



# A Curative Approach to Central Nervous System Metastases of Neuroblastoma

Kim Kramer, Brian H. Kushner, Shakeel Modak, Neeta Pandit-Taskar, Ursula Tomlinson, Suzanne L. Wolden, Pat Zanzonico, John L. Humm, Sofia Haque, Mark M. Souweidane, Jeffrey Greenfield, Ellen M. Basu, Stephen S. Roberts, Jorge A. Carrasquillo, Jason Stuart Lewis, Serge K. Lyashchenko, Steven M. Larson, Nai-Kong V. Cheung  
Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY

## Abstract

**Background:** Neuroblastoma metastatic to the central nervous system (CNS NB) is associated with significant mortality (median survival < 6 months, < 10% survival at 36 months). Intraventricular compartmental radioimmunotherapy (cRIT) with radio-iodinated murine IgG1 monoclonal antibody <sup>131</sup>I-8H9 targeting tumor cell-surface glycoprotein B7-H3 offers a therapeutic strategy. We analyzed overall survival of patients with CNS NB treated with intraventricular <sup>131</sup>I-8H9 cRIT at Memorial Sloan Kettering Cancer Center (MSK) since 2003.

**Methods:** After radiographic and/or pathologic confirmation of CNS NB, and assessment of adequate CSF flow, cRIT eligible patients underwent treatment on an IRB-approved protocol with either temozolomide/irinotecan-based CNS salvage regimen incorporating craniospinal radiation therapy, <sup>131</sup>I-8H9 cRIT plus systemic immunotherapy (group 1), or non-regimen therapies with <sup>131</sup>I-8H9 (group 2). cRIT administration involved a 2 mCi tracer of <sup>124</sup>I- or <sup>131</sup>I-8H9 with nuclear imaging and CSF sampling for dosimetry followed by 1 or 2 therapeutic injections up to 70 mCi <sup>131</sup>I-8H9. Disease surveillance included serial MR brain/spine, MIBG, CT, and bone marrow evaluation. Data are presented as overall survival after detection of CNS metastasis.

**Results:** 105 patients with CNS NB were evaluated; 80 patients (76%) were treated (57 group 1, 23 group 2). Of the 25 patients who were not eligible for cRIT, survival averaged 8.6 months. Of 19 patients with radiographic evidence of disease at the time of cRIT, 7 (36%) demonstrated post-cRIT radiographic improvement. At the time of data cutoff for the analysis, 45/80 (56%) patients were alive 4.8-152 months (median 58 months) after CNS metastasis, including 36 (45%) at 36 months and 23 (29%) > 60 months. Subgroup analyses of <sup>131</sup>I-8H9-treated patients identified age at NB diagnosis (≤18 months), relapse restricted to the CNS, and Group 1 status as factors positively correlated with survival. At the time of abstract preparation, 42/80 (52.5%) of patients remain alive.

**Conclusions:** 76% of patients with CNS NB treated at MSK received <sup>131</sup>I-8H9 cRIT. Despite advanced CNS involvement, over 50% of patients treated with <sup>131</sup>I-8H9 cRIT are still alive and nearly 50% have survived at least 36 months.

## Background

### Central Nervous System and Leptomeningeal (CNS/LM) Neoplasms

- There is a medical need for targeted innovative therapies to treat CNS/LM metastases.
- CNS/LM tumors are associated with significant mortality.
  - LM metastases occur in ~5% of all patients with cancer.
  - Median survival <6 months and 3-year survival is <10%.
- CNS is difficult to treat and represents a sanctuary site for metastatic cancer.
- Common approved treatment strategies may include:
  - Surgical debulking
  - Focal or whole brain irradiation
  - Combination chemotherapy

### B7-H3 and Iodine-131 Radiolabeled 8H9 Monoclonal Antibody (<sup>131</sup>I-8H9)

- Immunomodulatory glycoprotein B7-H3 is distributed on the cell membrane of solid tumors, but is limited in normal tissues.
- 8H9 is specific for 4Ig-B7H3 and recognizes the antigen on tumors of diverse lineage.
- <sup>131</sup>I-8H9 retains its immunoreactive properties for specific targeting of tumors.
- <sup>131</sup>I-8H9 (i.v.) suppresses tumor growth in mice with established RMS xenografts.

