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Targeted Radiolabeled Nanoliposomes for Rare CNS Cancers:
An Update on the ReSPECT Phase 1/2 Trials

Gordon Research Conference
Radionuclide Theranostics for the Management of Cancer
Clinical Trial Updates in Radionuclide Theranostics
08 July 24
11:30 am ET

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Forward Looking Statement/Disclosure

This presentation contains statements that may be deemed "forward-looking statements" within the meaning of U.S. securities laws, including statements regarding clinical trials, expected operations and upcoming developments. All statements in this presentation other than statements of historical fact are forward-looking statements. These forward-looking statements may be identified by future verbs, as well as terms such as "potential," "anticipating," "planning" and similar expressions or the negatives thereof. Such statements are based upon certain assumptions and assessments made by management in light of their experience and their perception of historical trends, current conditions, expected future developments and other factors they believe to be appropriate. These statements include, without limitation, statements regarding the following: the potential promise of rhenium (^{186}Re) obisbemeda including the ability of rhenium (^{186}Re) obisbemeda to safely and effectively deliver radiation directly to the tumor at high doses; expectations as to the Company's future performance including the next steps in developing the Company's current assets, which include our nanomedicine platform and commercializing rhenium (^{186}Re) obisbemeda and 188RNL-BAM; the Company's clinical trials including statements regarding the timing and characteristics of the ReSPECT-GBM, ReSPECT-LM and ReSPECT-PBC clinical trials; possible negative effects of rhenium (^{186}Re) obisbemeda; the continued evaluation of rhenium (^{186}Re) obisbemeda including through evaluations in additional patient cohorts; the intended functions of the Company's platform and expected benefits from such functions; and development and utility of the CNSide leptomeningeal metastases diagnostic test.

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Melissa Moore is an employee of Plus Therapeutics.

Radiotherapeutics for CNS cancers

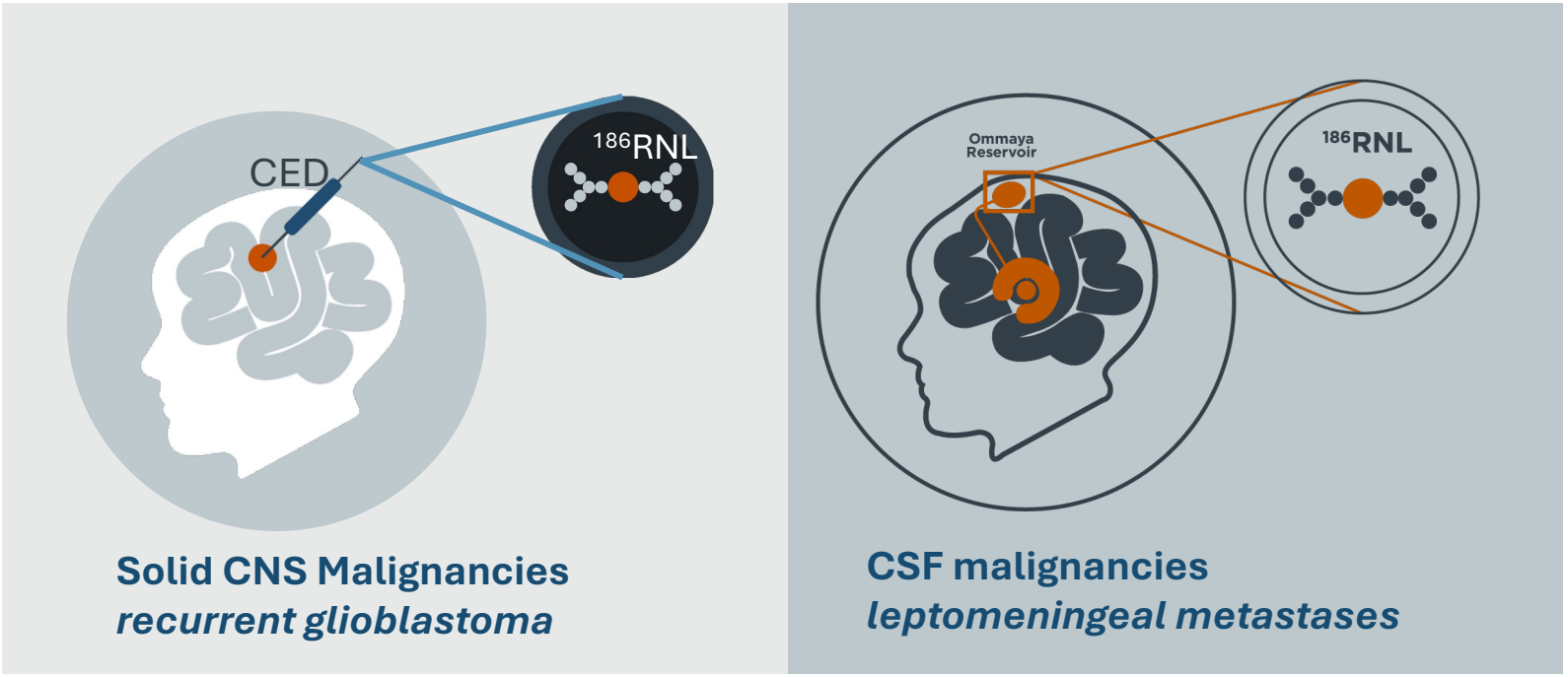
Direct targeted delivery of rhenium (^{186}Re) obisbemeda (rhenium-186 nanoliposomes, ^{186}RNL)

Why *direct delivery*?

Why *rhenium-186*?

Why *nanoliposomes*?

The right drugs for the right indications



Solid CNS Malignancies
recurrent glioblastoma

CSF malignancies
leptomeningeal metastases

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Significant challenges exist in therapeutic development for CNS cancers

BBB substantially limits therapeutic options, highly infiltrative, resistance develops, and radiation is limited

BBB/BSCB

+ Blood brain barrier (BBB)/blood cerebrospinal fluid barrier (BSCB)/meningeal barrier prevent most drugs from entering the CNS to maintain an optimal microenvironment
+ Only 2% of small molecules sufficiently cross the BBB (‘rule of 5’)
+ Blood brain tumor barrier (BBTB) is a disrupted BBB in malignant brain tissue (increased permeability) but heterogeneously that does not allow drugs to reach homogenous and effective concentrations within tumor tissue

Infiltrative Nature of Disease

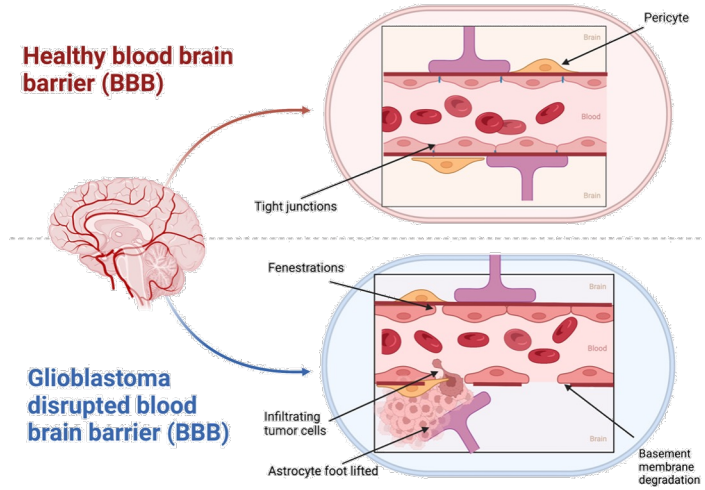
+ Most tumors recur within 2 cm of the initial tumor
+ Magnitude of resection correlates with increased survival, but 2 cm margins are not possible
+ Tumors reoccur after surgery because infiltrative disease not adequately treated

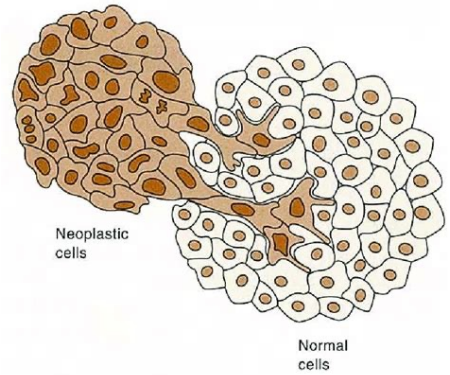
Resistance

+ Interpatient, intratumoral, functional, and molecular heterogeneity create barriers to chemotherapies
+ Hypermutation
+ Immune evasion

Radiation toxicity

+ Limiting factor is toxicity to surrounding normal tissue





Microscopic Level

2cm ‘at risk’ rim of brain without contrast enhancing tumor

Macroscopic Level

Cancers. 2023,15,2116.https://doi.org/10.3390/cancers15072116
Cancers 2024, 16, 236. https://doi.org/10.3390/cancers16010236

+ Get drug to the tumor
+ Keep the drug at the tumor
+ Kill the tumor while sparing healthy tissue
+ Repeat as necessary

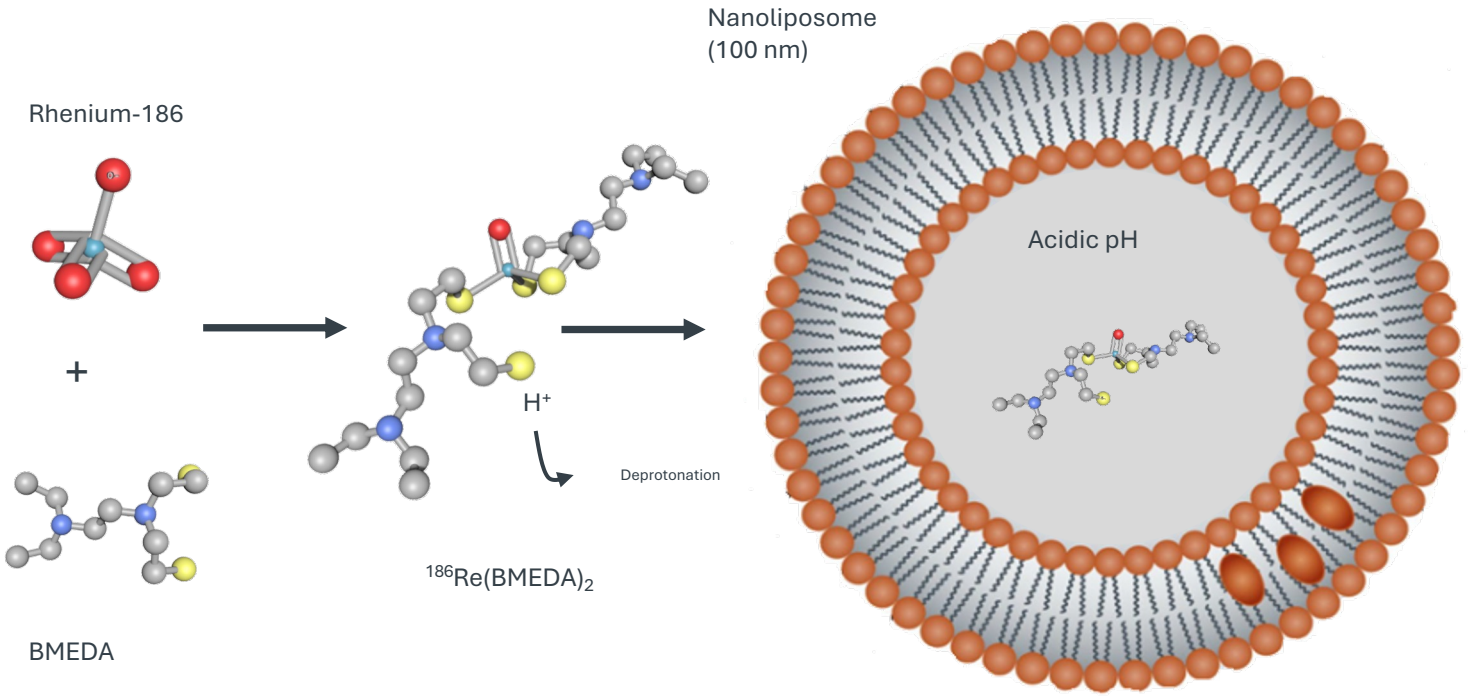
Direct Targeted Rhenium (^{186}Re) **O**bisbemeda

