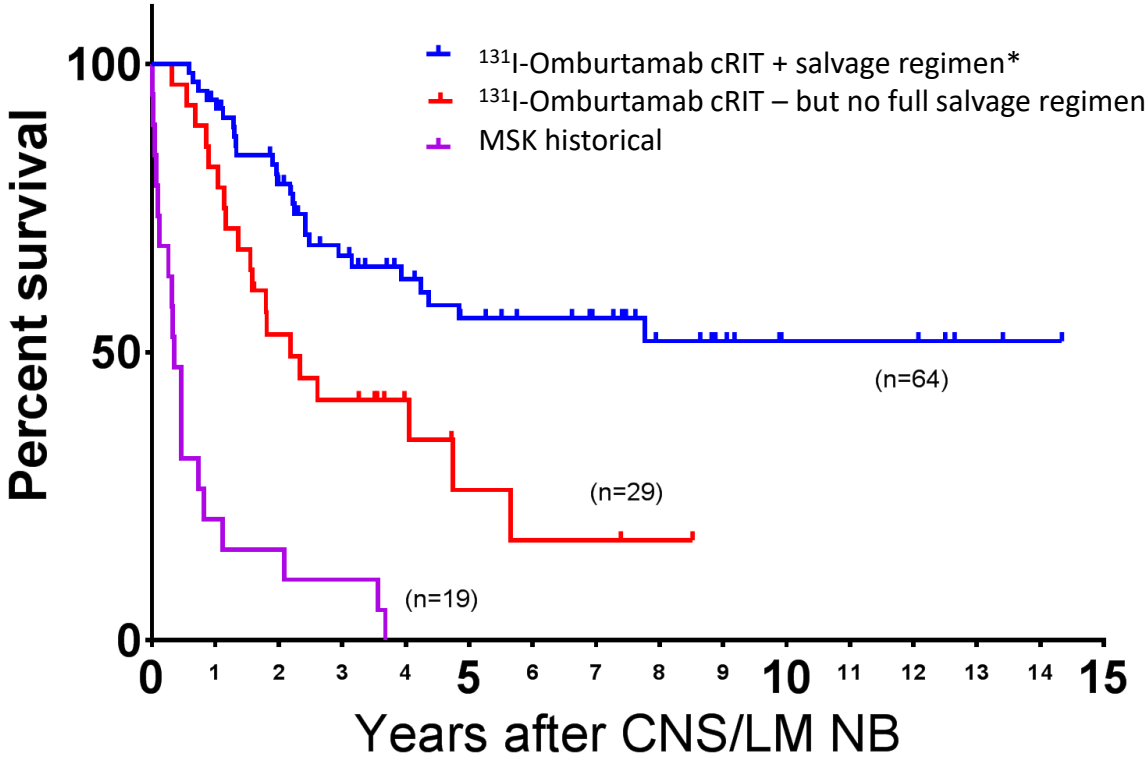
^{131}I-Omburtamab Overall Survival

DIAGNOSIS	No.	OS (months)	3 year OS (%)
Neuroblastoma	107	50. 8 (4-180)	61 (56%)

Time	Proportion	Two sided 95% CI for the proportion	
3 years	56%	45%	65%
5 years	44%	34%	54%
10 years	38%	27%	49%

