Preclinical and Preliminary Clinical Data in the Phase 1/2a Dose Escalation Trial of ^{186}RNL (Rhenium-186 Nanoliposome) (^{186}Re) Obisbemeda in Leptomeningeal Metastases (LM): The ReSPECT™-LM Trial

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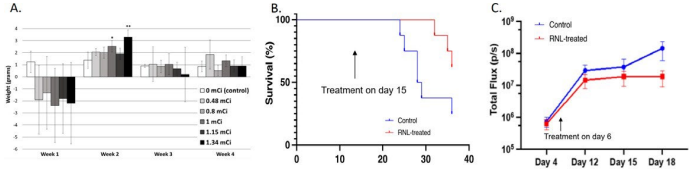
INTRODUCTION

- **Rhenium (^{186}Re) obisbemeda** (^{186}RNL), a next generation radiotherapeutic, is BMEDA-chelated ^{186}Re encapsulated in liposomal nanoparticles.
- ^{186}Re is a beta emitting therapeutic radionuclide with a 90-hour half-life, ~2 mm tissue path length, and optimal 137 keV γ-decay (~10% yield). This ^{186}Re γ decay optimally allows real-time imaging of the in vivo drug distribution using standard nuclear medicine imaging methods (e.g., SPECT/CT).
- Durable, localized treatment with beta emitters has the potential to dramatically widen the therapeutic window, increase the delivered dose, avoid normal tissue exposure, and extend survival in patients with glioma. ^{186}Re has the optimal half-life and beta decay energy for this application.
- Radiation exposure to adjacent normal brain tissue limits the use of External Beam Radiation Therapy (EBRT) to typical doses of ~30-50 Gray (Gy). Radiopharmaceuticals that can be delivered directly to the tumor and minimize adjacent exposure to healthy tissues are attractive treatment alternatives.
- Molecularly targeted radiation therapy improves upon EBRT, but is reliant on receptor specificity, is delivered systemically, and few cross the blood brain barrier (BBB). These limitations can lead to off-target effects and inefficient tumor treatment.
- ^{186}RNL uses **Direct Targeted Delivery**, which deposits high doses of radiation non-systemically and locoregionally to achieve thorough tumor coverage and retention with high absorbed radiation doses. For LM, ^{186}RNL is infused via Ommaya reservoir (intraventricular catheter).
- Leptomeningeal metastases (LM) is diagnosed in approximately 5% of patients with metastatic cancer. Survival is poor and limited to a few months in most patients. LM is a devastating clinical complication that occurs when cancer cells invade the leptomeninges and cerebrospinal fluid (CSF) of patients with malignant tumors.
- Typical treatment strategies include optimal systemic therapy for the primary disease, as well as neuroaxis directed therapy, which may include intrathecal chemotherapy or radiotherapy. 30 Gy given in 10 fractions is a typical radiation dosing scheme. However, no survival benefit of whole brain radiotherapy was observed in most retrospective studies of LM patients.
- Radiotherapy (EBRT) specifically in LM patients is limited by toxicity including myelopathy and marrow suppression given the dose to the brain, spinal cord, and surrounding tissues. Studies in proton craniospinal irradiation suggest incremental improvements in CNS PFS and OS can be achieved with more conformal techniques.
- In preclinical models of glioma, ^{186}RNL eradicated transplanted tumor cells when >100 Gy of radiation was delivered, with no evidence of neurologic compromise or other safety and toxicity markers. Furthermore, a study in beagles to assess toxicity of an intracranial, single dose administration of ^{186}RNL showed no test article-related pathologic changes at the highest administered amount (6 mCi).
- Preclinical evaluation of ^{186}RNL by intraventricular injection in non-tumor bearing rats with up to 1.34 mCi with corresponding absorbed doses of 1,075 Gy was without significant toxicity. The only significant histologic finding among treated rats was thickening of the leptomeninges overlying the median eminence suggesting a mild reactive meningeal hypertrophy. In 2 LM models (Wistar/C6 and NSG/MDA-MB-231) treatment with ^{186}RNL resulted in prolonged survival.