Tailored radiotherapeutic and delivery for CNS malignancies

1. Rhenium-186: Emits tumor-destroying radiation over short distances while sparing healthy tissue

2. BMEDA: Small molecule that chelates to rhenium and is loaded into the nanoliposome where it's irreversibly trapped

3. Nanoliposome: Carries the trapped BMEDA-chelated ^{186}Re to tumor



Rhenium (^{186}Re) Obisbemeda

Why direct delivery? *Get the drug to the tumor.*

Avoids the BBB challenge associated with systemic delivery

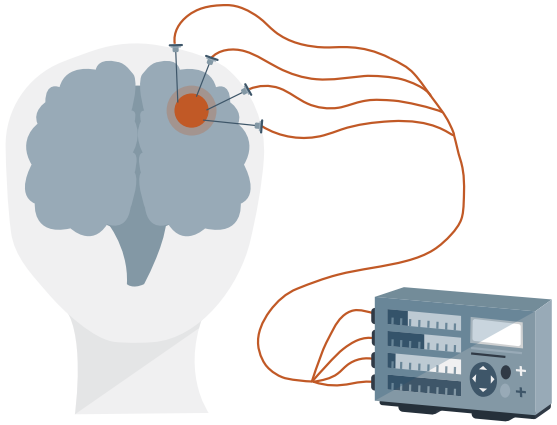
Intraventricular Catheter (Ommaya reservoir)

+ FDA-approved and utilized for 60+ years
+ Small subcutaneous reservoir with direct ventricle access
+ Allows multidosing and CSF sampling
+ Commonly placed in LM patients

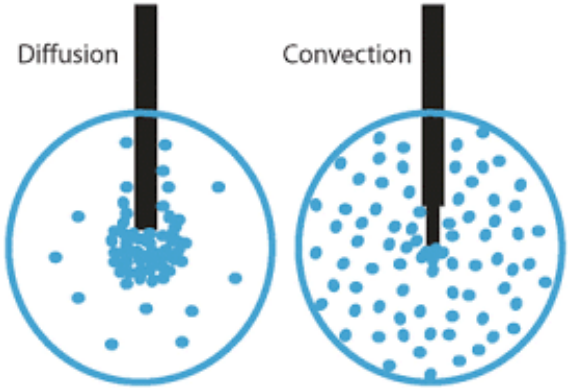
Cerebrospinal Fluid - LM

Convection-Enhanced Delivery (CED)

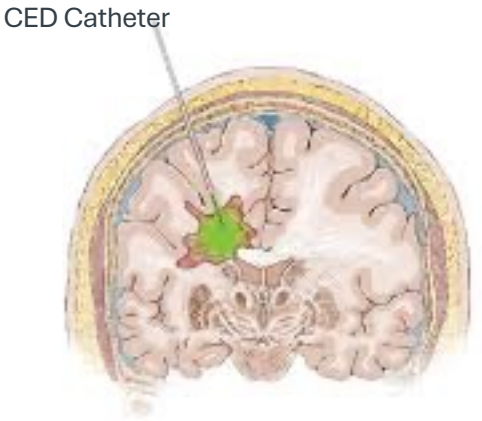
+ FDA-approved and utilized for 20+ years
+ Controlled pressure and flow are optimal for drug delivery to region of interest
+ Utilized for GBM and other brain tumors



Brain Parenchyma - rGBM



Diffusion vs. Convection



Highly Targeted to Tumor

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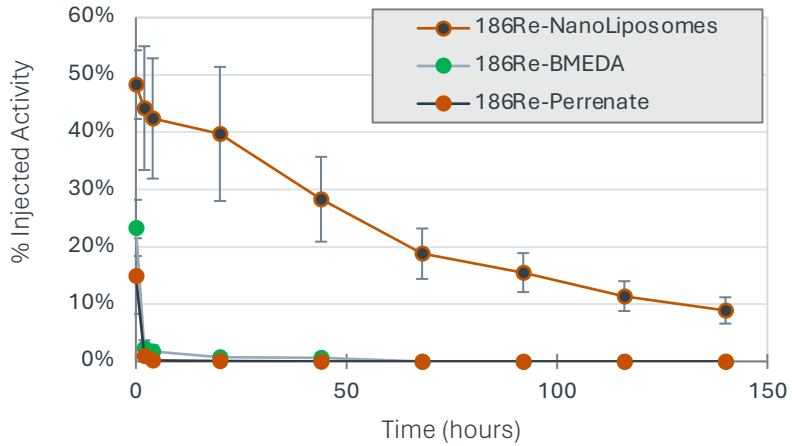
Why nanoliposomes? *Keep the drug at the tumor.*

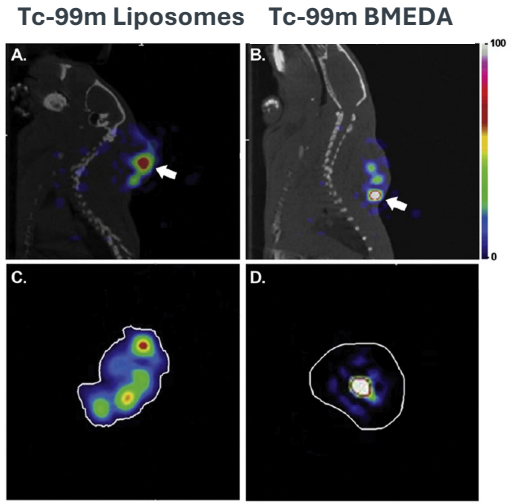
Prolongs persistence at tumor and optimizes distribution

- Spherical, self-assembling vesicles made up of one or more lipid bilayers in a central compartment
- Bilayers are naturally occurring and nearly identical to the lipid membranes of normal cells and use the same degradation pathways
- Ideal candidates as delivery vehicles for small molecules, proteins, nucleic acids, and imaging agents for therapeutic and diagnostic use
- Can deliver a variety of payloads and protects cargo from degradation to extend the half-life of drugs
- Decreases systemic side effects despite increased drug doses
- Can be given by various routes, e.g., parenteral, pulmonary, oral, transdermal, ophthalmic, and nasal
- Clinically approved products spanning both pharmaceuticals and cosmetics (e.g., Doxorubicin hydrochloride, Daunorubicin Amphotericin B, Cytarabine, Verteporfin, Morphine, Recombinant varicella-zoster virus glycoprotein E, etc.)

Tumor Retention



Improved Drug Distribution



The use of the nanoliposome greatly improves retention and distribution of the therapeutic agent within the tumor following CED compared to non-nanoliposome associated molecules

Advanced Drug Delivery Reviews. June 2019. DOI: 10.1016/j.addr.2019.05.012
Molecules. 27(4):1372. doi:10.3390/molecules27041372.
Adv Drug Deliv Rev. 2014 September 30; 76: 39–59. doi:10.1016/j.addr.2014.07.001.

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Why rhenium-186? *Kill the tumor while sparing healthy tissue.*

There are no best radionuclides, just better for a given application

CNS RT must haves

- Moderate path-length
- Moderate energy
- Moderate half-life
- Optimal chemistry and scalability
- Rapidly cleared by the kidneys
- Low to no bone avidity
- Real time visualization

- Rhenium has been used safely and effectively for over 30 years in Europe to treat various cancers [1,2]

Radioisotope	^{186}Re	^{225}Ac	^{90}Y	^{212}Pb	^{131}I	^{177}Lu
Emitter	**Beta**	Alpha	Beta	Alpha	Beta	Beta
Half-life (days)	**3.7**	9.90	2.67	0.44	8.0	6.65
Pathlength (mean/max)	**1.2mm 3.6mm**	0.05mm 0.08mm	3.6mm 11 mm	0.05mm 0.09mm	0.4mm 2.4mm	0.28mm 1.7mm
Therapeutic (mean)	**336.2 keV beta**	5.8-8.4 MeV alpha	2280 keV beta	6.1 MeV alpha	334 keV 606 keV beta	385 keV 498 keV beta
Imaging	**137.2 keV gamma**	218 keV 440 keV gamma	N/A	238.6 keV 511 keV 583 keV gamma	284 keV 364.5 keV 637 keV gamma	113 keV 208.4 keV gamma

Goal: Match radionuclide properties to the drug's residency time/formulation and anatomic and tumor characteristics to maximize therapeutic efficacy

^{186}Re: A 'Goldilocks' of isotopes for CNS cancers

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1. Cancers include skin cancer, liver cancer, and bone metastases. Oncidium Foundation
2. European Society for Medical Oncology (ESMO). "Rhenium-Based Therapies in Cancer Treatment."; German Cancer Research Center (DKFZ). "Innovations in Liver Cancer Treatment Using Rhenium.

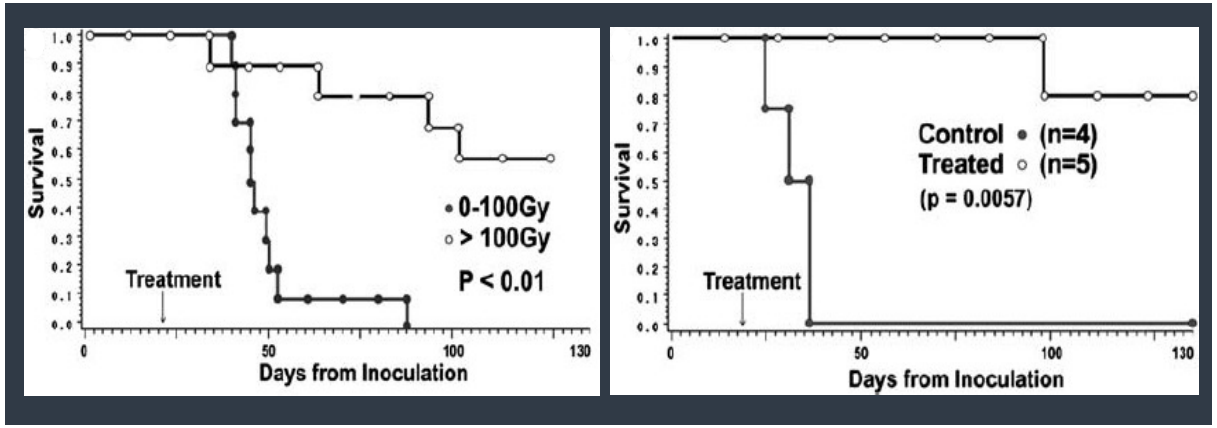
Preclinical proof-of-concept studies: GBM and LM

Preclinical: GBM and LM

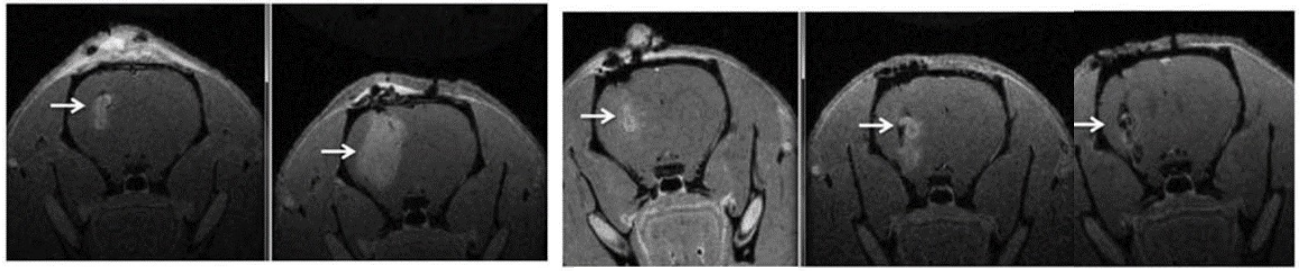
Rhenium (^{186}Re) obisbemeda significantly prolongs survival in GBM and LM tumor models