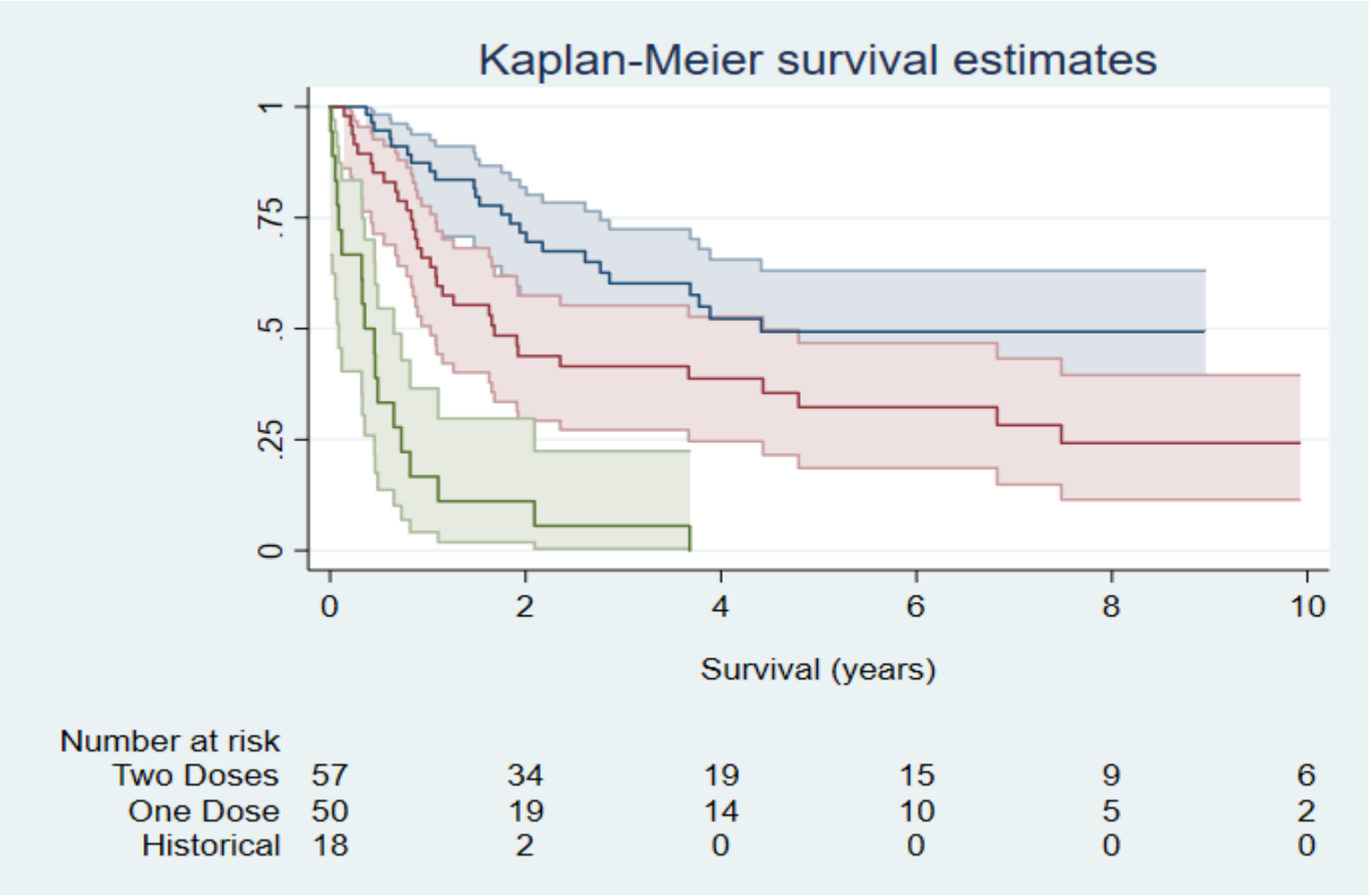
Estimates based on Kaplan-Meier survival distribution, calculated in SAS V9.4.