A. Weight post ^{186}RNL in non-tumor bearing Wistar rats. B. Survival curve for animals with intrathecal C6 treated with blank (blue) or ^{186}RNL (red). C. Bioluminescence of LM MDA-MB-231 in nude rats treated with blank (blue) or ^{186}RNL (red).

- We report initial results of the first 3 cohorts of Phase 1 in the ReSPECT-LM trial.

ReSPECT-LM STUDY DESIGN

- ReSPECT-LM is a multi-center, sequential cohort, open-label, dose-escalation, Phase 1 clinical trial to evaluate the safety and tolerability of a single dose of ^{186}RNL given by the intraventricular route (Ommaya reservoir) in adult LM patients.
- The primary objective is to determine a maximum tolerated dose and/or maximum feasible dose in up to 24 LM patients.
- The study utilizes a modified 3+3 design.
- Dose level 1 in the first cohort is based on results of the preclinical PK/biodistribution/dosimetry and toxicology studies. The starting dose is up to 6.6 mCi as a single dose, with dose doubling for the first three cohorts, followed by a FDA safety review prior to Cohorts 4-7.
- Expansion cohorts are planned for breast (n=20) and non-small cell lung cancer (n=20).
- **Inclusion Criteria:** Patient has proven and documented LM that meets the requirements for the study (EANO-ESMO Clinical Practice Guidelines Type 1 and 2 (with the exception of 2D) LM of any primary type); Karnofsky performance status of 60-100; standard organ function requirements.
- **Exclusion Criteria:** Obstructive or symptomatic communicating hydrocephalus; ventriculo-peritoneal or ventriculo-atrial shunts without programable valves or contraindications to placement of Ommaya reservoir; patients who had any dose to the spinal cord or whole brain radiation therapy, regardless of when the radiation treatment was delivered; standard concomitant illness restrictions.

METHODS & PATIENTS

Imaging and CSF Sampling Timepoints

Assessment	Day 1	Day 2	Day 3	Day 7
Whole body planar	EOI* and EOI+3.5 hours	EOI+24 hours (± 6 hours)	EOI+48 hours (± 6 hours)	EOI+96 hours (± 2 days)
SPECT/CT	EOI+30 minutes (after WBP)	EOI+24 hours (± 6 hours)		
CSF for PK and activity	5 hours post dose (± 20 minutes)	24 hours post dose (± 2 hours)	48 hours post dose (± 2 hours)	

Dose Escalation – Cohorts 1-3

Cohort	Infused Volume (mL)	Total 186RNL Activity (mCi)	Concentration (mCi/mL)	Increase	Patients Treated
1	5	6.6	1.32	N/A	3
2	5	13.2	2.64	100%	3
3	5	26.4	5.28	100%	4

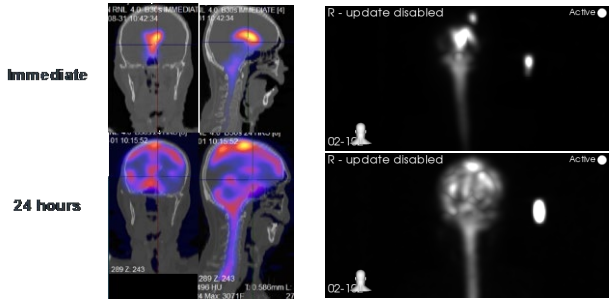
Patients

- Ten patients were treated in Cohorts 1-3.
- 3 were male and 7 were female.