- Doses of up to 1,845Gy were tolerated without weight loss or neurological deficit
- Statistically significant prolongation in survival with no residual tumor all treated animals
- 100Gy efficacy threshold observed in preclinical research

U87 **U251**



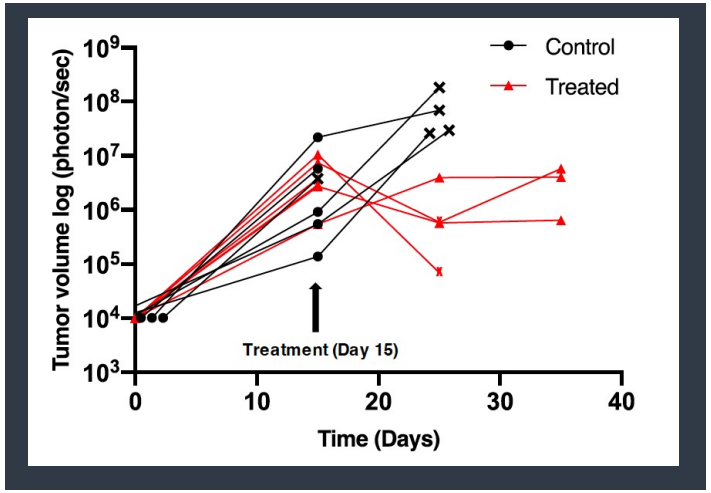
Control **^{186}Re-Liposome Treatment**



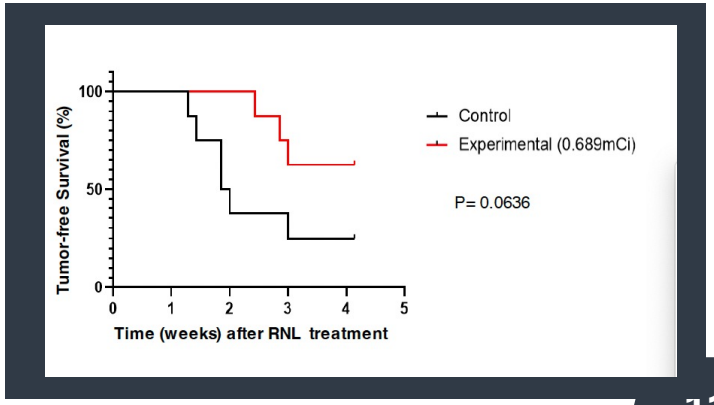
Day -1 **Day 14** **Day -1** **Day 14** **Day 70**

- A clinically relevant LMC rat model using C6-Luc glioma cells was created
- Administered dose ranged from 0.480 mCi to 1.340 mCi
- A corresponding maximum absorbed dose of 1075 Gy showed no evidence of toxicity in the treated animals over 3 months

- Tumor volume of control animals (black) compared with ^{186}RNL-treated animals (red). Control animals had bigger tumors and died faster than the ^{186}RNL-treated animals



- Tumor-free survival between control and ^{186}RNL-treated animals at 4 weeks



Clinical trials:
ReSPECT-GBM Phase 1/2 and ReSPECT-LM Phase 1

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Solid CNS Malignancies

ReSPECT-GBM

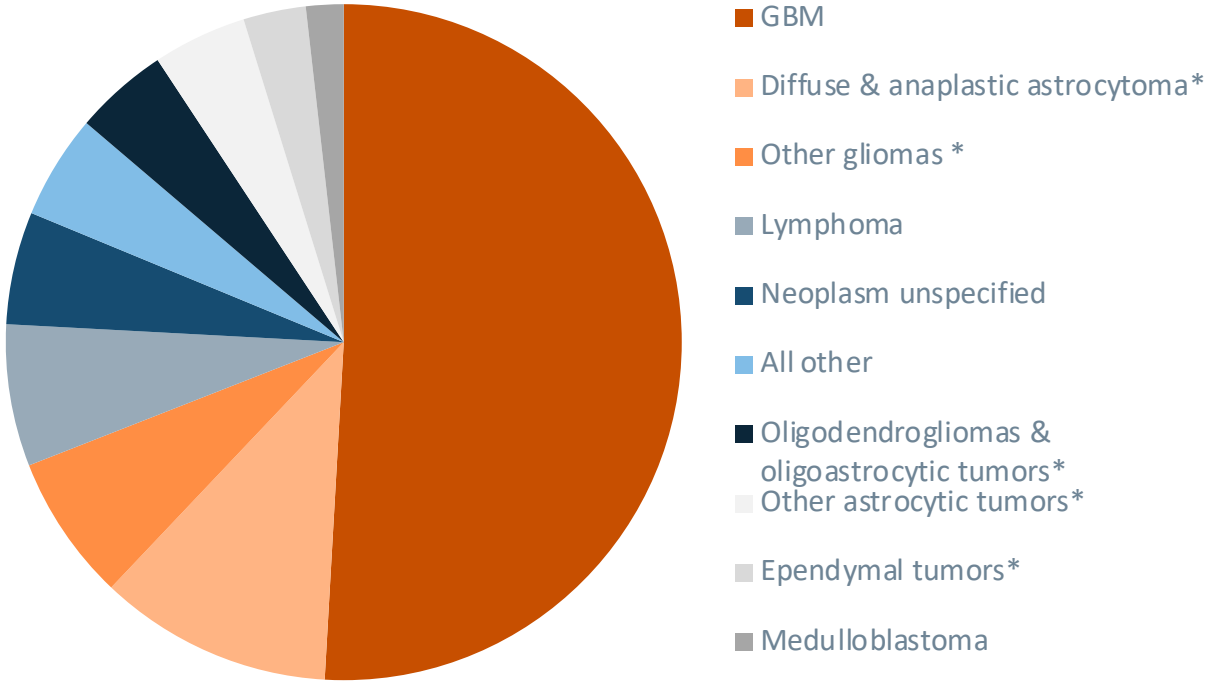
Power and precision in cancer radiotherapeutics

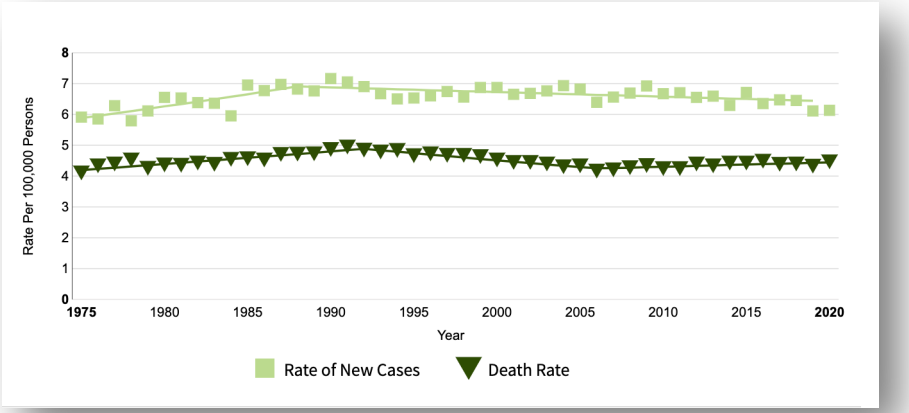
Malignant Gliomas

Aggressive course and serial recurrence is the norm, with mortality rates essentially unchanged over 50 years

GBM Epidemiology

- Brain and other central nervous system cases 2023: ~24,8101 (1.3% of all cancers in US)
- Deaths in 2023: ~18,9901 (3.1% of all cancers in US)
- People living with brain cancer in the US: ~180,0001 (33.8% 5-year relative survival rate)
- Affects all genders, ages, and races
- GBM is the most common primary malignant brain tumor in adults
- ~15,500 newly diagnosed GBM patients in US each year
- 5-year survival rate ~7%
- Highly aggressive and infiltrative
- Almost all patients recur following initial treatment
- >90% of patients recur at the original tumor location





New Cases, Deaths, and 5-Year Relative Survival for Brain and Other Nervous System Cancers in the US

Neuro-Oncol. 23(8):1231–1251. doi:10.1093/neuonc/noab106.
Neuro Oncol. 25(4):iv1–iv99, https://doi.org/10.1093/neuonc/noad149
Neurosurg Focus. 20(4):E3. doi:10.3171/foc.2006.20.4.2.
https://seer.cancer.gov/statfacts/html/brain.html

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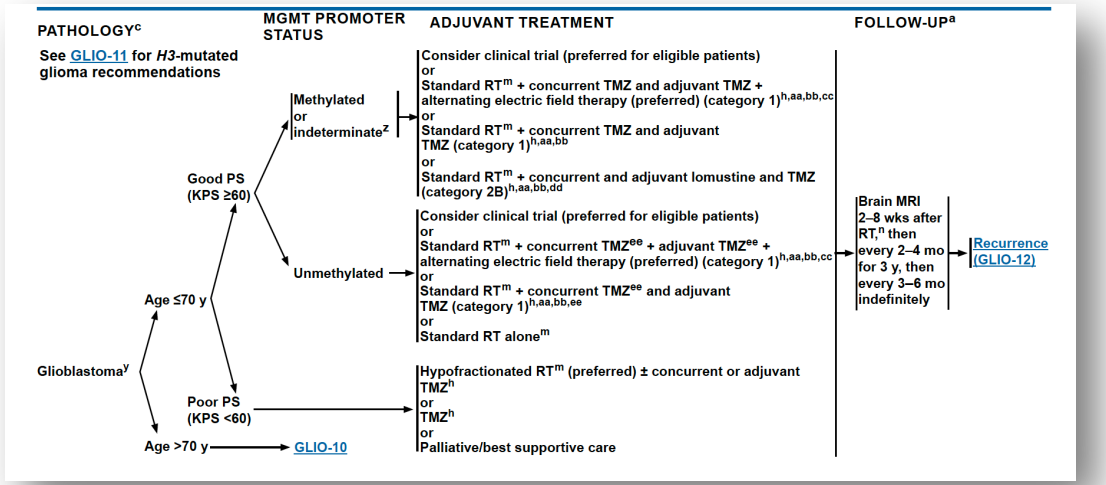
GBM Treatment Triad

Mix of surgery, radiotherapy, and chemotherapy

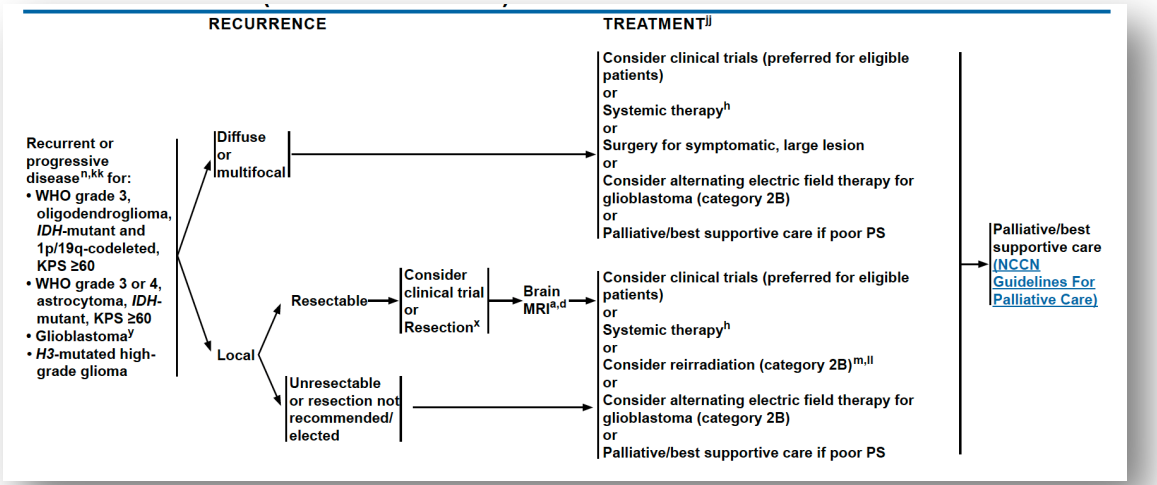
GBM Initial Treatment

- Molecular diagnosis has better defined GBM subsets and helped stratify disease severity
- Maximal safe resection is the best option if available
- Chemotherapy (temozolomide) and radiation (60 Gy, in fractions)
- Almost all patients with primary disease reoccur, relapse, or respond poorly to treatment



GBM Recurrence Treatment

- Repeat of resection, chemotherapy, and radiation (~35-50Gy, in fractions) depending on nature of recurrence
- Bevacizumab given for those with poor performance status, but does not prolong survival
- NCCN guidelines recommend clinical trials for CNS cancers upon recurrence



Batchelor, Tracy, Helen A. Shih, and Bob S. Carter. "Management of recurrent high-grade gliomas." *UpToDate [Internet]. Waltham (MA):* (2015).
Batchelor, Tracy, and Helen A. Shih. "Management of glioblastoma in older adults." *UpToDate [Internet]. Waltham (MA): UpToDate* (2017).