OS Subset Analyses CNS NB

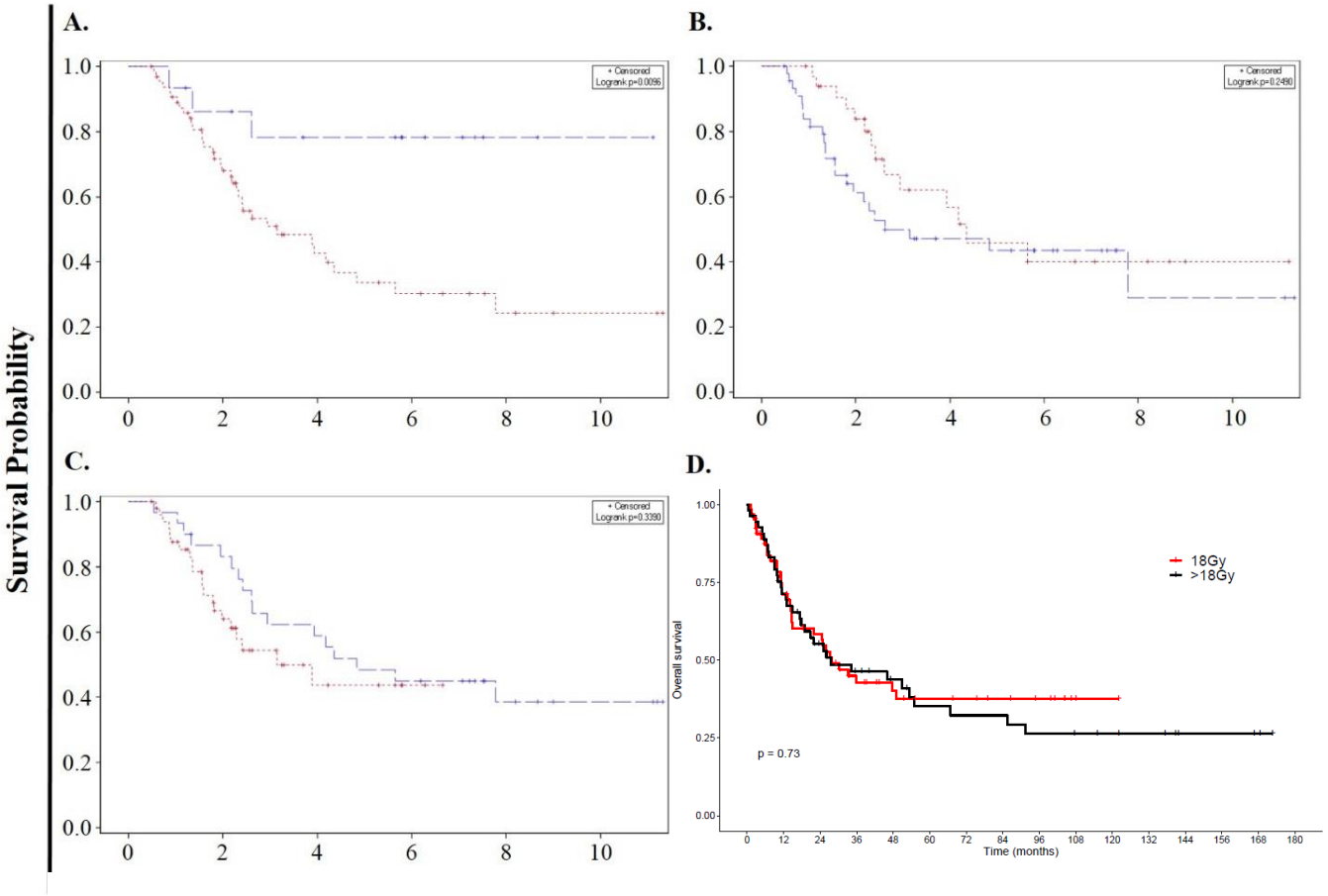


- Salvage regimen *(Kramer et al., JNO 97: 409, 2010)*
- **ANR 2018; N=93*

1 vs. 2 therapy doses ^{131}I-8H9-(Omburtamab)

