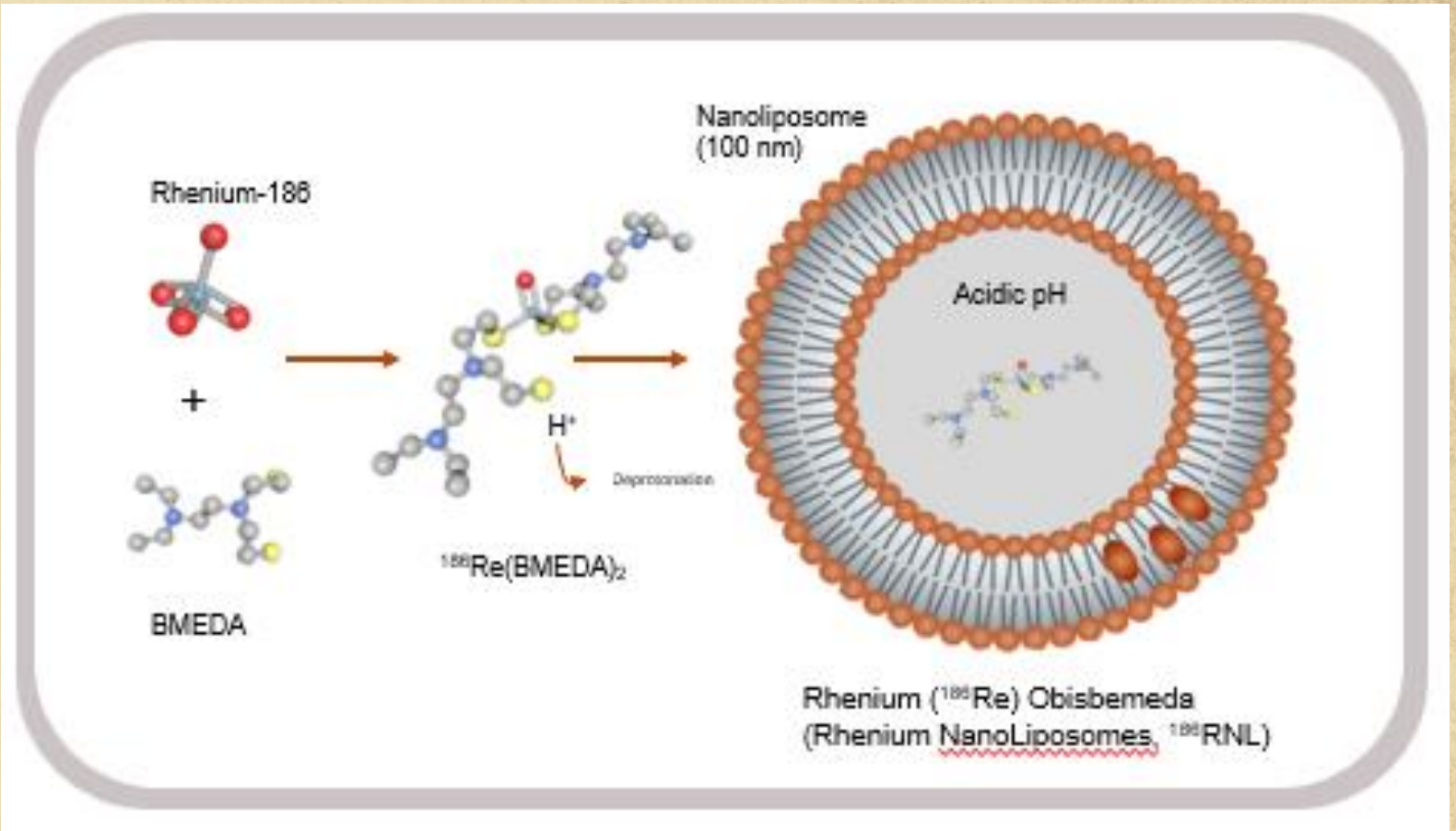
^{186}RNL for the Treatment of Leptomeningeal Metastases

Henriette Balinda, PhD

^{186}Rhenium Nanoliposome (^{186}RNL)

- **Nanoliposome-encapsulated radiotherapeutic delivering localized beta radiation**
- ^{186}Re beta particles cause DNA damage over ~2mm, sparing healthy tissue
- BMEDA chelation irreversibly traps isotope inside liposome
- **Liposomal encapsulation: superior retention (decay-driven) + enhanced tissue distribution**



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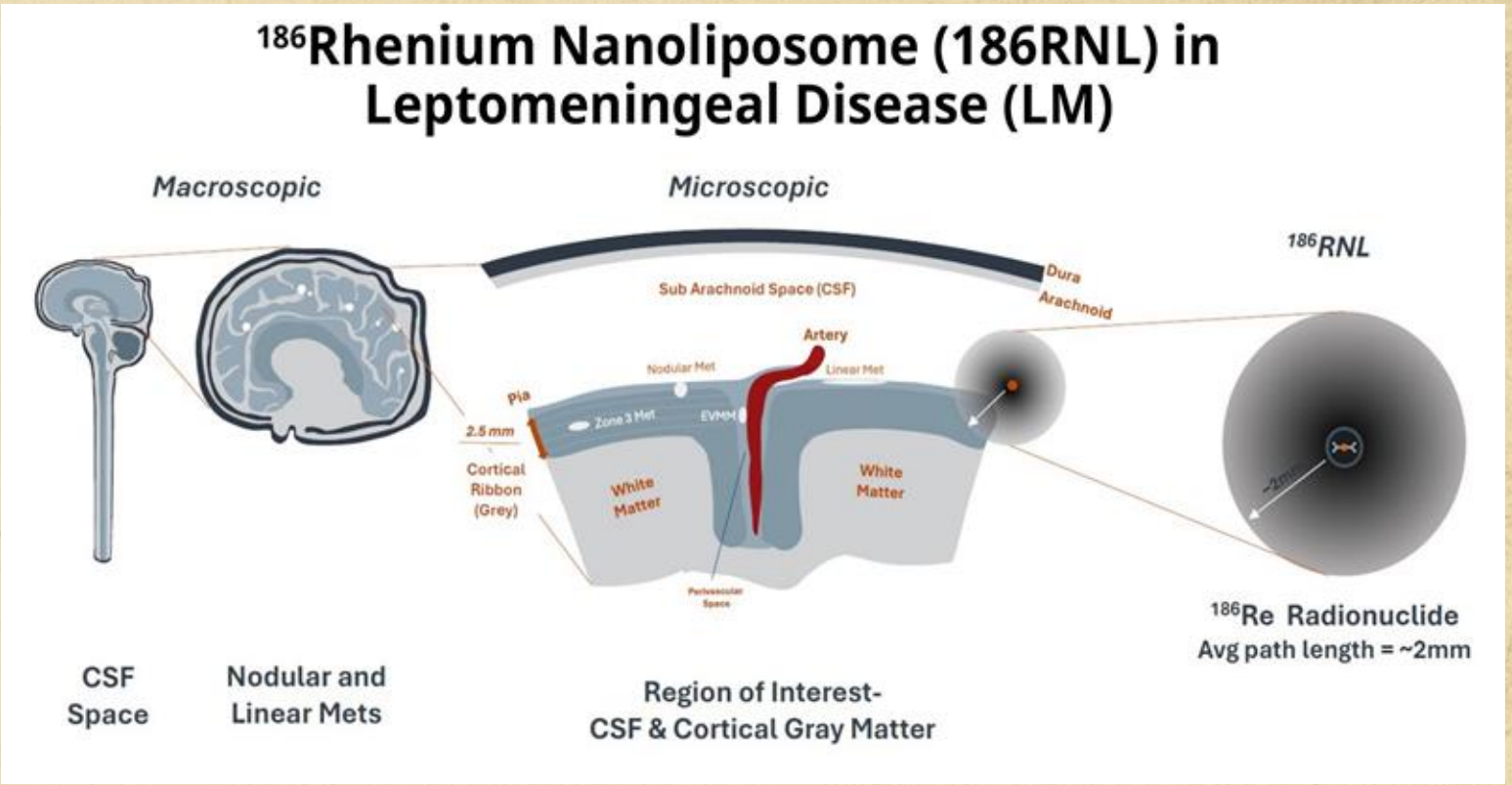
Leptomeningeal Disease: Unmet Clinical Need