ReSPECT-GBM Phase 1, single dose trial design

Single administration of Rhenium (^{186}Re) Obisbemeda by Convection Enhanced Delivery (CED)

- Dose escalation: 3+3 modified Fibonacci, currently enrolling in Cohort 8
- Primary objective
  - Maximum Tolerated Dose / Maximum Feasible Dose
- Secondary objectives
  - Dose distribution
  - Overall Response Rate (ORR)
  - Progression Free Survival (PFS)
  - Overall survival (OS)
  - Imaging
- Funding: NIH/NCI grant through Phase 2

Single Administration Phase 1 Dose Escalation Plan

	Cohort	Administered Volume (mL)	Administered Activity (mCi)	Administered Concentration (mCi/mL)
	1	0.66	1.0	1.5
	2	1.32	2.0	1.5
	3	2.64	4.0	1.5
	4	5.28	8.0	1.5
	5	5.28	13.4	2.5
RP2D	**6**	**8.80**	**22.3**	**2.5**
	7	12.3	31.2	2.5
Current	8	16.34	41.5	2.5

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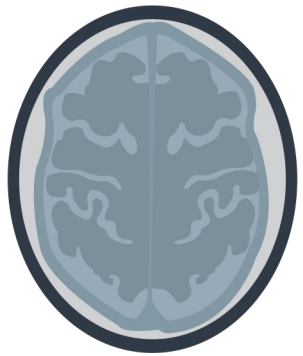
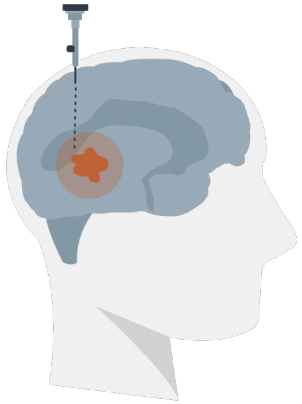
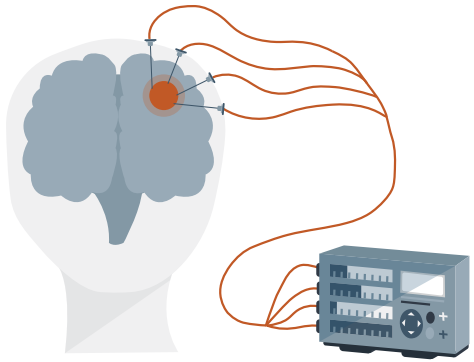
ReSPECT-GBM treatment workflow

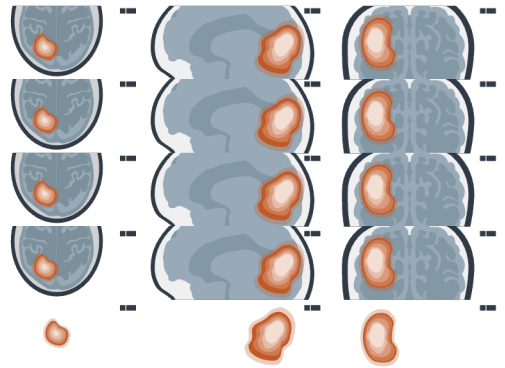
Inpatient single administration

Personalized Treatment Planning	SoC Biopsy and Catheter Placement	Drug Infusion	Patient Monitoring
Prior to Treatment	**Day 0**	**Day 1**	**Day 2-3**
MRI imaging to assess and plan catheter number, trajectory, and location	Confirmatory biopsy followed by neuro navigation & precision catheter placement	Single ~4-hour infusion with real-time SPECT/CT imaging in Nuclear Medicine	Catheter removal, patient discharge and follow dosimetry & imaging









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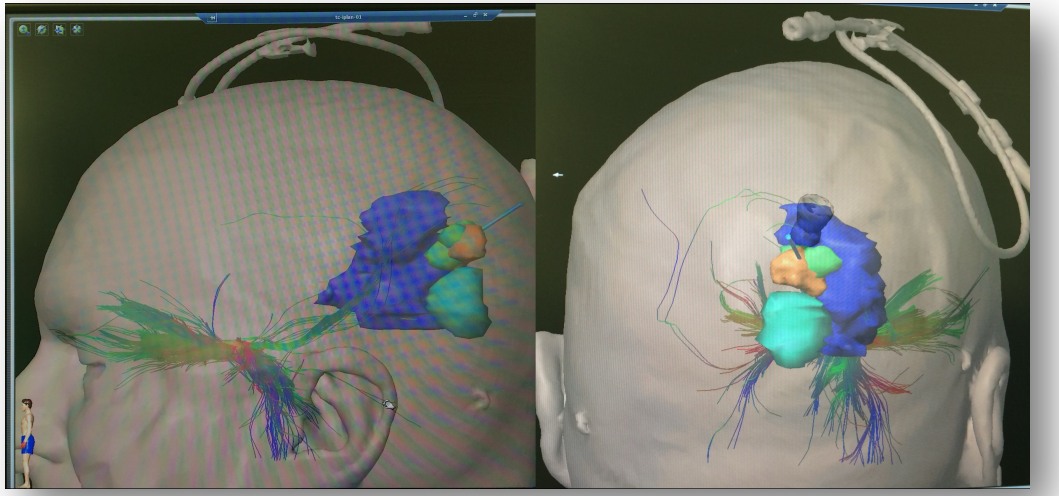
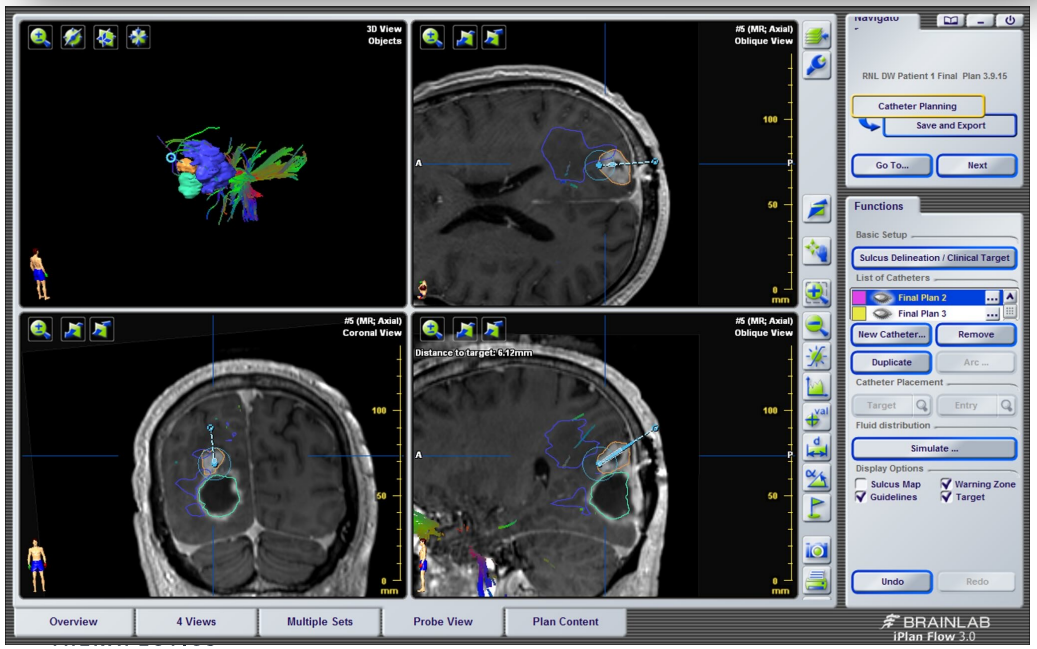
Personalized Case Planning with BrainLab iPlan Flow Software

High resolution imaging differentiates tumor and other critical brain structures





CED catheter in place after surgery is fixed in place with calvarial bone anchor to maintain catheter location and depth in preparation for drug infusion the next day

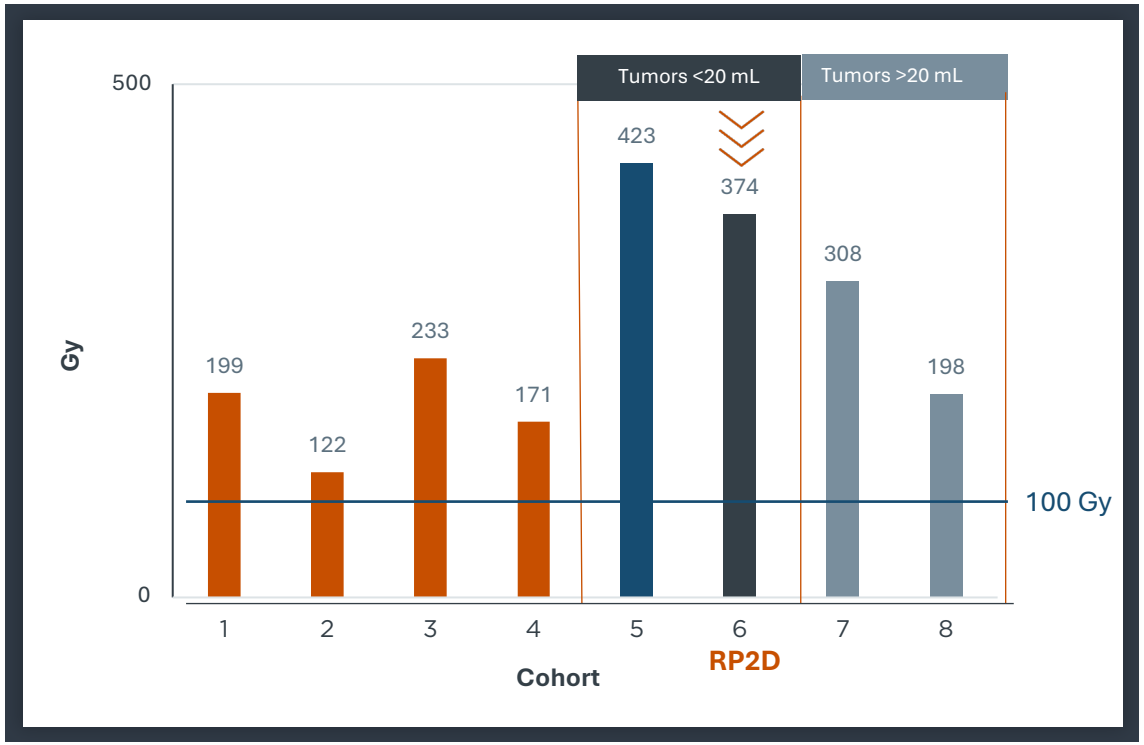
ReSPECT-GBM Phase 1 safety and RP2D selection

MTD/MFD not reached in dose escalation phase

- Generally safe and well tolerated over 28 patients in 8 dosing cohorts, enrollment ongoing
- No evidence of systemic radiation toxicity
- Most Phase 1 adverse events (AEs) were mild or moderate and resolved with treatment