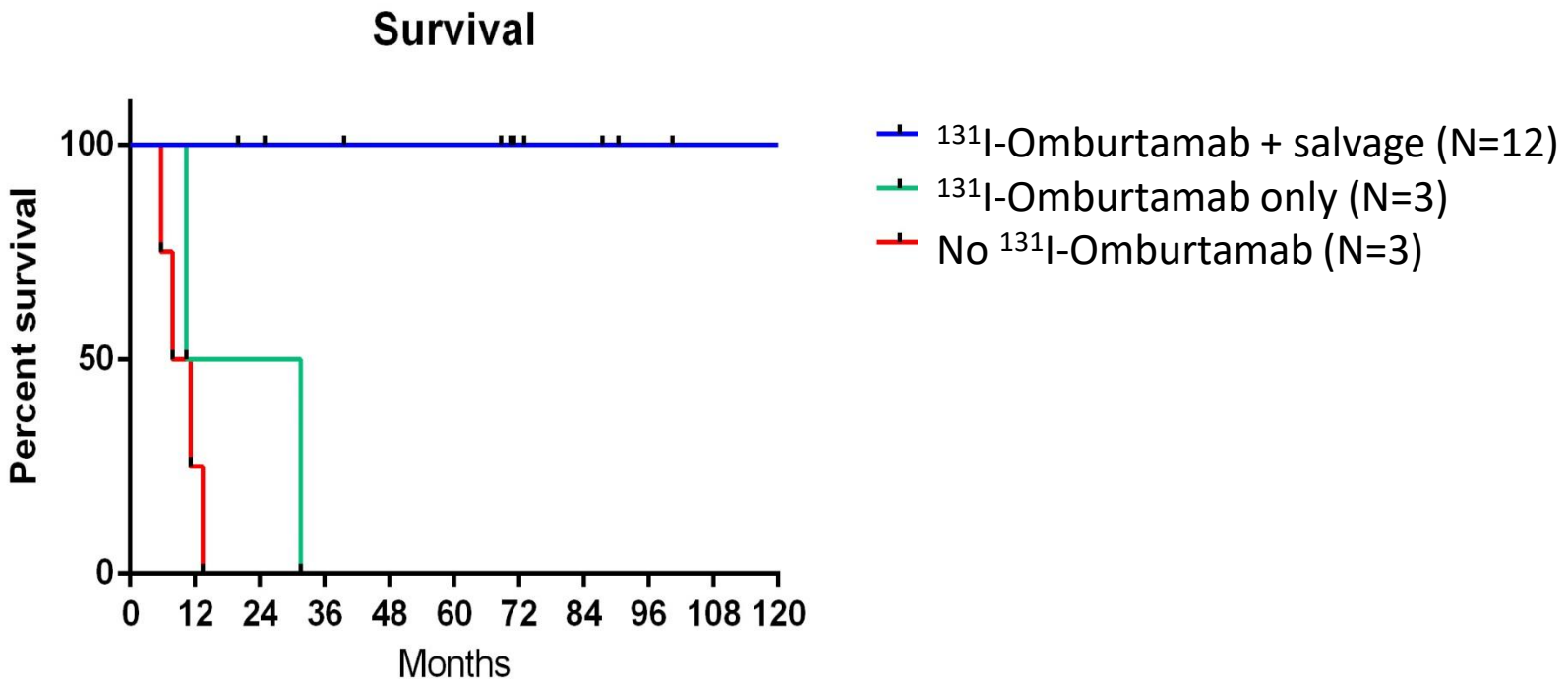


Few prognostic indicators for survival: CNS NB



A. Age < or > 18 months at initial Dx
B. MYCN status
C. Early enrollment vs expanded cohort
D. CSI dose

OS 18 Infants with CNS NB



High Curability of Brain Metastases Among Infants with Neuroblastoma following Adjuvant Treatment with 131I-8H9 Compartmental Radioimmunotherapy (ANR 2018)