- Fatal complication of advanced cancers affecting CNS fluid-lined structures
- ~110,000 U.S. cases/year (5% of cancer patients; 20% at autopsy)
- **No FDA-approved therapies**
- Standard treatment: RT + systemic/intrathecal chemo (palliative)
- Median survival 3-8.7 months; 2-year survival only 3%
- Most common primaries: breast, lung, melanoma, GI



^{186}Re beta path length (~2mm) matches the cortical ribbon, enabling precise CSF irradiation with minimal deep-tissue exposure

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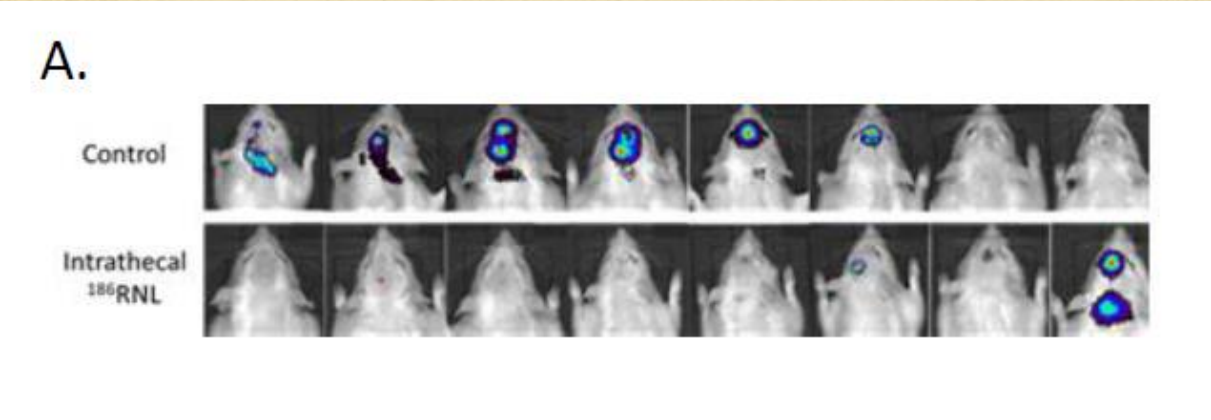
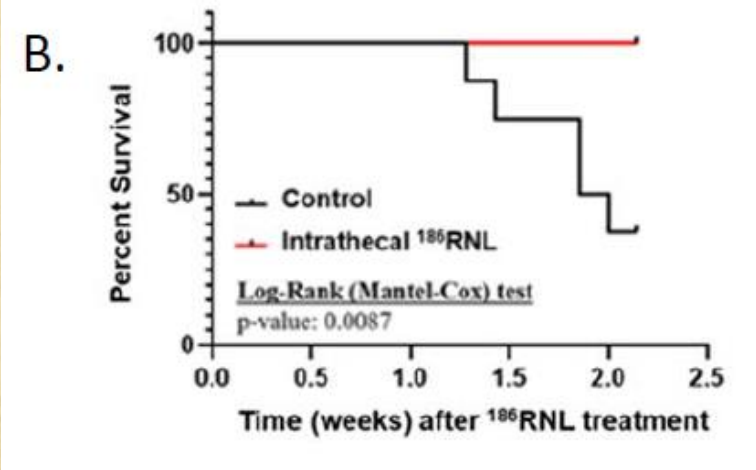
Preclinical Efficacy of ^{186}RNL in LM



A) Bioluminescence of **LM MDA-MB-231** in nude rats treated with empty liposomes (control) or 186RNL.



B) Survival curve for animals with intrathecal **C6** treated with empty liposomes (control) or 186RNL

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ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

Trial design: single administration delivery via standard Ommaya reservoir

- Dose escalation: 3+3 modified Fibonacci
- Primary objective: Safety and tolerability
  - Maximum Tolerated Dose (MTD) / Maximum Feasible Dose (MFD) via Ommaya reservoir
- Secondary objectives: Efficacy
  - Overall Response Rate (ORR)
  - Duration of Response (DoR)
  - Progression Free Survival (PFS)
  - Overall survival (OS)
- Other objectives: Analysis on CSF, pK
  - CSF circulating tumor cells (CTCs)
  - Pharmacodynamic (PD) markers & dosimetry

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
5	5	66.14	13.23
6	5	75.0	15.00
7	5	TBD	TBD

ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

Study Completed- Final Data Monitoring and Study Report in Progress

Summary

+ Study completed
+ 29 patients dosed over 6 cohorts
+ Demonstrated feasibility, safety, and showed efficacy signal