Trial Safety Summary		
Grade	>5% AEs	**SAEs**
Grade 1 66.67% Grade 2 25.71% Grade 3 7.62%	Headache (6.67%) Fatigue (5.24%)	17

Average Absorbed Dose to Tumor by Cohort



- The average absorbed dose to the tumor for all Phase 1 patients was 264 Gy (n=28, range: 8.9-739.5 Gy)
- Average absorbed dose to the tumor at the recommended Phase 2 dose (RP2D) was 374.5 Gy

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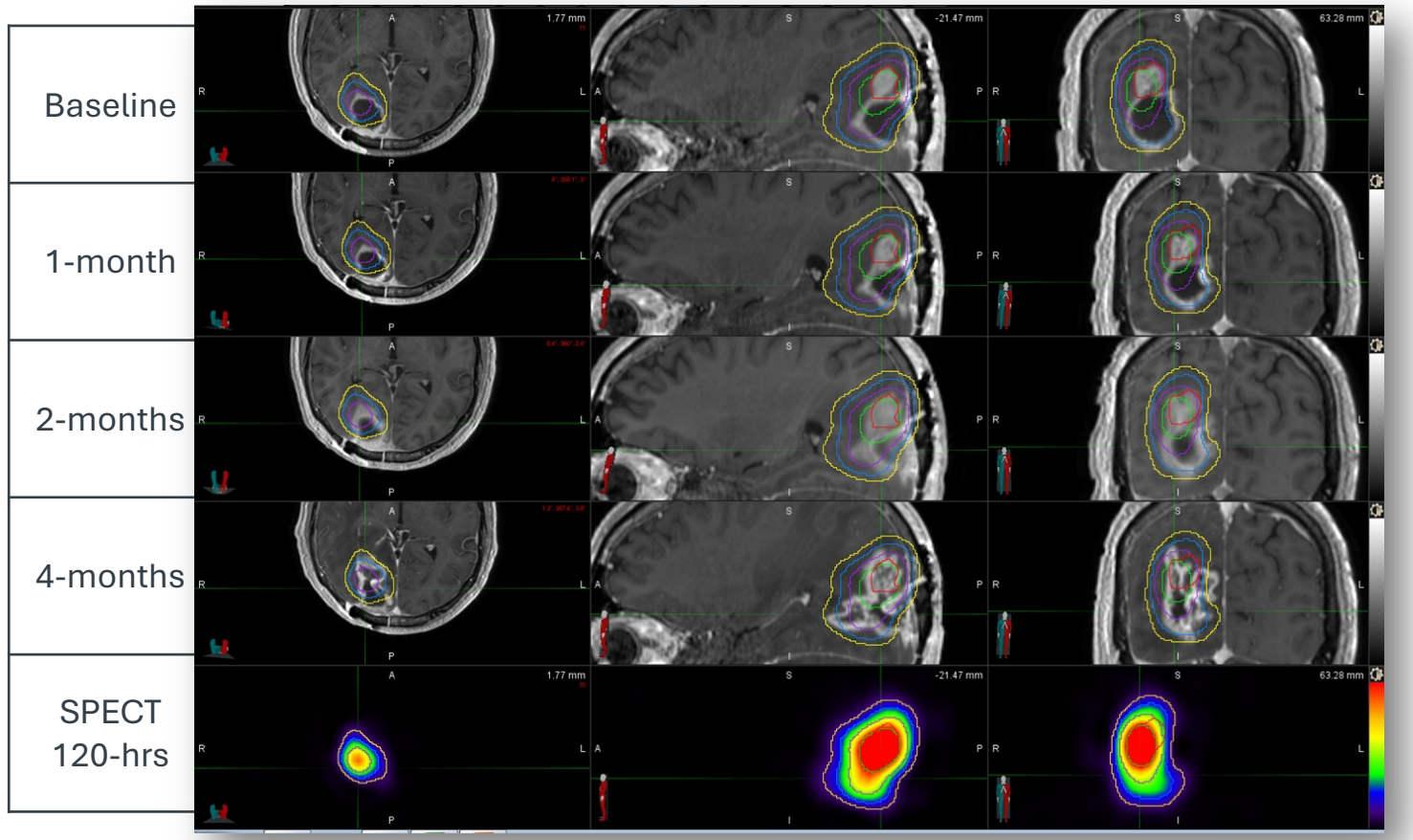
ReSPECT-GBM Phase 1 case study

Early cohorts (1-3) first ensured safety across all variables, with one catheter and small drug volumes

Phase 1, Cohort 1: Patient 01-001

Dose	Vol	Cath	Tumor	AADT	PTC	OS
1.0 mCi	0.66 mL	1	3.50 mL	143 Gy	83.41%	909 days

- 54-year-old male, MGMT unmethylated, IDH WT
- Immediate dispersion of small amount of radioactivity to a volume of edema
- Volume of tumor with lower radioactivity is located adjacent to surgical cavity (lower resistance)
- Patient tolerated procedure well with minimal AEs
  - Most mild (grade 1) and unrelated to study
  - One definite attribution was due to CED procedure (scalp pain, grade 1)
- Organ doses were low
- Patient lived for 909 days (29.88 months)



Baseline MRI, co-registered MRI, and co-registered SPECT

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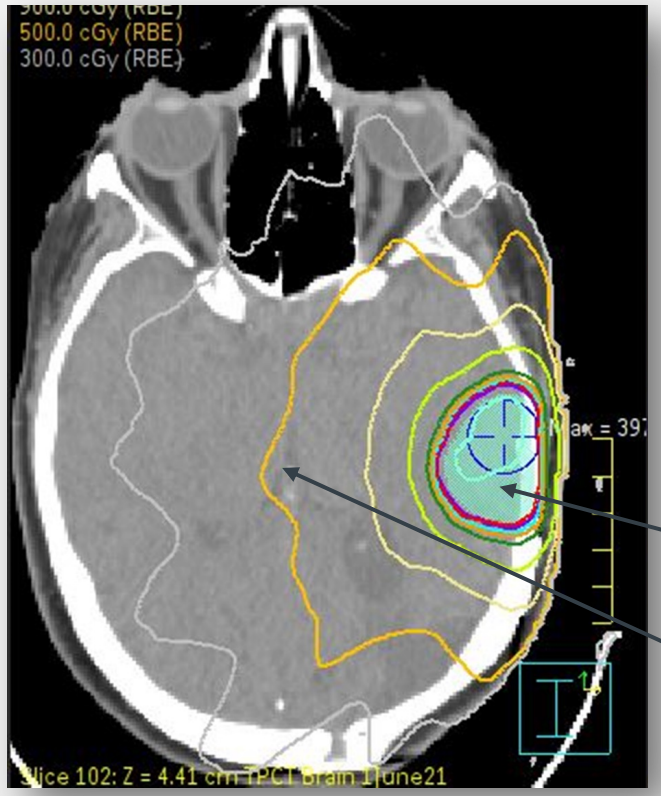
Dose = administered dose; Vol = administered volume; Cath = number of catheters used; Tumor = tumor size; AADT = average absorbed dose to tumor; PCT = percent tumor volume treated at 120 hours; OS = overall survival

Rhenium (^{186}Re) Obisbemeda advantage over EBRT gold standard

More targeted radiation delivery with 10X increase in maximum absorbed dose

EBRT



EBRT
vs.
Rhenium (^{186}Re)
Obisbemeda

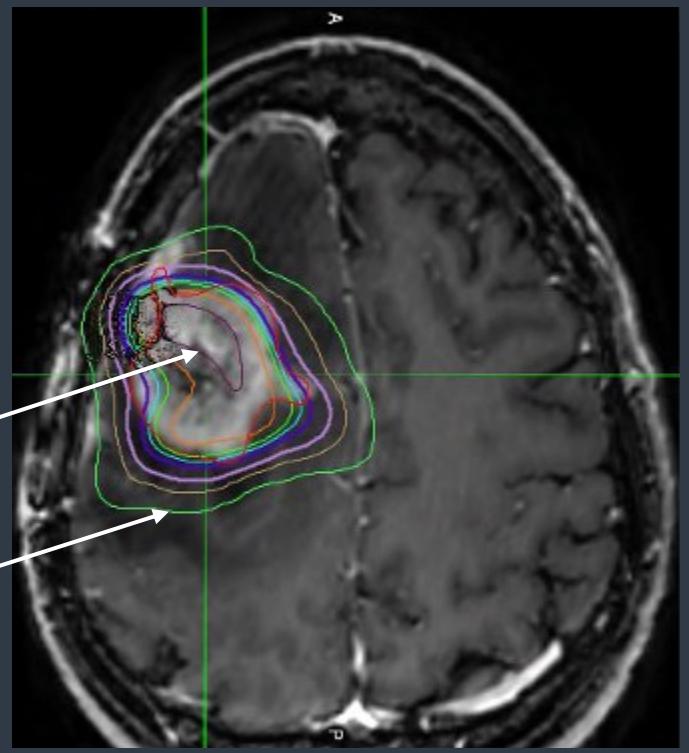
28.5 Gy
Max dose

5 Gy

250 Gy
Max dose

5 Gy

Rhenium (^{186}Re) Obisbemeda



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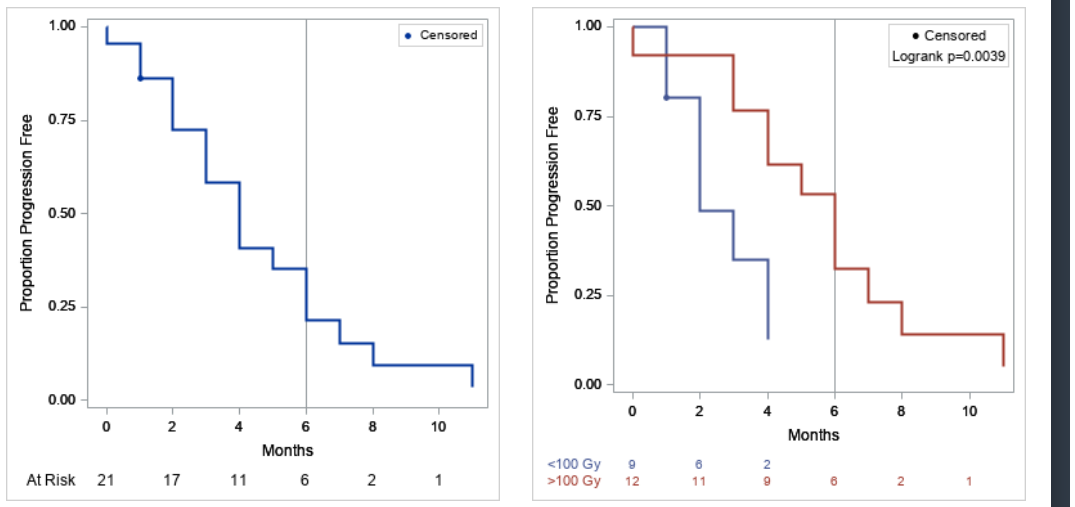
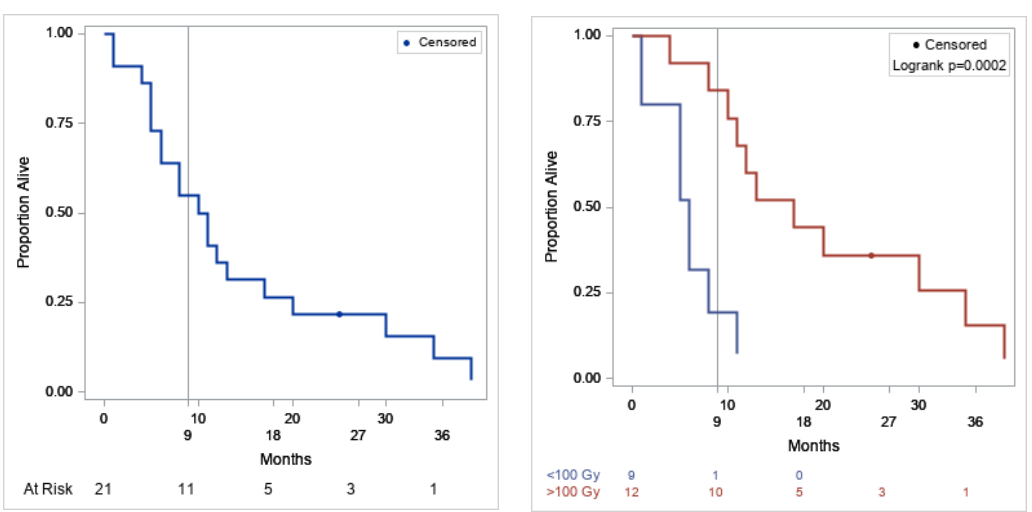
ReSPECT-GBM Phase 1 efficacy