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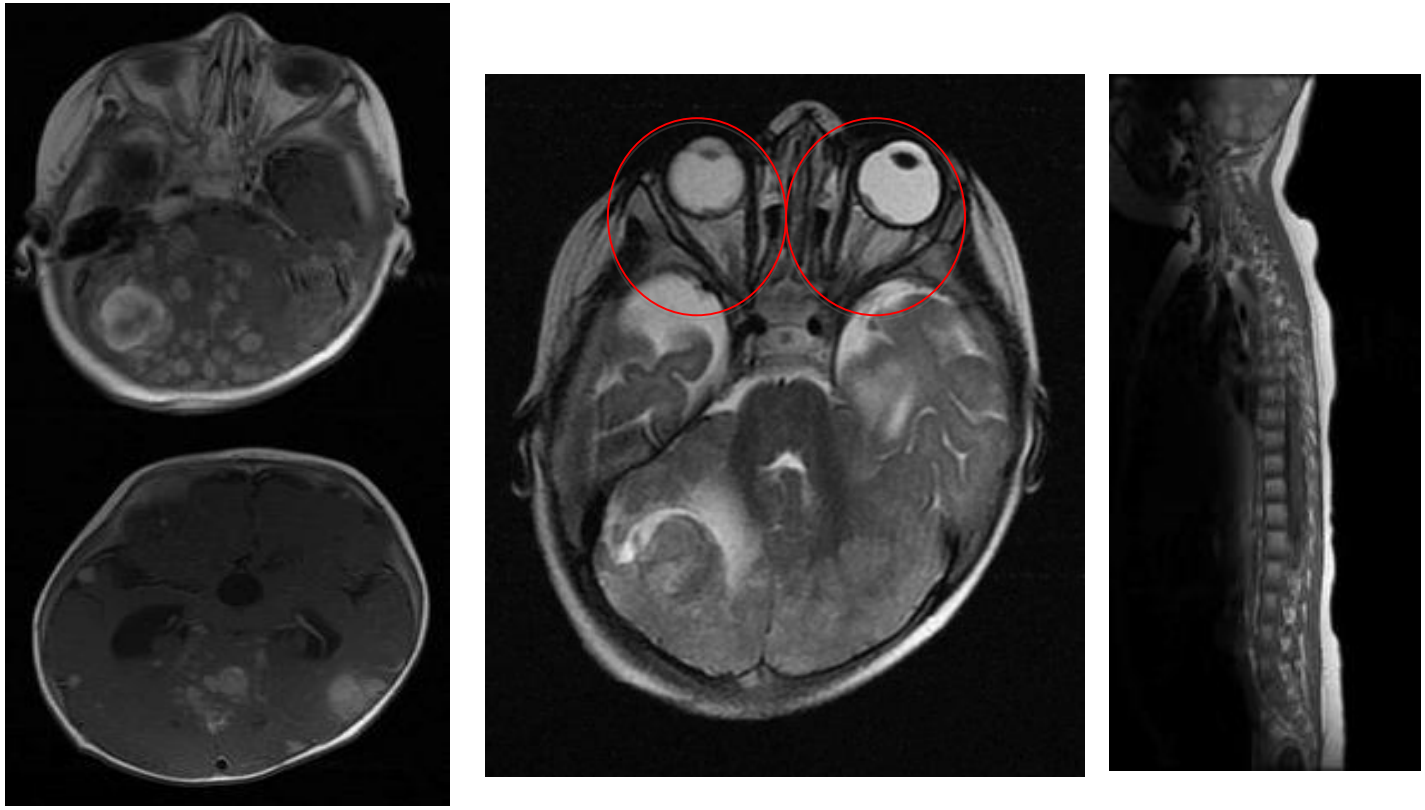
Multifocal CNS NB – 8 years in remission



MRI brain/spine: extensive cerebral, cerebellar, spinal, intraocular lesions

Conclusions cRIT ^{131}I-Omburtamab (8H9)

- Favorable safety profile
- Manageable acute AEs, transient myelosuppression most common
- Favorable CSF: blood ratio
- Clinical utility to treat CNS NB

Questions Remain

- What is the lower limit of CSI Gy with cRIT?
- Is there a difference in efficacy or long term adverse events with proton CSI?
- What is the minimum dose CSF cGy/mCi by cRIT to eradicate CSF NB?
- Long term toxicities
  - Neurocognitive
  - Second malignancies

