SAFETY AND EFFICACY OF INTRAVENTRICULAR 131I-LABELED MONOCLONAL ANTIBODY 8H9 TARGETING THE SURFACE GLYCOPROTEIN B7-H3

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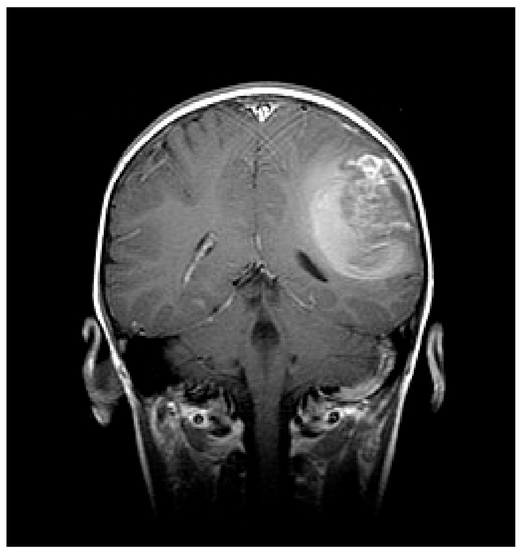
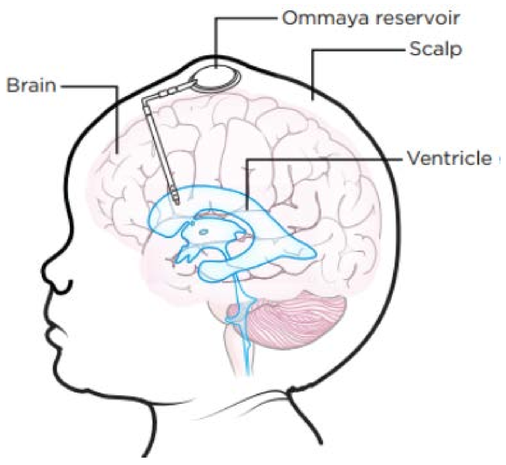
Background

- The CNS is a sanctuary site for metastatic cancer.
- CNS metastases occur in 5% of patients with cancer including 15% of patients with high risk neuroblastoma (NB)
- Tumors metastasizing to the CNS are associated with significant mortality.
- Despite treatment (surgical debulking, focal or whole brain RT, combination chemotherapy) CNS metastases are associated with significant mortality; CNS NB is uniformly lethal





Hypothesis

- Intraventricular compartmental radioimmunotherapy (cRIT) with radio-labeled tumor specific monoclonal antibodies offers a therapeutic strategy.

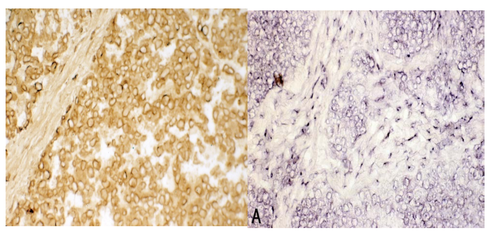
B7-H3

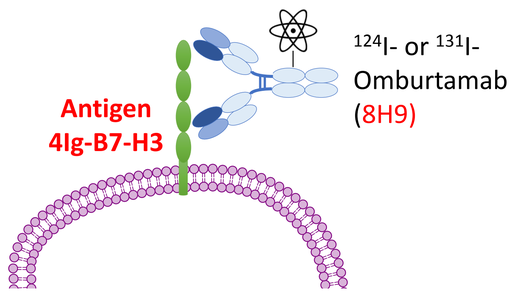
- Transmembrane protein: predicted secondary structure highly homologous to other B7 members
- Immunomodulatory glycoprotein: possibly an inhibitory ligand for NK cells /T cells
- Over-expressed among many human solid tumors: embryonal tumors including CNS, DIPG, sarcomas, NB and carcinomas (Modak S. *Cancer Research* 2001; 61: 4048-4054)
- Limited expression in normal tissues
- Tumor B7-H3 expression strongly correlates with disease spread at time of surgery, increased risk of recurrence and cancer-specific death in the following tumors:

prostate ca	pancreatic ca
clear cell renal ca	glioblastoma
urothelial cell ca	osteosarcoma
ovarian ca	neuroblastoma

Murine Monoclonal Antibody Omburtamab (8H9)

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





Eligiblity

- Recurrent CNS or LM Malignancy
- B7H3- Reactive Tumors
- >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

Methods

Phase I/II : ^{131}I-Omburtamab

- **Phase 1 dosing: 10-80 mCi ^{131}I-8H9/injection x 2**
  - **Dose limiting toxicity 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

Imaging

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

Wk2
Therapy dose
50 mCi

- Toxicity : CTCAE v.3.0 over 5 weeks
- Repeat clinical, radiographic evaluation at 5 weeks;
- Repeat therapy dose if no serious adverse event and no progressive disease