Dichotomous stratification of patients based on 100 Gy absorbed dose threshold



Median Progression Free Survival



Median Overall Survival

Progression free survival or PFS

- All patients: mPFS 4.0 m (95% CI 2.0-6.0 m, PFS6=0.21±0.11)
- Patients with <100 Gy: mPFS of 2.0 m (95% CI 1.0-4.0 m, PFS6=0.0) (blue)
- Patients with ≥100 Gy: mPFS of 6.0 m (95% CI 3.0-8.0 m, PFS6=0.32±0.16) (red)

Median overall survival or mOS

- All patients: mOS was 11.0 m (95% CI 5.0-17.0 m, OS9=0.55±0.11)
- Patients with <100 Gy: mOS of 6.0 m (95% CI 1.0-11.0 m, OS9=0.19±0.18) (blue)
- Patients with ≥100 Gy: mOS of 17.0 m (95% CI 8.0-35.0 m, OS9=0.84±0.11) (red)

*At time of analysis, November 2023

ReSPECT-GBM Phase 2 safety and efficacy

Phase 2 data similar to Phase 1 data

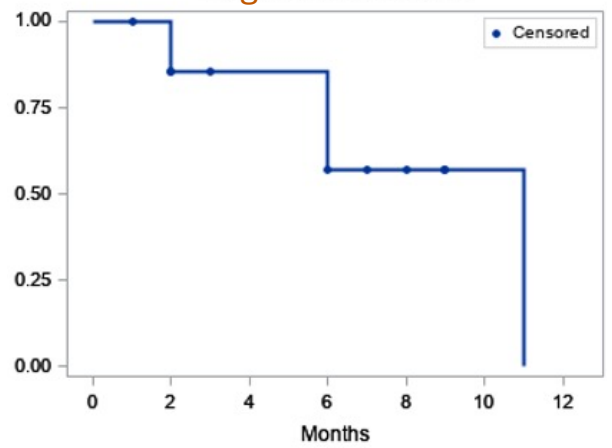
+ Histologically confirmed glioblastoma, WHO 2021
+ IDH wild type, grade IV
+ Limited to 1 recurrence
+ Tumor sizes 20cm^3 or less
+ 1-5 catheters
+ Bevacizumab-naïve

Dose to tumor (avg, Gy)	Percent of treated tumor (avg)
309.14	87.2%

Grade	>5% AEs	**SAEs**	Notes
Grade 1 66.35% Grade 2 25% Grade 3 8.65%	Headache (12.50%) Fatigue (5.77%)	7	Majority of AEs and SAEs are unrelated/unlikely

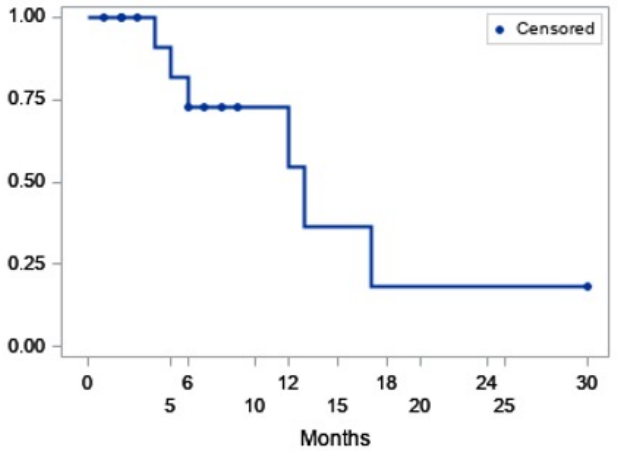
+ Safety profile trending to Phase 1 trial with majority of SAEs unrelated or unlikely to be related to treatment
+ No evidence systemic toxicity

Median Progression Free Survival



+ PFS: 11 months (95% CI 6-11 months)

Median Overall Survival



+ OS: 13 months (95% CI 5 months-NA)

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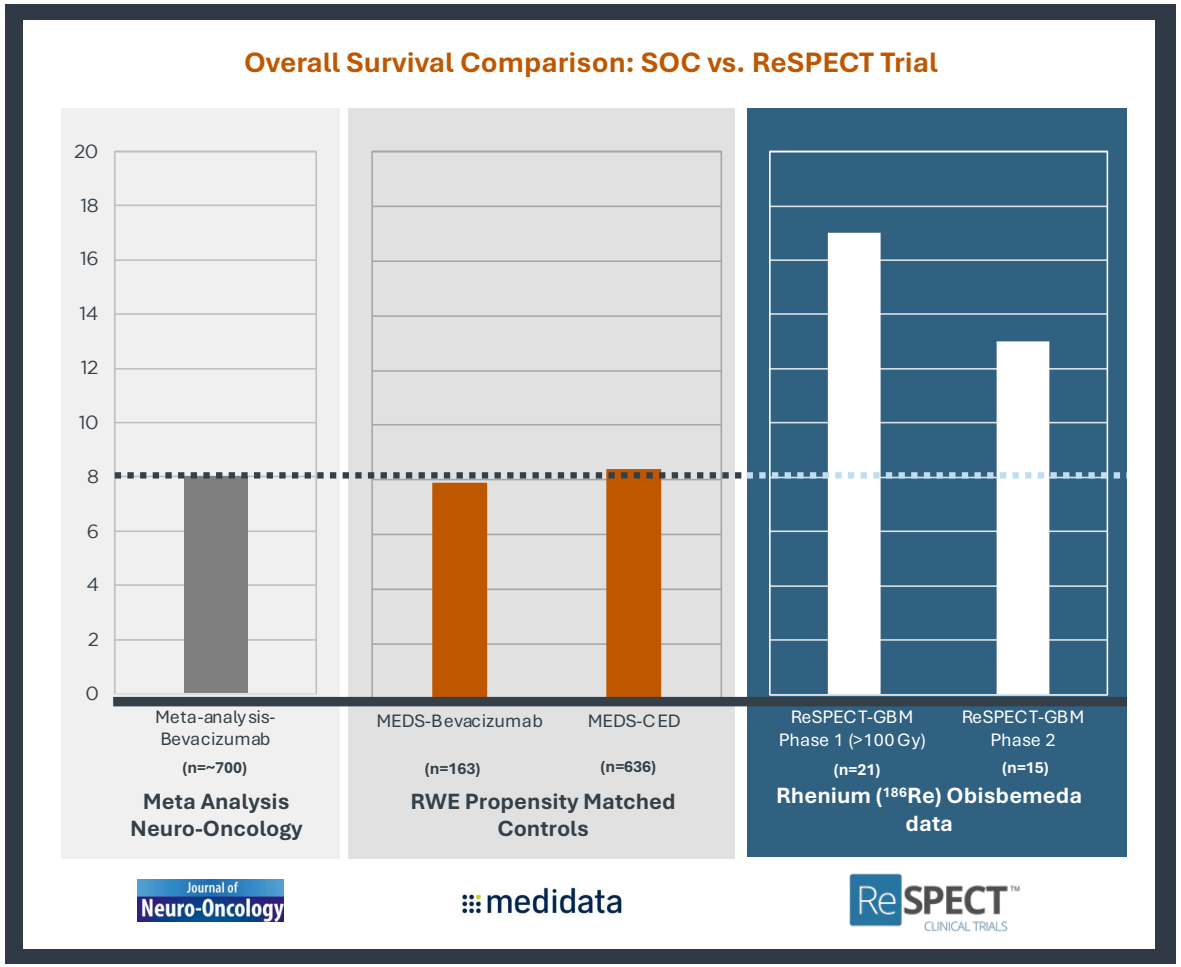
*At time of analysis, November 2023

ReSPECT-GBM vs. SOC median overall survival

Comparative survival data

- Standard of care performance comparison:
  - Published meta-analysis of >700 rGBM patients
  - Plus/Medidata propensity matched RWE control arms
- Phase 1:
  - All patients: 38% improvement over RWE control for Phase 1 (through RP2D)
  - 113% improvement over RWE control in patients receiving therapeutic dose radiation (>100 Gy)
- Phase 2: 63% improvement in Phase 2 patients (n=15)



*Data sourced from miffs the Medidata Enterprise Data Store (MEDS) of deidentified patient-level historical clinical trial data, study and patient-level data from historical rGBM CED studies [D'Amico, J Neurooncol 2021], and from on-going ReSPECT-GBM study.
** At time of analysis, 12Mar24

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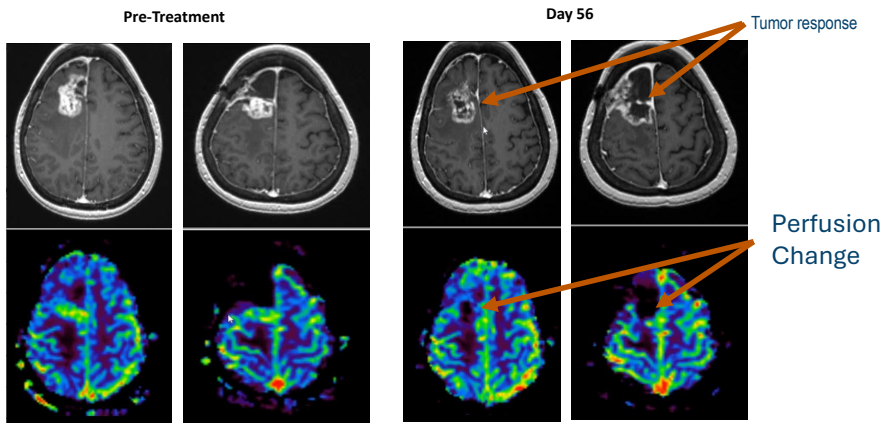
ReSPECT-GBM Tumor Response Data

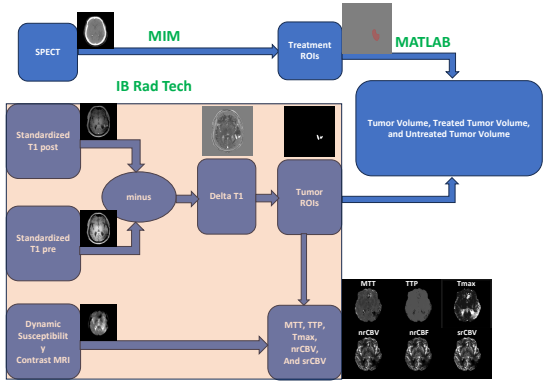
Differentiation tumor response, progression vs. pseudoprogression