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June 08, 2017

FDA GRANTS: Breakthrough Therapy Designation for Metastatic Neuroblastoma

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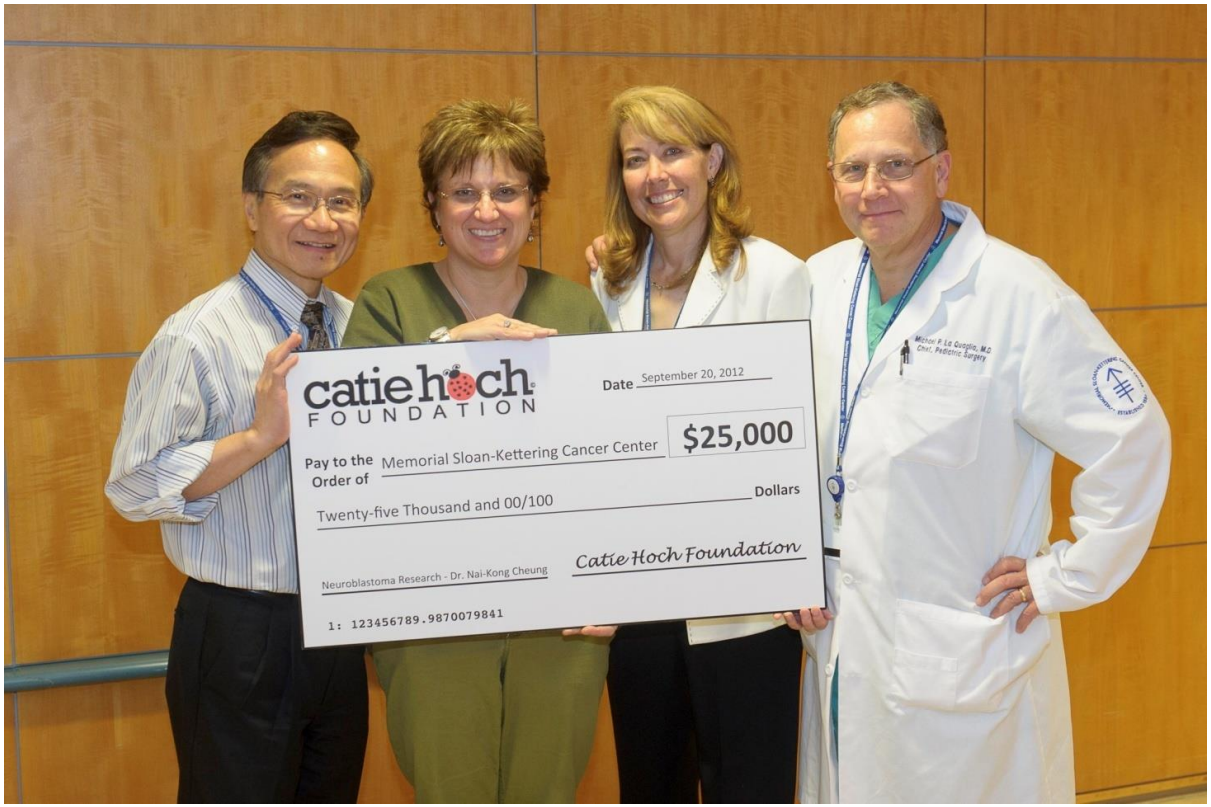
metastatic neuroblastoma.

The US Food and Drug Administration (FDA) granted Breakthrough Therapy Designation to ^{131}I-8H9 pediatric relapsed/refractory metastatic neuroblastoma with central nervous system or leptomeningeal metastasis.[1]

Ongoing Initiatives

A Multicenter Phase 2/3 Trial of the Efficacy and Safety of Radioimmunotherapy using ^{131}I-Omburtamab for Neuroblastoma CNS/LM Metastases

- Sponsor: Y-mAbs, Therapeutics
- MSK Lead; USA; Europe
- Primary objective
  - Overall survival at 3 years
- Secondary objective
  - ORR, PFS, Dosimetry, PK, Safety
- Ongoing recruitment; 18 of 32 patients



FDA Orphan Drug Program
National Institute Health R21
Robert Steel Foundation
Catie Hoch Foundation
Kallan's Klan
Katie's Find A Cure Fund
Leptomeningeal Research Fund
Y-mAbs, Therapeutics, Inc.
Aubrey Fund
Kids V Cancer
Luke's Lollies
The Dana Foundation,
Evan Foundation
Cookies for Kids Cancer
Experimental Therapeutics Center, MSK

Patients and Families

MSK Kids
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