Safety

+ 1 DLT in cohort 5, 1 DLT in cohort 6
+ 1 death due to sepsis deemed unlikely related in cohort 6
+ No DLTs or SAEs in cohort 4
+ DSMB review of cohort 6 Feb 2025
+ RP2D (44.1 mCi) and MFD determined

Results

+ Median OS of 9 months in cohorts 1-4 (RP2D) (2-6 months commonly reported in lit.)
+ CSF tumor cell enumeration decreased up to 100% following Reyobiq treatment
+ 5 of 7 patients with >80% reduction in CTC by CNSide survived at least 1 year

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
RP2D	4	5	44.10	8.82
	5	5	66.14	13.23
Trial Stopped	6	5	75.00	15.00
	7	5	109.96	21.99

ReSPECT-LM Phase 1 Dosing, PK, and Absorbed Dose Data

Excellent target/off-target absorbed dose ratio

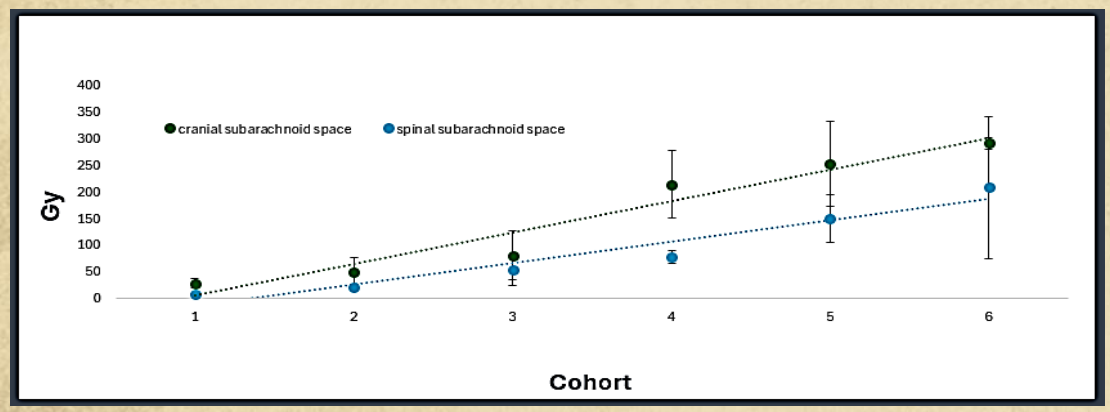
- Target/off-target radiation absorbed dose ratio >100/1
- Low radiation exposure to critical organs
- Radiation measured in CSF space for 7 days
- Complete CSF circulation of drug seen by 3.5-hour imaging timepoint

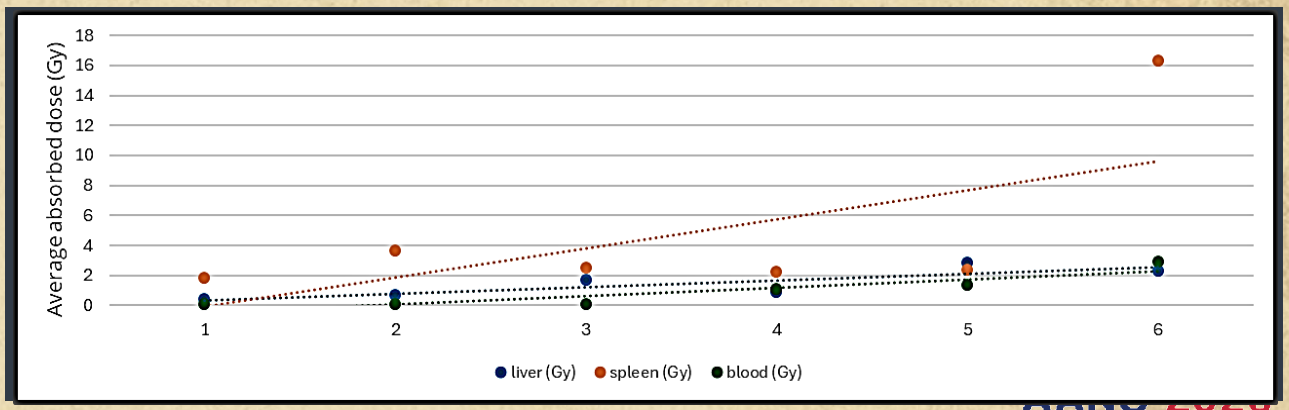
RP2D

Trial completed

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
5	5	66.14	13.23
6	5	75.0	15.00
7	5	TBD	TBD

Average Absorbed Dose by Cohort





General toxicity limits: Liver: ~35-50 Gy; Spleen: ~40 Gy; Bone marrow: ~2–5 Gy

ReSPECT-LM Phase 1 Safety Data

Single dose Reyobiq for patients with LM was well tolerated up to 66.14 mCi/253Gy

- N = 37 enrolled, 8 screen failures, 29 intent to treat, 22 per treatment evaluable
- A single DLT noted at 66.14 mCi administered dose (thrombocytopenia)
- A single DLT noted at 75 mCi administered dose (thrombocytopenia and neutropenia)
- DSMB: determined Recommended Phase 2 Dose of 44.10 mCi (cohort 4 dose) No DLTs or SAEs at this dose
- Adverse Events
  - Most AEs mild (grade 1, 55%) and moderate (grade 2, 25%)
  - Most AEs unrelated (32%) or unlikely related (26%) to study drug
  - Two AEs (headache) deemed definitely related to study drug (1 was grade 3 and resolved with treatment)
- Serious Adverse Events
  - 21 SAEs (9% of AEs)
  - 5 SARs (SAEs with at least 'possible' attribution) – (1) encephalopathy (also attributed to steroid taper, resolved spontaneously), (2) headache (resolved with treatment), (3) thrombocytopenia (resolved with treatment) (4) WBC count decrease (resolved with treatment) and (5) lymphocytopenia (resolved spontaneously)

Treatment Related Adverse Events	Total N=21	
	Any Grade	Grade ≥ 3
Any TRAE	21 (100)	7 (33)
Headache	10 (48)	0
Lymphopenia	8 (38)	4 (19)
Vomiting	8 (38)	0
Thrombocytopenia	7 (33)	4 (19)
Nausea	6 (29)	0
Hypoalbuminaemia	5 (24)	0
Leukopenia	4 (19)	2 (10)
Alanine aminotransferase increased	2 (10)	0
Anaemia	2 (10)	0
Dizziness	2 (10)	0
Eye pain	2 (10)	0
Fatigue	2 (10)	0
Gait disturbance	2 (10)	0
Hyperglycemia	2 (10)	0
Muscle weakness	2 (10)	0