Qualitative Response - rCBV Analysis

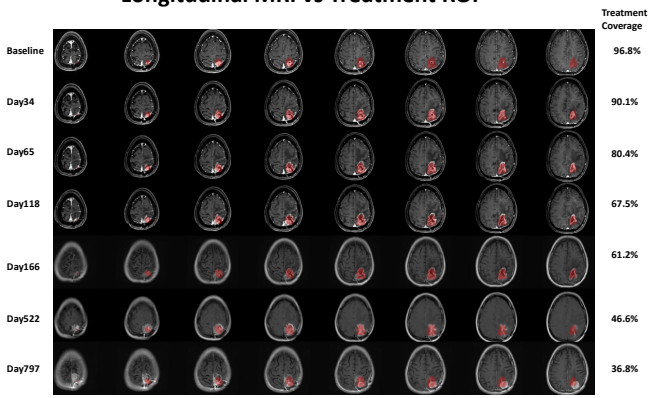
Patient 01-017 MRI and rCBV



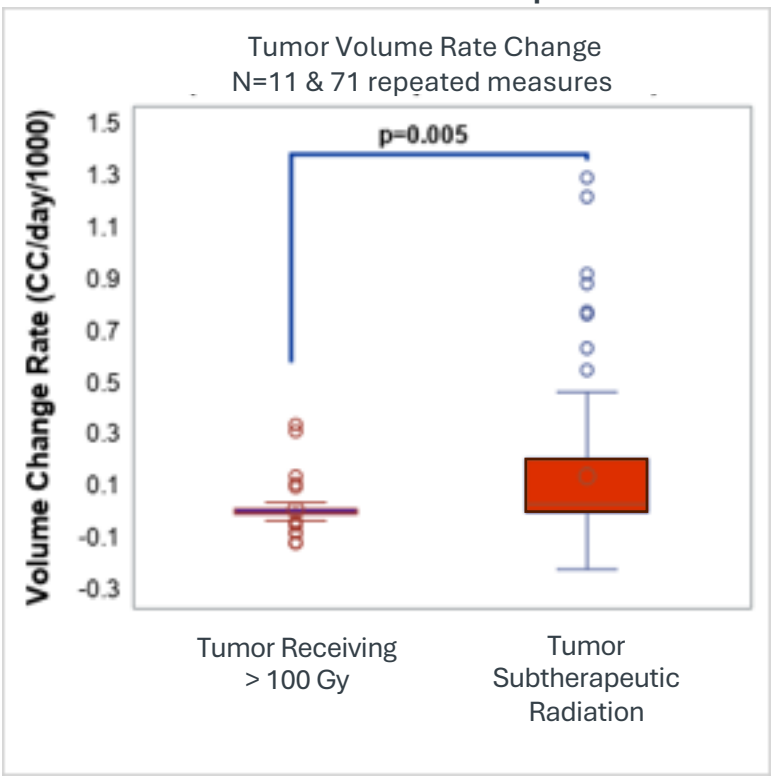
Quantitative Response - Treated vs. Untreated Tumor by Patient



Longitudinal MRI vs Treatment ROI



Tumor Volumetric Response*



*At time of analysis, presented at SNO- November 2023

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CSF Malignancies

ReSPECT-LM

Power and precision in cancer radiotherapeutics

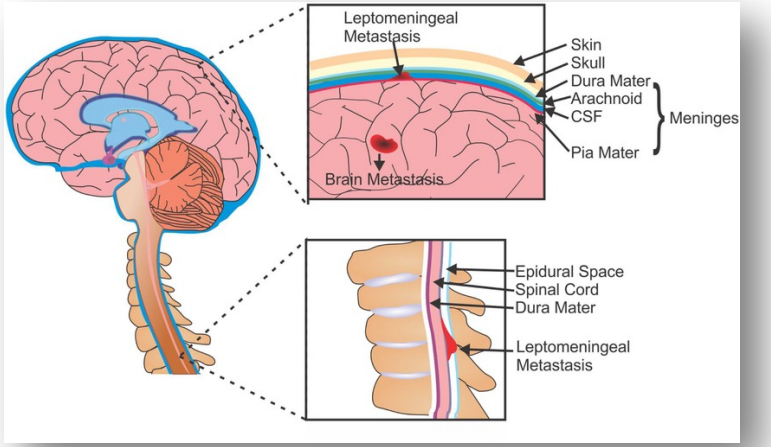
Leptomeningeal Metastases

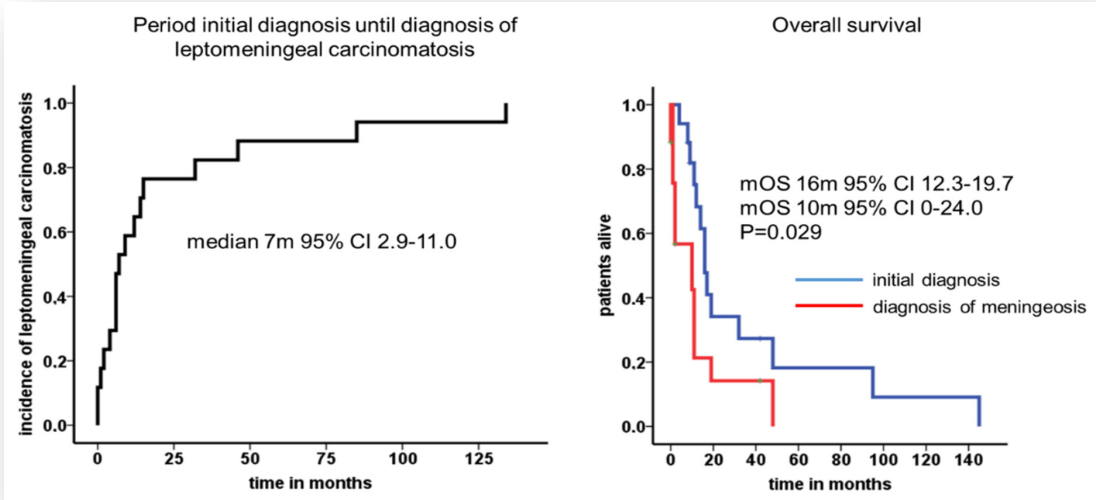
A devastating complication of primary cancers resulting in metastatic spread to the leptomeninges and CSF

LM Epidemiology

- Annual incidence is at least 5-15% of all cancer patients
- Increasing frequency as control of primary cancer improves, with ~155k US patients per year
- 60-70% have progressive systemic disease at time of diagnosis
- 38-83% have concurrent or prior brain metastases
- Most common primary cancers leading to LM are breast, lung, and melanoma, but LM can arise from any cancer
- Likely 2-4x underdiagnosed based on autopsy findings
- Dire survival statistics, once diagnosed: 4-6 weeks without treatment and only 2-6 months with treatment
- In addition to their primary cancer, LM patients brings suffer from high intercranial pressure, spinal cord compression, and cranial nerve, spinal cord, and nerve root symptoms including pain and weakness

Primary Tumor Type	U.S. Incidence (% solid tumors)	Standard of Care: Median Overall Survival
Breast	12-34%*	3.5-4.4 months
Lung	10-26%*	3-6 months
Melanoma	17-25%*	1.7 to 2.5 months
Other	5%*	2-4 months





*Le Rhun, E., et. al. (2013). Surgical neurology international. https://doi.org/10.4103/2152-7806.111304

[1] L. Apostolidis, J. Schrader, H. Jann, A. Rinke, and S. Krug, "Leptomeningeal Carcinomatosis: A Clinical Dilemma in Neuroendocrine Neoplasms," Biology, vol. 10, no. 4, p. 277, Mar. 2021, doi: 10.3390/biology10040277.

LM diagnosis is difficult and few positive outcomes from treatment

Like GBM, EBRT and chemotherapy are mainstays

LM Diagnosis

- CSF cytologic analysis with sample taken by lumbar puncture or intraventricular catheter
- ~50-75% sensitivity, ~50% false negative rate, and ~10% of patients with LM show persistently negative results
- Sensitivity and specificity of brain and spinal MRI with gadolinium is ~70%
- MRI poorly assesses LM in the absence of nodular disease
- Clinical neurologic assessment is difficult as symptoms can result from other factors
  - e.g., brain metastases, neurosurgical procedures, complications from systemic therapy, etc.
- Symptoms may be subtle early in disease progression

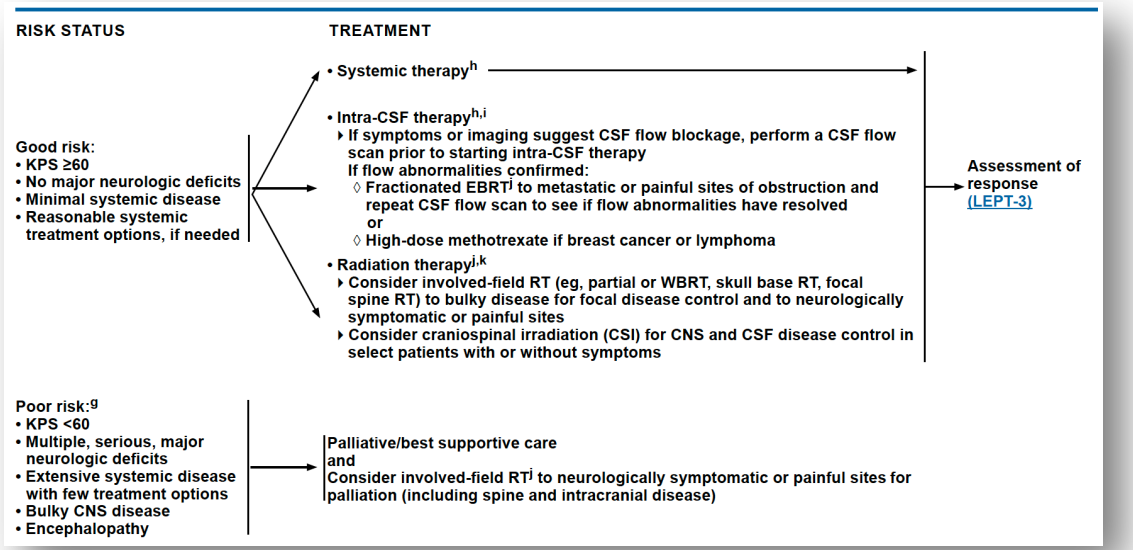
Diagnostic criteria and level of evidence for LM

		Cytology/biopsy	MRI	Confirmed	Probable[a]	Possible[a]	Lack of evidence[b]
Type I: positive CSF cytology or biopsy	IA	+	Linear	+	NA	NA	NA
	IB	+	Nodular	+	NA	NA	NA
	IC	+	Linear + nodular	+	NA	NA	NA
	ID	+	Hydrocephalus	+	NA	NA	NA
	ID	+	Normal	+	NA	NA	NA
Type II: clinical findings and neuroimaging only	IIA	− or equivocal	Linear	NA	With typical clinical signs	Without typical clinical signs	NA
	IIB	− or equivocal	Nodular	NA	With typical clinical signs	Without typical clinical signs	NA
	IIC	− or equivocal	Linear + nodular	NA	With typical clinical signs	Without typical clinical signs	NA
	IID	− or equivocal	Hydrocephalus	NA	NA	With typical clinical signs	Without typical clinical signs
	IID	− or equivocal	Normal	NA	NA	With typical clinical signs	Without typical clinical signs

Adapted from Le Rhun et al.[1]
Type A: LM with typical linear MRI abnormalities; type B: LM with nodular disease; type C: LM with both linear and nodular disease; type D: LM without MRI abnormalities (except hydrocephalus).
CSF, cerebrospinal fluid; LM, leptomeningeal metastasis; MRI, magnetic resonance imaging; NA, not applicable.
[a]Requires a history of cancer with a reasonable risk of LM and consideration of alternative diagnoses.
[b]Including in patients with a history of cancer.

LM Treatment

- **External Beam Radiation Therapy**: Mostly for symptomatic management of bulky tumor, but unlikely to prolong survival
- **Systemic Chemotherapy**: Depends on the blood brain barrier being "leaky" to get the drug to its target
- **Intrathecal Chemotherapy**: Retrospective studies show little to no change in median overall survival when compared to systemic chemotherapy/radiation
- **Novel Treatments**: Speculative impact on survival
- *Palliative care and reducing tumor burden are key drivers for therapy*



NCCN Guidelines for LM.
EANO-ESMO criteria for LM.