## Methods

After radiographic/pathologic confirmation of CNS NB, patients were treated on an approved protocol with <sup>131</sup>I-8H9 cRIT (Figure 1) according to the following treatment regimens:

- **Group 1 (n = 57):** All eligible patients underwent CNS salvage regimen detailed in Table 1 with <sup>131</sup>I-8H9 cRIT.
- **Group 2 (n = 23):** Patients not eligible for full salvage regimen received non-regimen therapies with <sup>131</sup>I-8H9 cRIT.

Long-term follow-up of subjects for survival and disease surveillance by MRI, CT, MIBG, and BM evaluation.

Table 1. cRIT-based Treatment Plan for CNS NB

Time	Intervention
Day 0	Resection of CNS disease (if possible); Ommaya catheter placement
Day 7	Irinotecan 50 mg/m <sup>2</sup> /dose (i.v. daily × 5)
Day 14	Craniospinal irradiation 1080-2160 cGy/boost 2560-3000 cGy
Week 7	Irinotecan 50 mg/m <sup>2</sup> /dose daily × 5 Temozolomide 250 mg/m <sup>2</sup> /dose daily × 5 Carboplatin 500 mg/m <sup>2</sup> /dose daily × 5 Stem cell rescue (if needed)
Week 14	Serial injections of intra-Ommaya <sup>131</sup> I-8H9
Week 30	GMCSF/3F8 (i.v.) every 3-4 weeks (4 cycles)
Weeks 40-104	Alternating cycles: Cis-retinoic acid (oral) 160 mg/m <sup>2</sup> /day × 14 days (6 cycles) Temozolomide (oral) 75 mg/m <sup>2</sup> /day × 42 days (4-5 cycles)

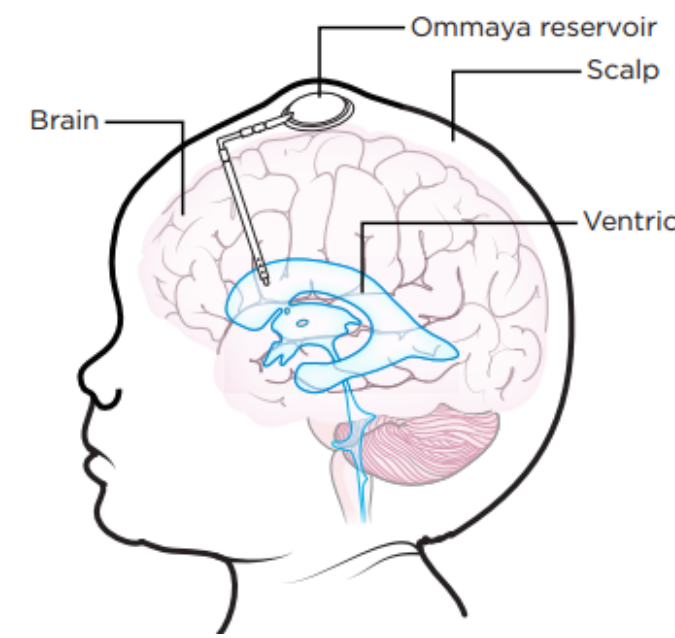


Fig 1. Ommaya reservoir placement. Copyright MSK.

## Results

Table 2. Summary of Survival: <sup>131</sup>I-8H9 and Historically-treated CNS NB Patients

Overall Survival Statistics		<sup>131</sup> I-8H9 Patients (n = 80)		Historic Patients (n = 19)		
Overall Survival	Number alive at reporting*	42 (53%)		0		
	Median (95% CI)	58 m (35.2 m – NC)		5.5 m (1.1–8.7 m)		
	Range	4.8–152 m		2 d – 44 m		
	>6 m	79 (99%)		6 (32%)		
	>12 m	68 (85%)		4 (21%)		
Cause of Death Statistics	>36 m	36 (45%)		2 (11%)		
	>60 m	23 (29%)		0		
	Cause of Death Statistics		<sup>131</sup> I-8H9 Patients (n = 38)		Historic Patients (n = 19)	
		n (%)	Survival†	n (%)	Survival	
	CNS disease	11 (29%)	2.9–44	NA	NA	
CNS and systemic disease	7 (18%)	2.4–33.2	NA	NA		
Systemic disease without CNS recurrence	16 (42%)	3.3–57.5	NA	NA		
Other (not related to neuroblastoma)	4 (11%)	18.3–89.8	NA	NA		

d = day; m = month; NA = not available; NC = not calculable.  
\* At time of abstract preparation; † From diagnosis of CNS metastasis.