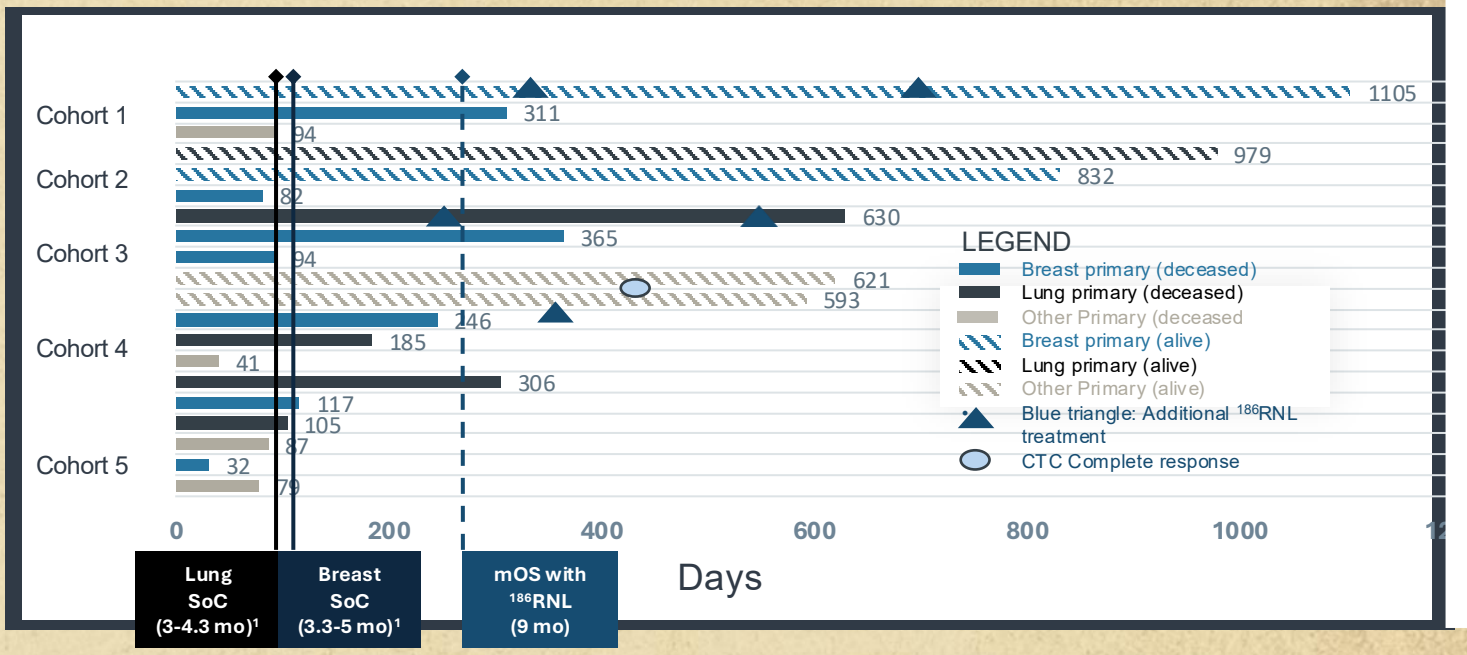
ReSPECT-LM Phase 1 Response & Efficacy Data

Positive efficacy signal in dose escalation phase

+ Overall survival
  - mOS of 9 months, compared to 4-6 months reported
  - n = 16 patients, Cohorts 1-4 (RP2D)
  - 5 patients remain alive (June 2025)

+ CSF tumor cell enumeration showed consistent decreases in the study population following treatment

+ Five of 7 patients with CTC response >80% survived at least 1 year (3 multiple treatment patients via compassionate use)



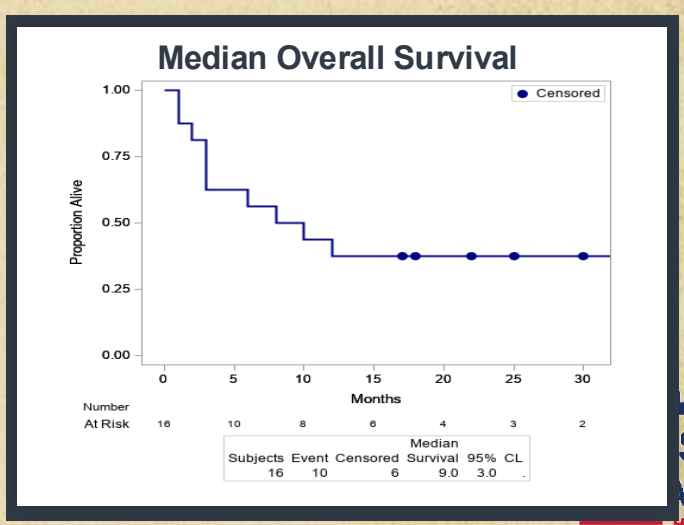
Single dose response assessed from pretreatment through 4 months (112 days) follow-up							
Response Measure[1]	Response	Stable Disease	Clinical Benefit Rate	Progression	Evaluable Patients	Data Not Available	Total Patients
CTC	13	1	14	1	15	5	20
Imaging	5	8	13	4	17	3	20
Clinical	2	11	13	2	15	5	20

Clinical Benefit Rate (CR+PR+SD)

CTC response: 93% (14/15)