OVERALL SUBJECT STATUS (Cohorts 1-3)	
Status	**Number of Subjects**
Consented and Screened	13
Withdrew Consent	1
Screen Failures	2
Enrolled (treated)	10
Discontinued Early	0
Disease Progression	2
Deceased	4
Alive	6
Alive Without Progression	4
Alive With Progression	2
Lost To Follow-Up	0
Alternative Treatment	0

Case Study

- Real-time SPECT/CT and Planar imaging shows distribution in the CSF space



RESULTS

CSF Tumor Cell Count per mL by Microfluidic Chamber Assay

Patient	Predose	5-hr	24-hr	48-hr	28-d	56-d
02-101	70.77	8.33	39.79	6.12	7.05	182.63
01-101	85.94	155.00	133.13	14.35	40.16	30.83
01-102	839.13	551.03	455.29	506.73	395.51	1133.40
02-102	51.79	31.76	46.41	24.44	48.46	122.05
02-104	None Detected	None Detected	None Detected	None Detected	None Detected	None Detected
01-103	629.25	96.00	789.12	Not Acquired	664.86	Pending
01-104	5.26	Not Acquired	5.16	Not Acquired	Not Acquired	Pending
01-105	8.89	10.74	Not Acquired	22.83	0.93	Pending
05-101	Not Acquired	Not Acquired	1,041.19	3,504.41	Pending	Pending
02-105	2,147.95	858.97	796.36	2,012.53	406.62	2,239.59

Radiation Absorbed Dose

C	Patient	Infused Volume (mL)	Total ^{186}RNL Activity (mCi)	Conc (mCi/mL)	% Total Activity Increase	Liver Absorbed Dose (Gy)	Spleen Absorbed Dose (Gy)	Ventricles and Subarachnoid Absorbed Dose (Gy)	Ventricles Absorbed Dose (Gy)	Cranial SA Space Absorbed Dose (Gy)	Spinal Fluid (Gy)
1	02-101	5	6.6	1.32	N/A	0.25	3.59	29.04	14.52	37.27	8.97
1	01-101					0.73	1.56	18.68	6.83	25.32	5.92
1	01-102					0.15	0.32	26.8	36.44	21.25	5.76
2	02-102		13.2	2.64	100	0.53	1.13	55.34	13.17	79.2	16.9
2	02-104					0.63	7.53*	24.17	12.32	30.84	18.79
2	01-103					0.76	2.17	43.07	50.81	38.42	26.51
3	01-104		26.4	5.28	100	0.83	2.18	82.03	56.04	101.57	19.25
3	01-105					2.10	2.56	59.27	8.27	87.23	35.06
3	05-101					0.95	1.11	25.04	12.88	31.94	84.32
3	02-105					2.00	3.75	88.98	26.65	122.17	37.63
4	N/A		44.10	8.82	67	N/A	N/A	N/A	N/A	N/A	N/A
5	N/A		66.14	13.23	50						
6	N/A		87.97	17.59	33						
6	N/A		109.96	21.99	25						

Safety

- A single dose of ^{186}RNL was generally well-tolerated and no patients had treatment related adverse events (AEs) greater than Grade 1.The most common AE was headache.

CONCLUSIONS

Interim results of this Phase 1 trial showed that one treatment with ^{186}RNL in ten patients with LM decreased CSF tumor cell count and was well-tolerated.

- ^{186}RNL administered through a standard intraventricular catheter (Ommaya reservoir), showed prompt and complete distribution throughout the CSF through Day 7.
- A single dose of ^{186}RNL between 6.6 mCi and 26.4 mCi achieved absorbed doses up to 88.98 to the ventricles and subarachnoid space.
- All study participants in Cohorts 1-3 tolerated 186RNL administration.
- The safety observations were typically minor and resolved. Subarachnoid 186RNL distribution was complete, prompt, and durable.
- Favorable reductions in tumor cell counts/ml were measured and durable.
- As expected, and validated by imaging and dosimetry, the liver and spleen have the most prominent ^{186}RNL clearance but are still well below any absorbed dose concerns for a critical organ (e.g., EBRT typically tries to keep liver and spleen doses to less than 30 Gy).
- A continued dose escalation design to MTD/MFD (Cohorts 4-7) will open following FDA review, and repeated dosing will be explored. An expansion in Cohort 3 is still enrolling.

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To learn more about Rhenium (^{186}Re) Obisbemeda and the ReSPECT-LM clinical trial, visit https://www.respect-trials.com/lm/
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