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ReSPECT-LM Phase 1, single dose trial design

Targeted delivery of Rhenium (^{186}Re) Obisbemeda by Ommaya reservoir

- Dose escalation: 3+3 modified Fibonacci
- Primary objective
  - Maximum Tolerated Dose (MTD) / Maximum Feasible Dose (MFD)
- Secondary objectives
  - Overall Response Rate (ORR)
  - Duration of Response (DoR)
  - Progression Free Survival (PFS)
  - Overall survival (OS)
- Exploratory objectives: Analysis on cerebral spinal fluid (CSF) pre- and post-administration
  - CSF tumor cell enumeration
  - Pharmacodynamic (PD) markers
  - QoL assessments
- Funding: $17.6M grant from largest state funding agency (CPRIT)

Single Administration Phase 1 Dose Escalation Plan

Cohort	Administered Volume (mL)	Administered Activity (mCi)	Administered Concentration (mCi/mL)
1	5	6.6	1.32
2	5	13.2	2.64
3	5	26.4	5.28
4	5	44.10	8.82
CURRENT **5**	**5**	**66.14**	**13.23**
6	5	87.97	17.59
7	5	109.96	21.99

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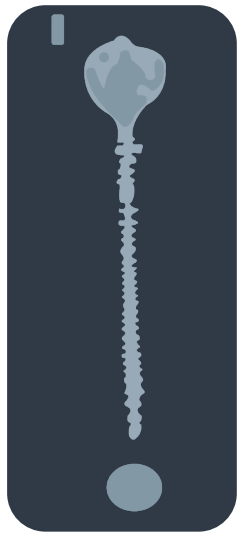
ReSPECT-LM treatment Workflow

Outpatient single administration

Personalized Treatment Planning	Drug Infusion	Patient Monitoring
Prior to Treatment	Day 1	Day 2-3
CSF flow study to confirm no flow obstruction	Single 5-minute injection in outpatient setting	Imaging and PK/PD assessments



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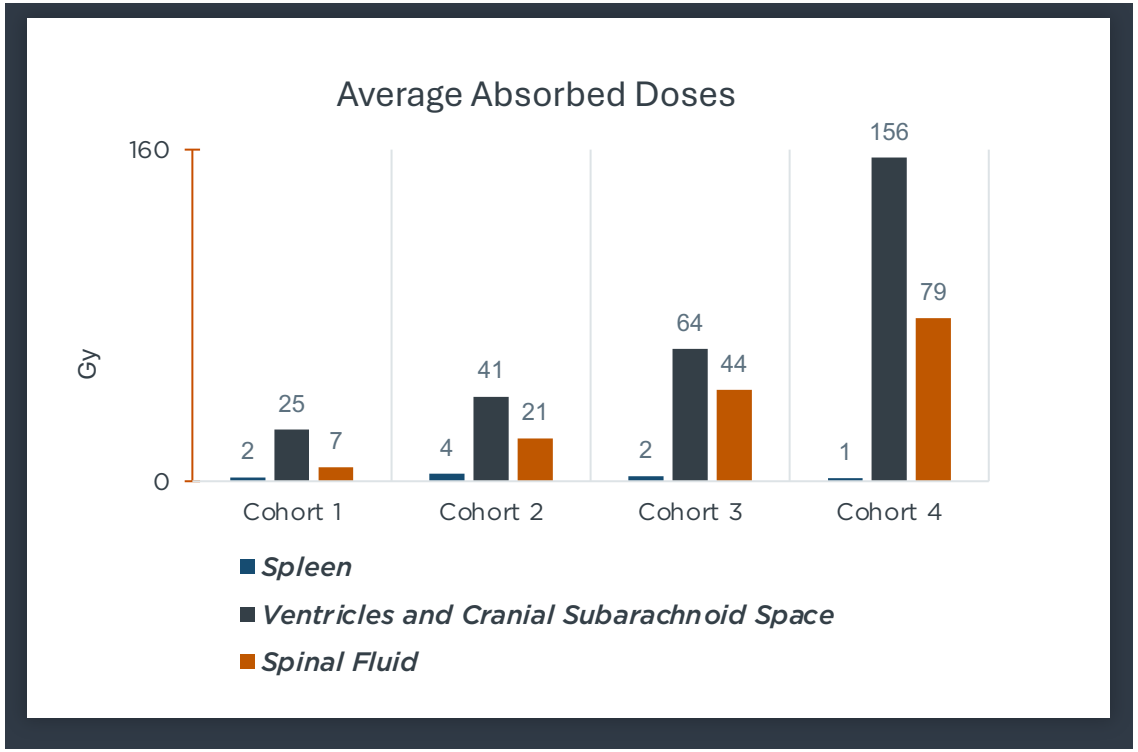
ReSPECT-LM safety

MTD/MFD not reached to date

- Generally safe and well tolerated
- Complete CSF circulation of drug within hours and duration at least 7 days
- No evidence of systemic radiation toxicity
- Absorbed doses to key therapeutic areas increase with administered dose
- Absorbed doses to critical organs remains low
- All but one SAE unrelated to study drug



Trial Safety Summary

Grade	%	n	>5% AEs	SAEs
Grade 1 Grade 2 Grade 3 Grade 4 Grade 5	64.10% 27.35% 7.27% 0.91% 0.91%	(68) (31) (8) (1) (1)	Headache (5.45%)	5

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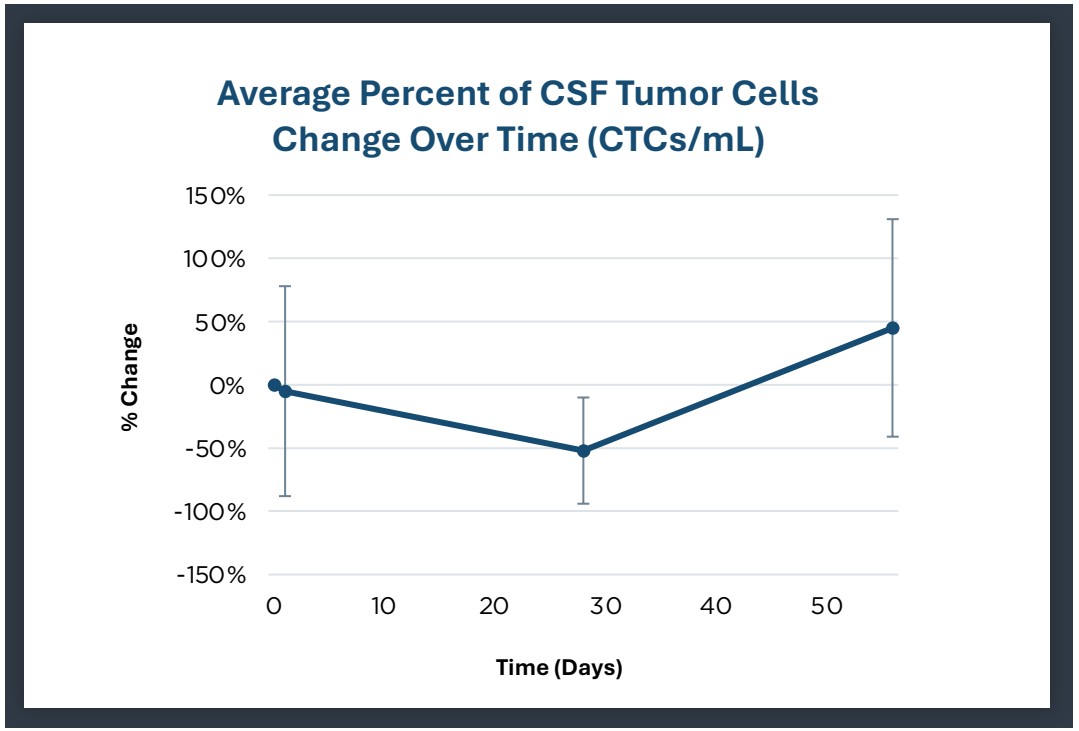
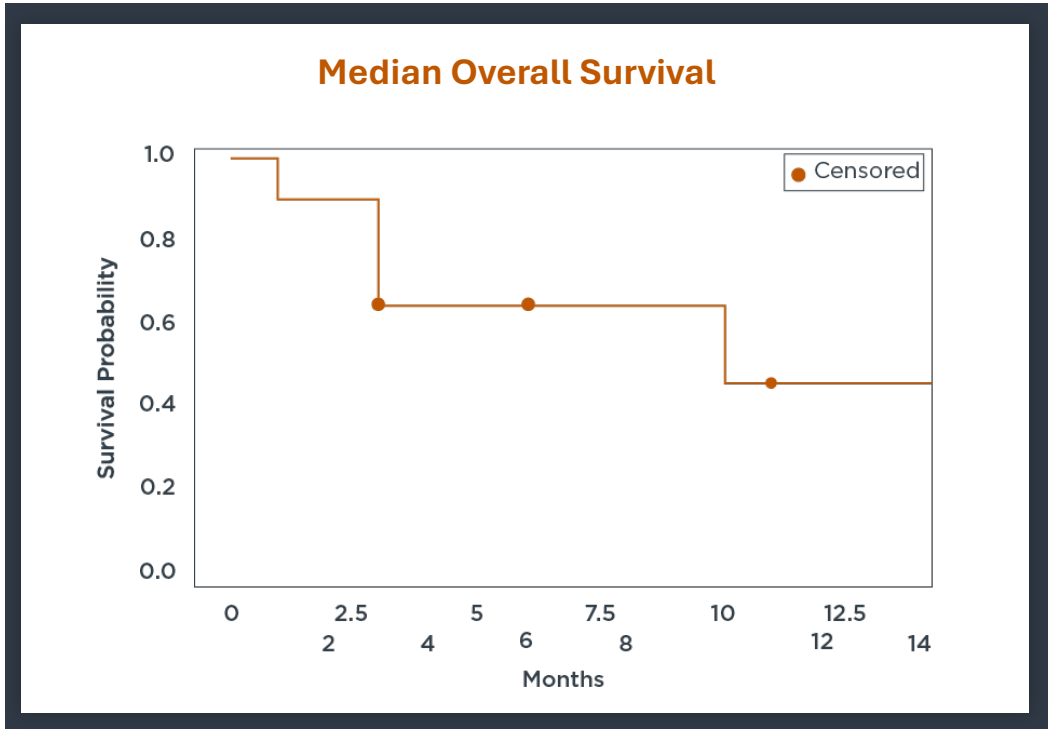
ReSPECT-LM Phase 1 treatment response

Median overall survival and percent CSF tumor cell change show effect of treatment





- N = 13 evaluable patients
- Max percent reduction in CSF tumor cells at D28 was 90%
- Average of 53% CSF tumor cell reduction at D28

- N = 10 patients, cohorts 1-3
- mOS was 10 months*
- 4 of these patients remain alive**

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*August 1, 2023
**As of 01Jul2024

Summary

ReSPECT-GBM

+ Reliably deliver up to 20x radiation vs. gold standard EBRT
+ High therapeutic index with minimal systemic toxicity
+ Derived RP2D of 22.3 in 8.8 mL for patients with tumor volumes of 20 mL or less
+ Continue to dose escalate in phase 1 for larger tumors; MTD not reached thus far
+ Tumor imaging response data highly correlates with absorbed radiation dose and mOS
+ Promising mOS signal in both Phase 1 and ongoing Phase 2 trial
+ New paradigm for delivery of radiation for solid CNS malignancies
+ ReSPECT-PBC trial in late 2024 (ependymoma and high-grade glioma)

ReSPECT-LM

+ Reliable delivery modality treats entire region of interest: CSF space and leptomeninges
+ Rhenium (^{186}Re) Obisbemeda remains in CSF for at least 7 days
+ High dose radiation to CSF with minimal systemic toxicity
+ Ongoing LM single administration basket dose escalation trial shows safety, feasibility, and response
+ ReSPECT-LM multidose trial in late 2024

Acknowledgements

Thank you to:

Patients and Caregivers participating in the ReSPECT Clinical Trials

Plus Therapeutics team

Principal Investigators and consultants

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