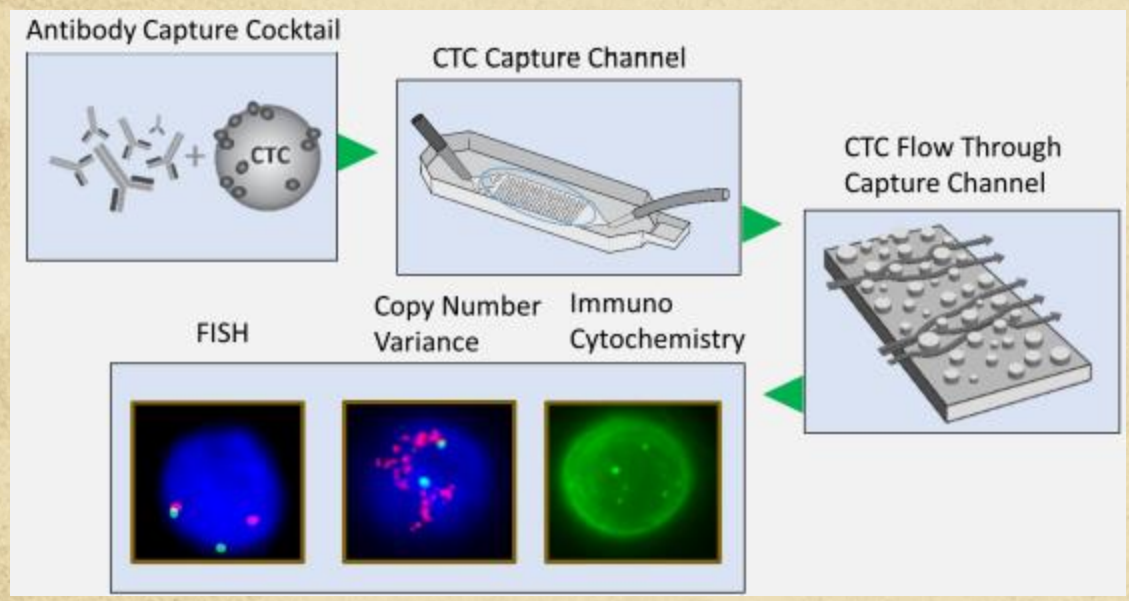
MRI Imaging response: 76% (13/17)

Clinical response: 87% (13/15)



ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

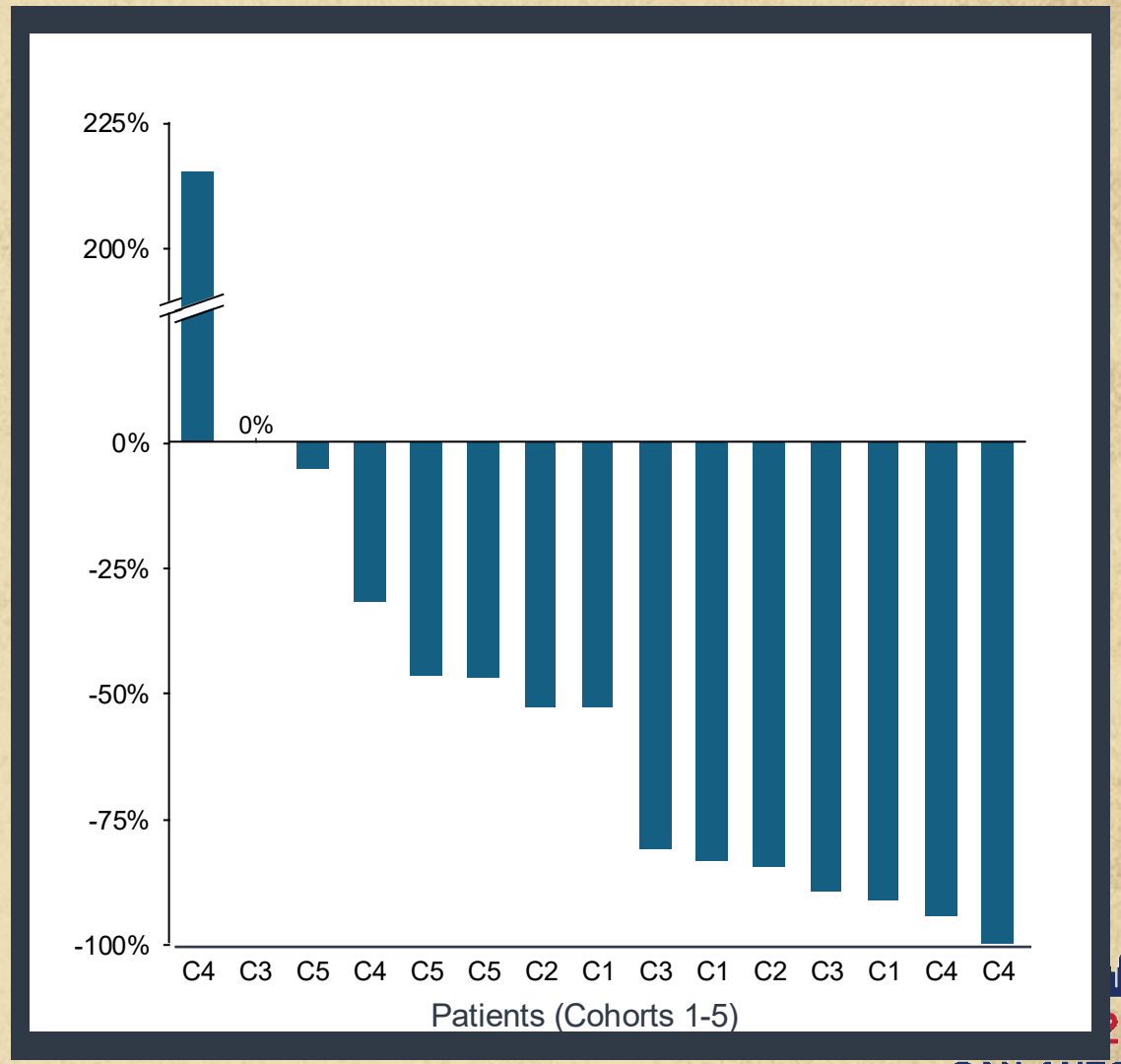
Best response in tumor cells (CTCs) vs. baseline