Fig 2. Overall Survival and Subgroup Analyses

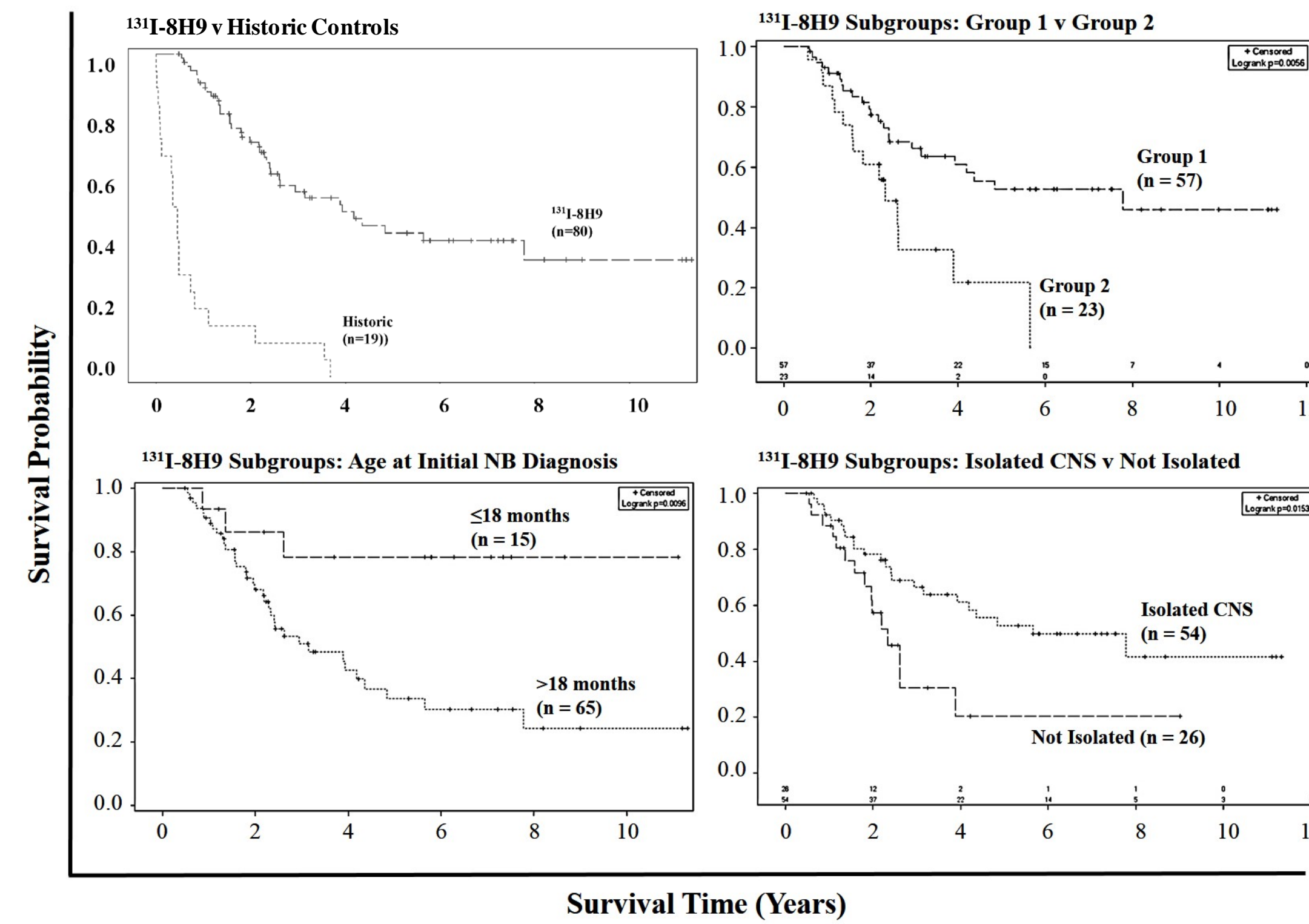


Fig 3. Time to First Radiological Improvement

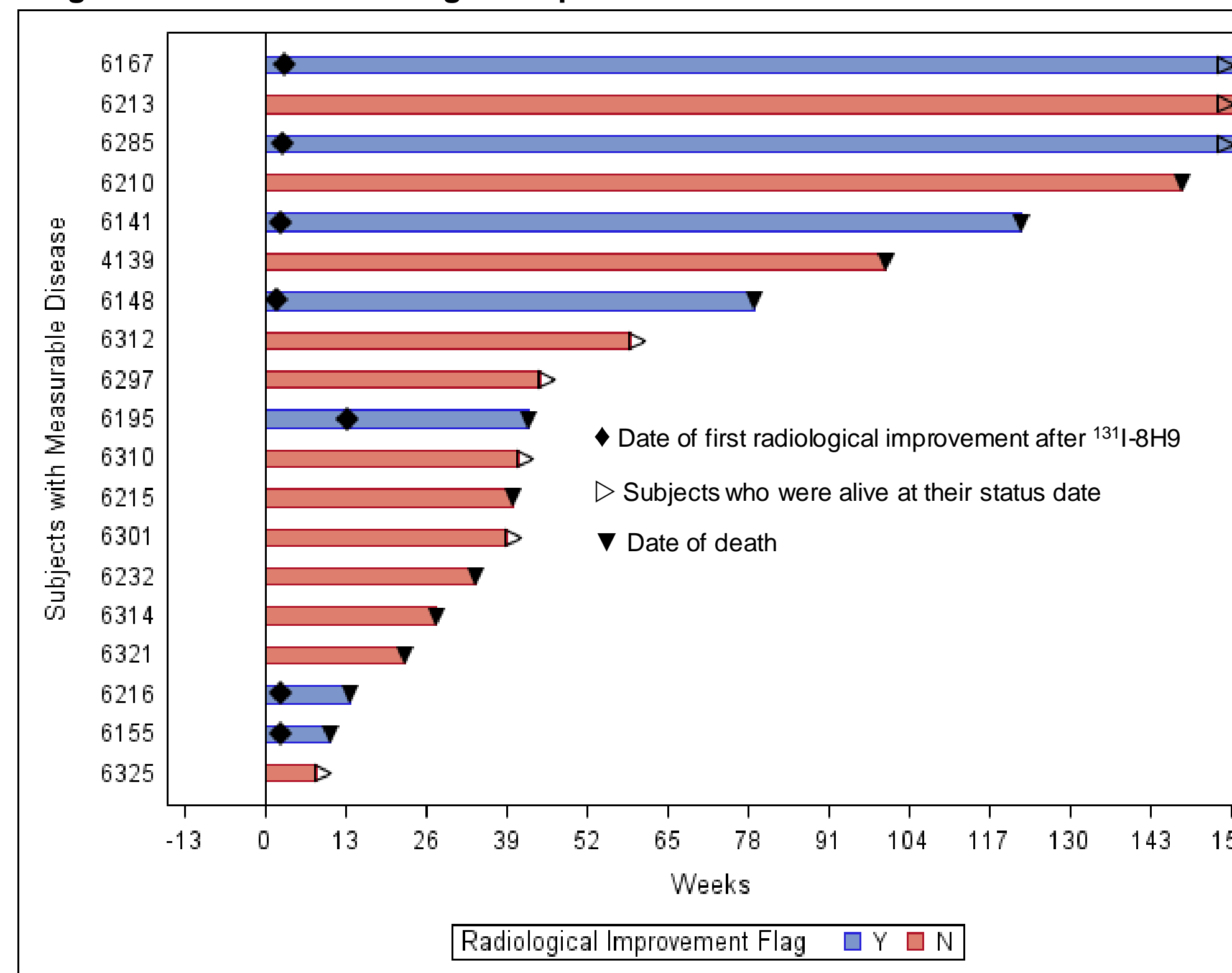
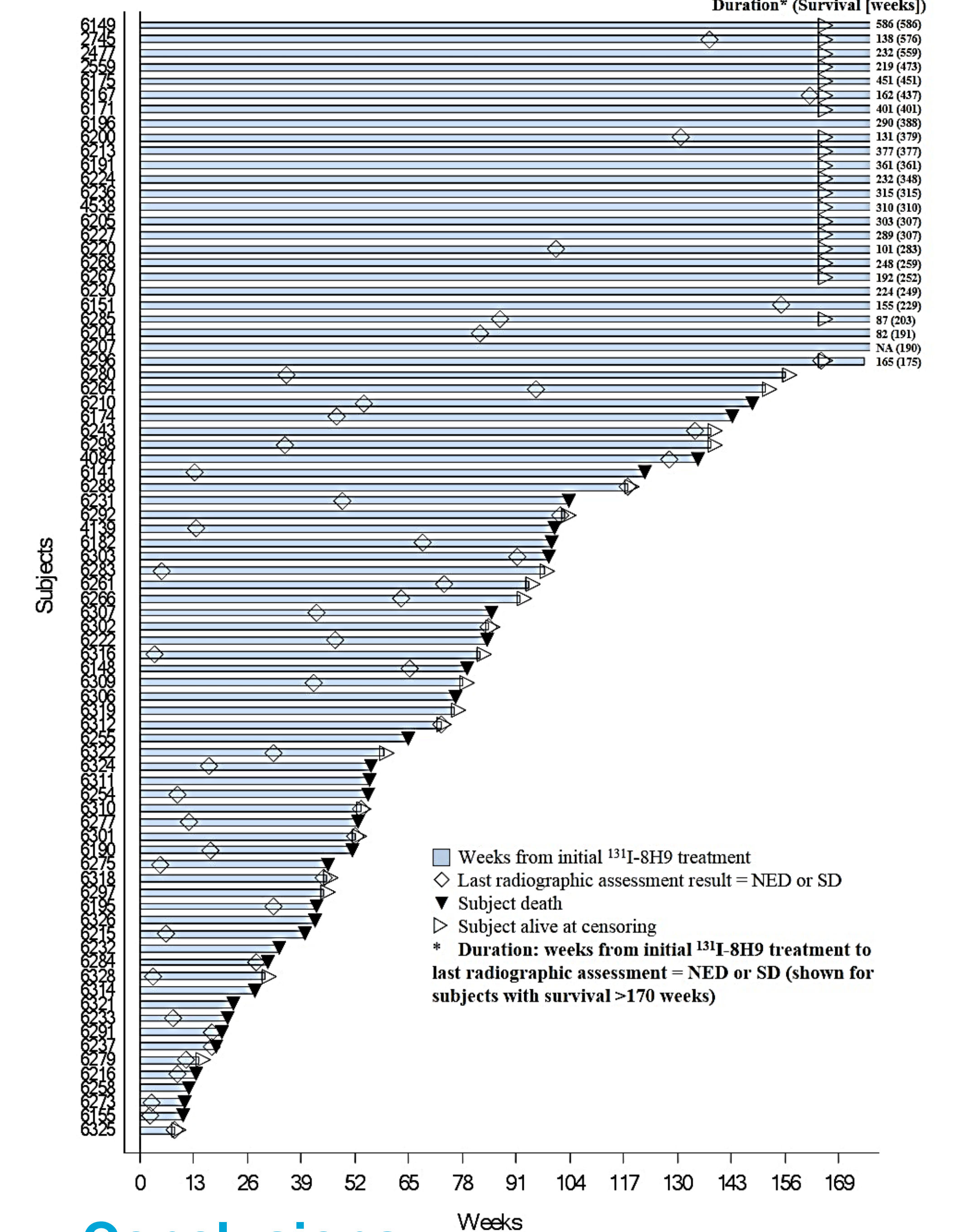


Fig 4. Last Radiographic Assessment of CNS Disease



## Conclusions

- <sup>131</sup>I-8H9 cRIT has clinical utility to treat B7-H3<sup>+</sup> CNS/LM tumors.
  - Median overall survival >50 months; nearly 50% survive at least 36 months
  - 57% of treated patients still alive
- <sup>131</sup>I-8H9 cRIT produces objective measurable evidence of efficacy in pediatric patients with CNS NB.
  - Acute radiographic improvement in 36% of subjects with measurable disease
  - Duration of response by radiographic assessment ranged 2.6 – 586 weeks (median 49 weeks)