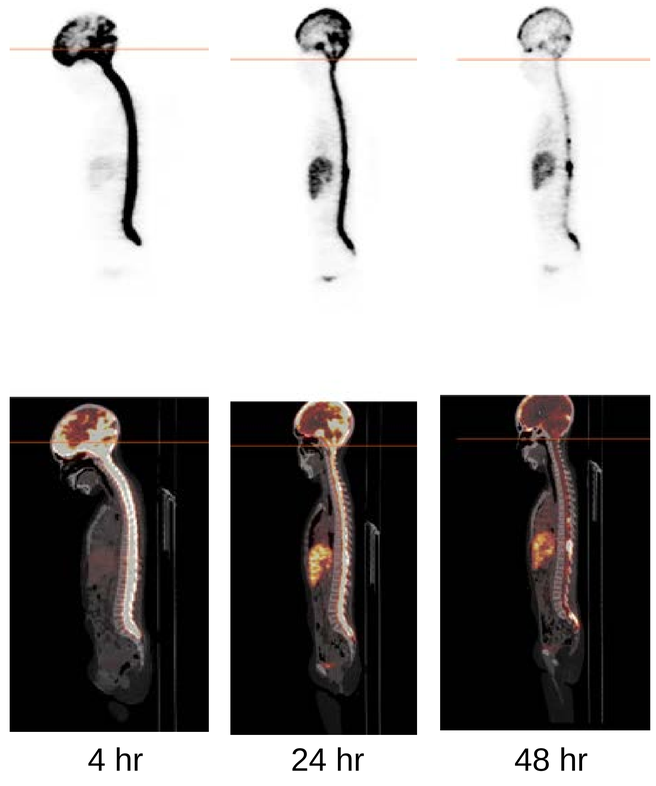
Results

Toxicity Profile

- Rare grade 1 pr 2 transient headache, fever, vomiting (self-limited, manageable with acetaminophen, anti-emetics
- Grade 3 or 4 myelosuppression in patients ts with prior CSI, poor BM reserve (<100K at treatment; no non-myelosuppressive DLT reached)

Dosimetry

- High mean CSF: blood absorbed dose (ratio) achieved
  - 104.9 : 2.6 cGy/mCi
  - Average CSF Clearance T½: 6.69 hours



4 hr 24 hr 48 hr

DIAGNOSIS	No. patients	No. Injections
Neuroblastoma	109	340
Medulloblastoma/PNET	27	72
Ependymoma	9	40
EMTR	4	10
Sarcoma	9	26
Melanoma	5	11
Other (ATRT , choroid plexus ca, ovarian ca, retinoblastoma)	14	42
TOTAL	177*	541

DIAGNOSIS	No.	OS (months)	No. Alive (%)
Neuroblastoma	109	50.8	52 (48%)
Medulloblastoma/ PNET	27	15.6	12 (44%)
Ependymoma	9	18.7	2 (22%)
ETMR	4	28.8	3 (75%)
Sarcoma	9	12.6	1 (11%)
Melanoma	5	3.0	0 (0%)
Other (ATRT , choroid plexus ca, ovarian ca, retinoblastoma)	14	22.1	8 (57%)
TOTAL	177		

DIAGNOSIS	No.	Adverse Event (CTC 3.0) Possibly/Probably/ Definite	Percent Myelosuppression
Neuroblastoma	109	Gr 3 or 4 myelosuppression (ANC, hgb, platelets) (88) Gr 4 Hypersensitivity reaction (1) Gr 3 ALT/AST (5) Gr 3 Chemical Meningitis (3) Gr 4 MDS/AML (6) Gr 3 Headache (1)	85%
Medulloblastoma/ PNET	27	Gr 3 or 4 myelosuppression (8) Gr 3 or 4 Chemical meningitis (2) Gr 4 MDS/AML (1) Gr 3 Ataxia (1) Gr 4 Hydrocephalus (1) Gr 4 Encephalopathy (1)	57%
Ependymoma	9	Gr 3 or 4 myelosuppression (3) Gr 3 Headache (1) Gr 2 Nausea/Vomiting (1)	50%
EMTR	4	Gr 3 or 4 myelosuppression (2) Gr 1 Fever (1) Gr 2 Vomiting (1)	50%
Sarcoma	9	Gr 3 or 4 myelosuppression (3) Gr 4 AML (1)	75%
Melanoma	5	Gr 3 Myelosuppression (2) Gr 3 Nausea (1) Gr 3 Hypokalemia (1)	50%
Other (ATRT , choroid plexus ca, ovarian ca, retinoblastoma)	14	Gr 4 MDS/AML (1) Gr 3 Vomiting (1) Gr 3 Headache (1)	
TOTAL	177		

Conclusions

We conclude that cRIT ^{131}I-Omburtamab

- has a favorable safety profile (manageable acute adverse events (transient myelosuppression is most common)
- has a favorable CSF: blood ratio
- Has clinical ultity to treat B7-H3-positive CNS tumors:
  - CNS NB
  - Recurrent Medlulloblastoma
  - Recurrent ETMR
  - Recurrent CPC

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