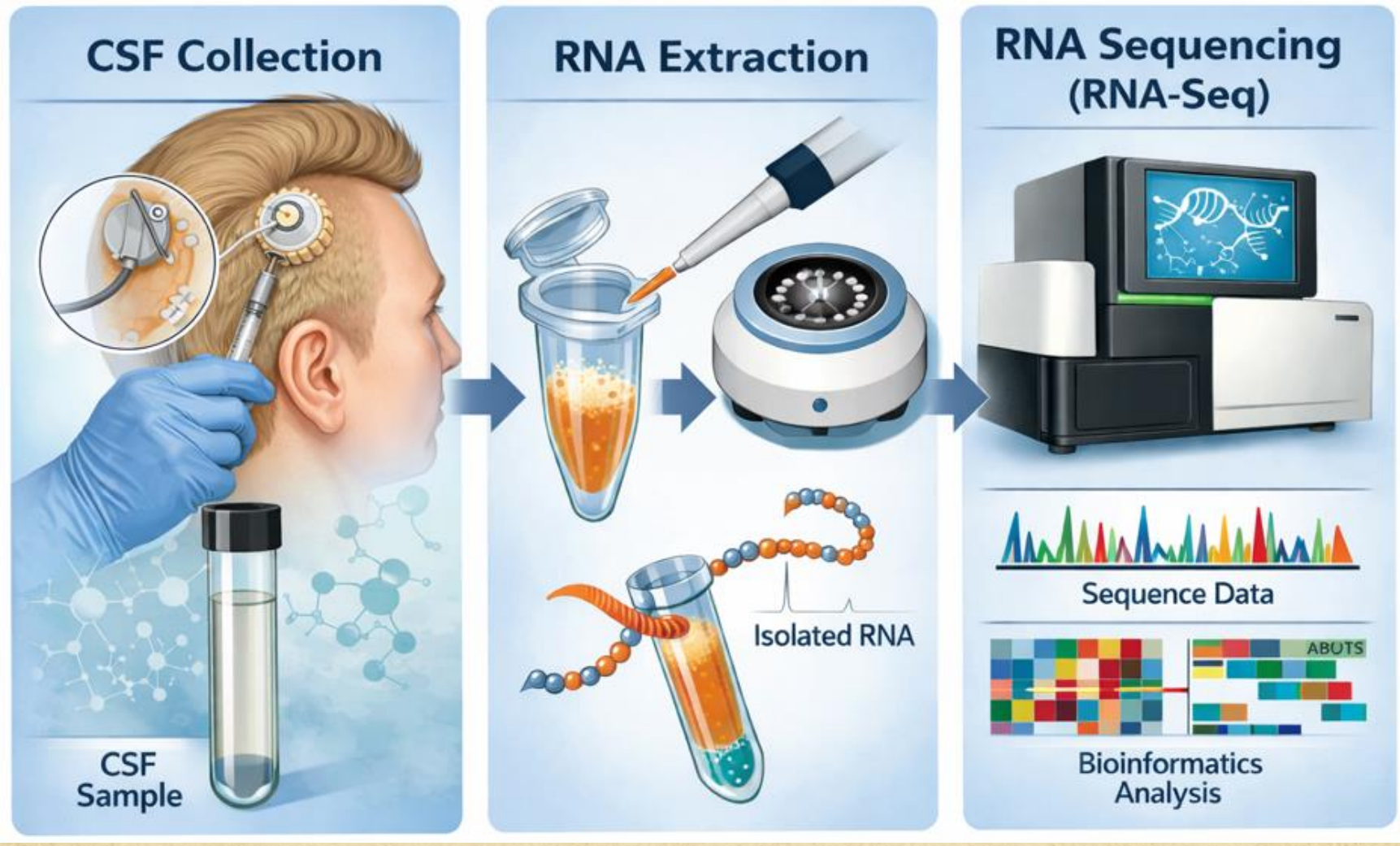
+ 13/16 showed reduction in CSF-TCs following ^{186}RNL treatment

+ 5/7 showing >80% response survived 1 yr or more

Best Response Following ^{186}RNL Single Administration



^{186}Rhenium Nanoliposome (^{186}RNL) in LM – Clinical Trial



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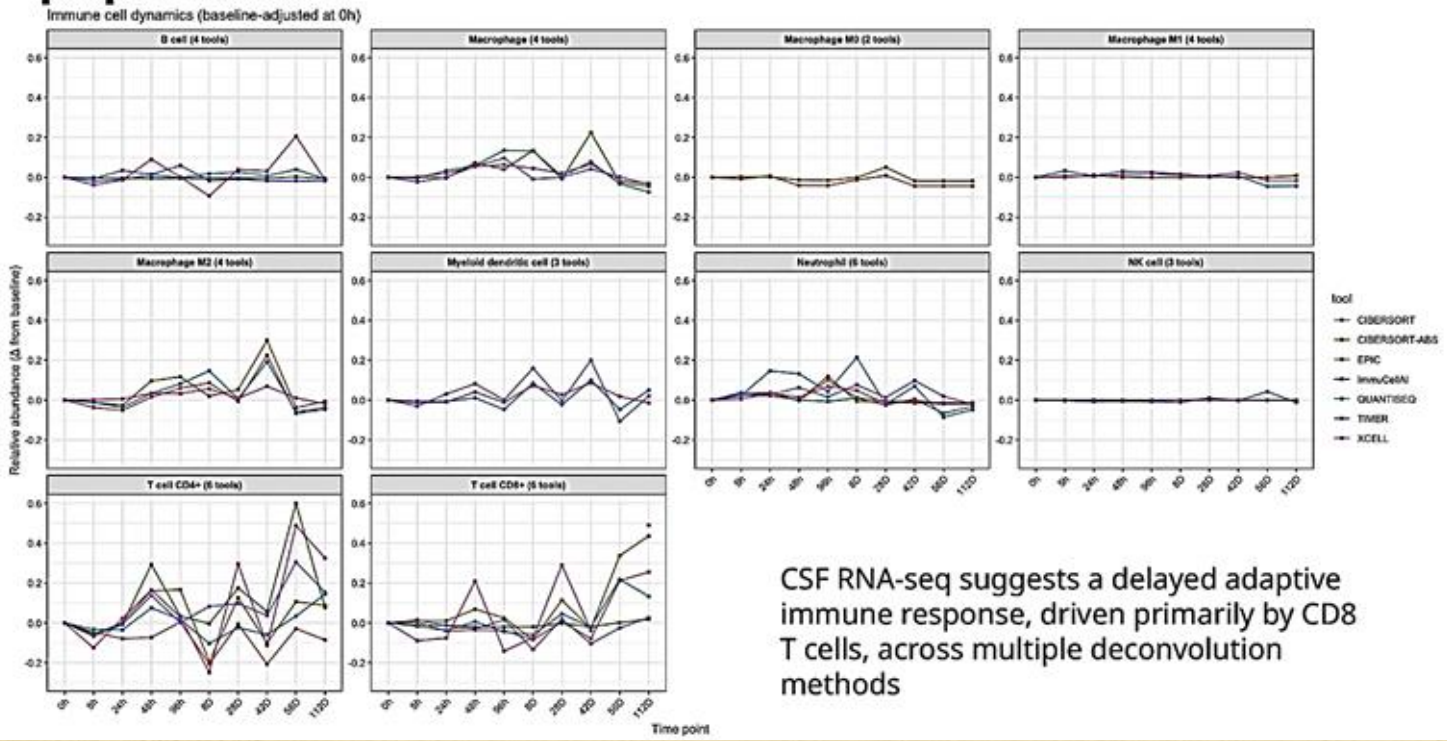
CSF Transcriptomics: Immune Remodeling After ^{186}RNL



- RNA-seq: 11 patients, 60 samples (0h to Day 112)

Temporal clustering reveals two programs:

- Cluster 1: Inflammation / innate immunity (early)
- Cluster 2: Proliferation / DNA repair

TIMER3 immune deconvolution:

- Delayed adaptive response driven by CD4+ and CD8+ T cells
- Immune remodeling, not exhaustion

Radiotherapy primes the tumor microenvironment, creating a window for immunotherapy

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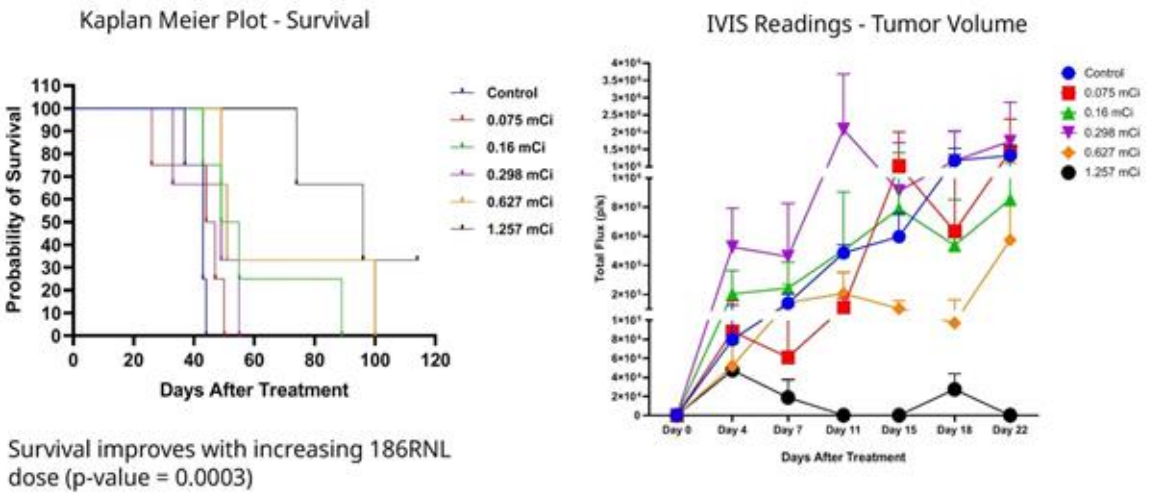
^{186}RNL + Anti-PD1: Preclinical Combination Efficacy

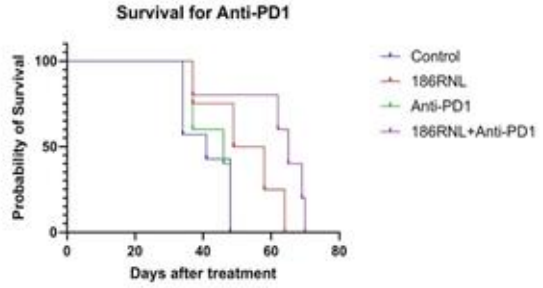
ID8agg syngeneic ovarian cancer model

^{186}RNL improves survival in a dose-dependent manner in a preclinical ovarian model



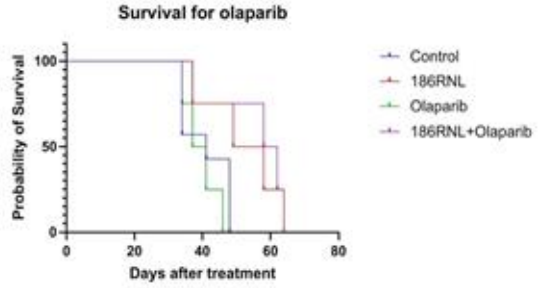
Survival improves with increasing 186RNL dose (p-value = 0.0003)

Combination Therapy with ^{186}RNL and Anti-PD1 or Olaparib in Ovarian cancer



	Control	186RNL	Anti-PD1	186RNL+Anti-PD1
Median survival (Days)	41	53.5	46	65

P-value = 0.008



	Control	186RNL	Olaparib	186RNL+Olaparib
Median survival	41	53.5	39	60

- ^{186}RNL alone: dose-dependent survival (p=0.0003)
- **^{186}RNL + Anti-PD1: median survival 65 days vs. 41 days control (p=0.008)**
- Combination outperforms both ^{186}RNL alone (53.5 d) and Anti-PD1 alone (46 d)
- Well-tolerated: transient weight loss with recovery

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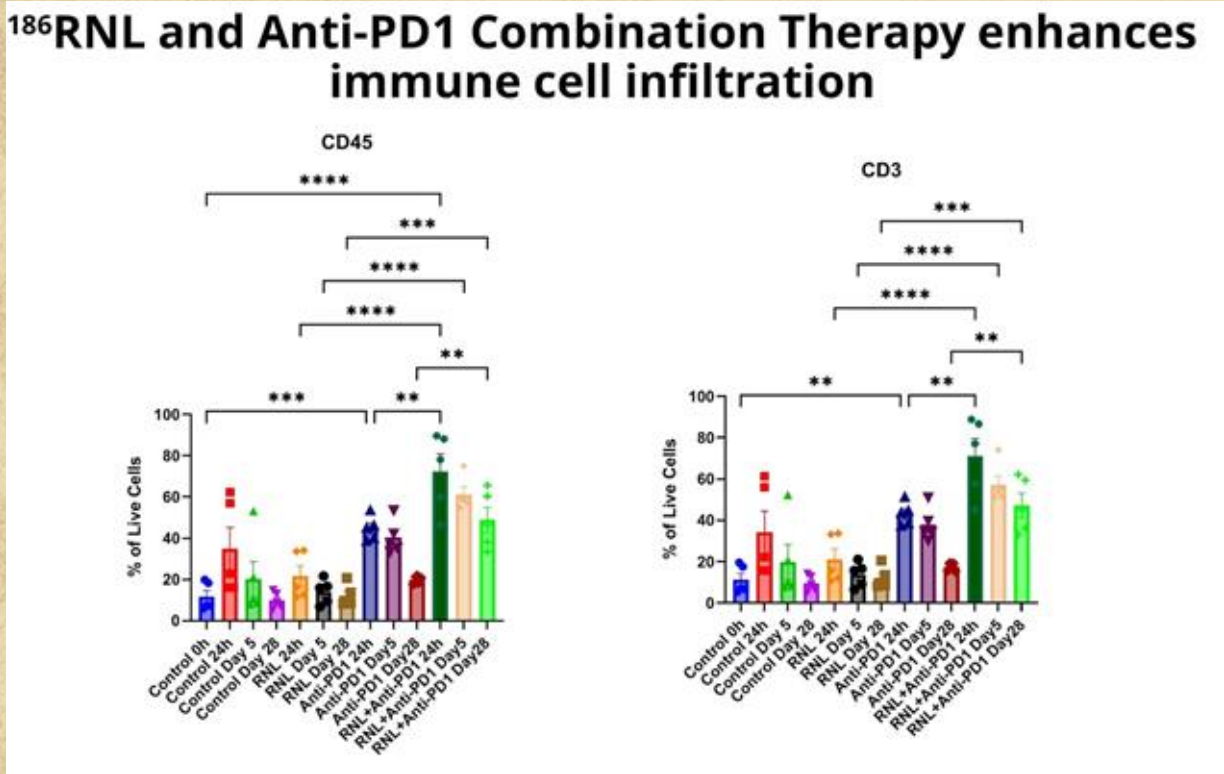
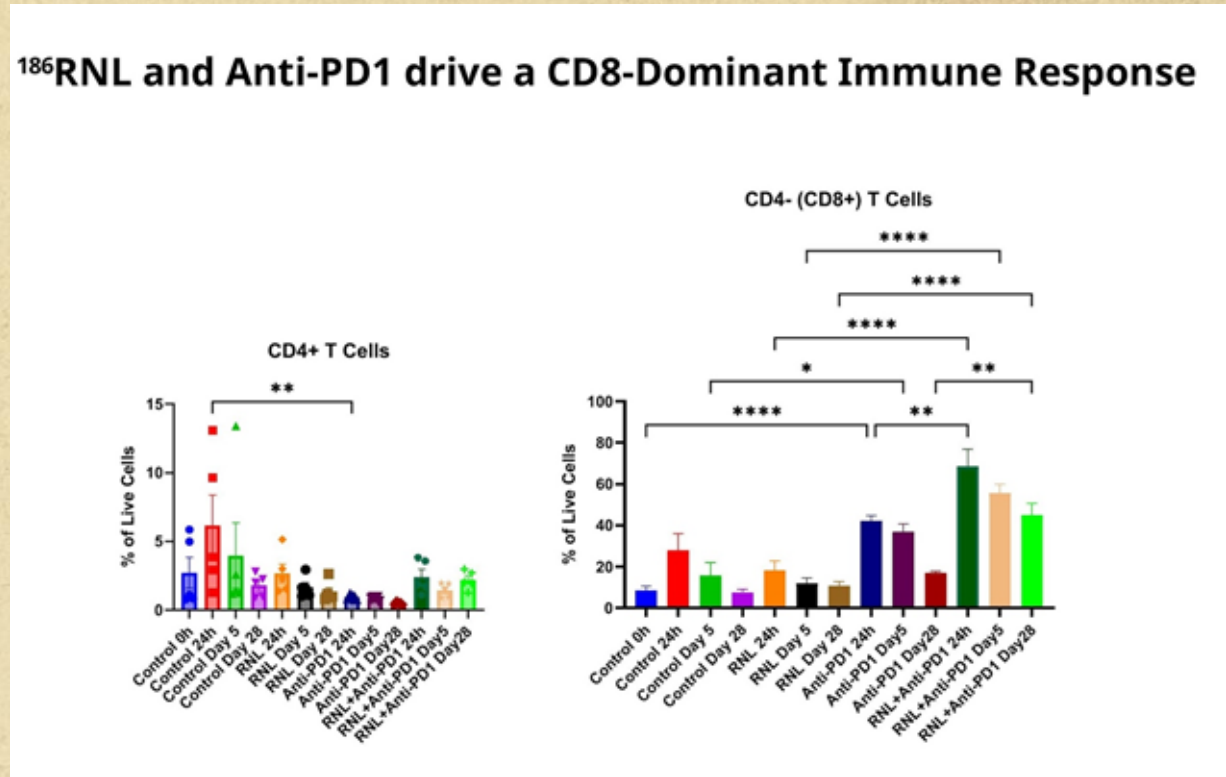
Combination Drives CD8-Dominant Immune Response





- Significant increase in CD45+ and CD3+ T cell infiltration
- CD8+ T cells robustly expanded; CD4+ unchanged
- Effector T cells preferentially expanded over Tregs
- Reduced monocytes + enhanced NK cells in tumor environment
- **^{186}RNL remodels the TME from immunosuppressive to immunostimulatory**

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ReSPECT-LM Phase 1 Multiple Dose Trial Overview

Key elements

A Multicenter Phase 1 Study to Determine the Safety and Efficacy of Multiple Doses at Defined Intervals of Rhenium (^{186}Re) Obisbemeda (Rhenium-186 NanoLiposome, ^{186}RNL) Administered via Intraventricular Catheter for Any Primary Solid Tumor Cancer with Leptomeningeal Metastases

Primary Objectives: To characterize the safety and tolerability of multiple doses at defined intervals of ^{186}RNL administered via intraventricular catheter (i.e., Ommaya reservoir) for patients of any primary solid tumor cancer with leptomeningeal metastases and identify an MTD/MFD for a given dose, interval duration, and number of doses

Study now enrolling at UTHSCSA

Phase/Part	Cohort	Dose (mCi)	% Total Activity Increase	Dosing Interval	Doses/Patient	~Total Time of Dosing (months)	Total Administered Dose (mCi)
Phase 1/Part A	1	13.2	NA	56 days	3	4	39.6
	2	13.2	NA	28 days	3	3	39.6
	3a	13.2	NA	14 days	3	1.5	39.6
	3b	13.2	NA	14 days	6	3 months	79.2

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Current Status

- **Phase 1 ReSPECT-LM single dose escalation study completed**
  - Rhenium-186 NanoLiposome via intraventricular administration is feasible, safe at recommended Phase 2 dose (RP2D), with signs of efficacy in LM- study also supports the value of circulating tumor cell (CTC) counts

- **LM Multiple Dose/Dose Optimization- now opened at UTHSCSA**
  - Goals of study are dose level and interval optimization- safety and efficacy
  - Treating patients at defined intervals (56, 28, and 14 D with 3 doses)
  - Aligns with FDA's initiative Project Optimus

- **Bulk RNA sequencing from 14 patients at multiple timepoints has been conducted, including at progression and retreatment- continuing analysis**
  - Single Cell RNA Sequencing of samples collected from the multiple dose trial

- **Further exploring TME modulation, including immune cell infiltrations following Rhenium-186 NanoLiposome**
  - DNA Damage markers

Thank You!

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