A Two-Part, Phase 1/2a Trial to Determine the Maximum Tolerated Dose, Safety, and Tolerability of Rhenium-186 Nanoliposome (^{186}RNL) in Supratentorial Recurrent Pediatric Ependymoma and High-Grade Glioma: a First-in-Pediatrics Study

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INTRODUCTION

Ependymoma and high-grade glioma (HGG) are difficult-to-treat pediatric brain tumors. These tumors are frequently aggressive, and in recurrent settings, can carry an extremely poor prognosis. While external beam radiation therapy (EBRT) remains a central component of the management of pediatric gliomas, it is limited by tolerance of the surrounding normal brain tissue.

Pediatric High-Grade Glioma

Pediatric HGG's differ from adult HGG in terms of molecular characterization, effectiveness of standard treatments, and outcome. Imaging characteristics also differ with adult HGG's presenting as defined contrast enhancing lesions while pediatric HGG's are more diffuse with T2 hyperintensity and variable contrast enhancement. Pediatric HGG's are more frequently midline and harbor unique genetic alterations like mutations in histone H3.3 (*H3F3A*) and amplification of platelet-derived growth factor receptor-α (PDGFRα).[1] Unlike in adult HGG, O^6-methylguanine DNA methyltransferase (MGMT) is infrequently methylated in pediatric tumors. As a result, concomitant chemoradiation with temozolomide (TMZ) and adjuvant TMZ have not resulted in improved event-free (EFS) or overall survival (OS). In the Children's Oncology Group (COG) study ACNS0126, the 3-year EFS and OS was 11% ± 3 and 22% ± 5, respectively.[2] In the HERBY study, the addition of bevacizumab to RT + TMZ did not improve EFS in pediatric patients unlike adult studies.[3] Here, the median EFS with bevacizumab + RT + TMZ was 8.2 months and 1-year EFS was 38%. Surgical resection and EBRT remain the only standard-of-care treatment for pHGG and prognosis remains dismal.

Pediatric Ependymoma

Gross total resection (GTR) and EBRT remain the mainstay of pediatric ependymoma treatment as well. In the COG trial ACNS0121, a 5-year EFS of 61.4% for supratentorial tumors observed after GTR, 37.2% for tumors which underwent subtotal resection followed by conformal radiation, and 68.5% for tumors which underwent near total resection/GTR followed by conformal radiation therapy (CRT). CRT included a total dose of 59.4Gy with a 1.0-cm clinical target volume margin.[4] In a COG phase III trial of post-radiation chemotherapy in patients with newly diagnosed ependymoma, ACNS0831, "as treated" analysis showed a possible benefit to EFS with adding maintenance chemotherapy to subjects who had undergone GTR or near-total resection but no benefit was observed if they had undergone a STR.[5] Recurrent ependymoma remains a challenge and is limited by the role of re-resection and re-irradiation. Tolerance of normal surrounding brain tissue to repeated rounds of irradiation limits the effective management of these patients and results in poor survival in this population.[6]

Rhenium-186 NanoLiposome (^{186}RNL)

Rhenium-186 or ^{186}Re is a potent source of electrons with a short path length (2mm), low dose rate, and high radiation density. ^{186}Re emits therapeutic beta particles and every 10th isotope decay produces a gamma photon. The emitted gamma photons have similar photon energy to those emitted by ^{99m}Tc, allowing for imaging of the isotope within the body. Lipid nanoliposomes operate as the carrier to deliver this isotope to the brain and maintain its localization at the desired site. Rhenium-186 nanoliposomes (^{186}RNL) are delivered as treatment for solid tumors via convection enhanced delivery (CED). CED has been previously used in the pediatric population to delivery chemotherapy agents and/or targeted therapeutics to brain tumors with good safety profiles.[7-9] The precise administration of ^{186}RNL may help overcome current obstacles in treating pediatric brain tumors including blood brain barrier penetration and limitations of EBRT by tolerance of normal surrounding brain tissue.

ReSPECT-GBM Phase 1/2a Clinical Trial

ReSPECT-GBM is a Phase 1/2a, multi-center, sequential cohort, open-label, volume and dose finding study of the safety, tolerability, and distribution of ^{186}RNL given by convection-enhanced delivery (CED) to adult subjects with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment. Currently, the trial has enrolled twenty-three subjects and is enrolling cohort 8 (see chart below).

Patient Demographics

Gender	Male: 15 (65%) Female: 8 (35%)
Tumor Volume (cm^3)	Average: 8.1 Range: 0.9-22.8
Prior Treatments	Average: 1.7 Range: 1-3
Prior Bevacizumab	5 (22%)
IDH Mutational Status	Wild type: 19 (82%) Mutated: 2 (9%)
MGMT Status	Methylated: 4 (17%) Unmethylated: 12 (52%)
Glioma Grade	Grade IV: 21 (91%) Grade III: 2 (9%)

Dose Escalation

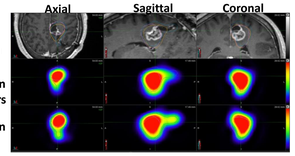
Cohort	Infused Volume (mL)	Total 186 RNL Activity (mCi)	Concentration (mCi/mL)	Average Absorbed Dose (Gy)	Status
1	0.66	1.0	1.5	198	Enrolling Cohort 8 (n=24 subjects)
2	1.32	2.0	1.5	122	
3	2.64	4.0	1.5	234	
4	5.28	8.0	1.5	171	
5	5.28	13.4	2.5	423	
6a	8.80	22.3	2.5	287	
6b*	8.80	22.3	2.5	584	
7	12.28	31.2	2.5	TBD	
8	16.34	41.5	2.5	TBD	

* Cohort 6b utilized same volume & dose as Cohort 6a but with increased maximum flow rate to 20 microliters/minute

Methods

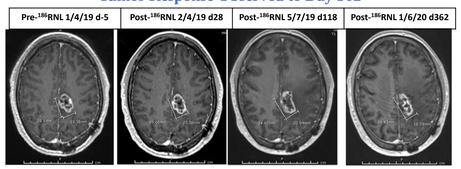
Brainlab iPlan Flow software was used to plan SmartFlow catheter placement in the tumor volume while avoiding white matter tracts and CSF spaces. Frameless image-guided catheter placement was achieved with Brainlab Varioguide Stereotactic system. A single administration of ^{186}RNL was delivered by CED utilizing 1-4 catheters at a maximum flow rate of 20µL/min/catheter.

Cohort 5 / Subject 01-014: MRI & SPECT



+ Tumor volume was 6.5mL & tumor coverage >90%; absorbed dose delivered to tumor: 419 Gy

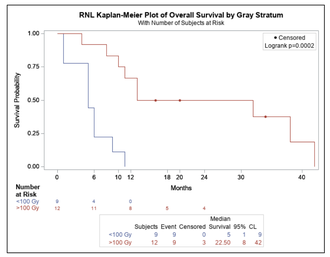
Tumor Response Observed to Day 362

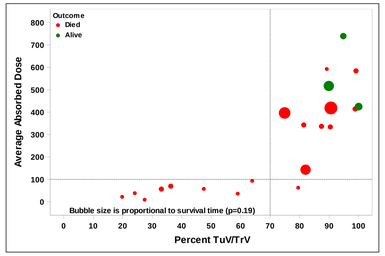


+ MRI scans revealed initial increase in size peaking at day 118 with associated edema followed by tumor shrinkage out to at least day 362; patient survival >950 days.

Results

Twenty-three subjects across seven dosing cohorts received a range of 1.0-31.2mCi in a volume of 0.6-12.3mL. The maximum CED administration rate was 5-20µL/min and 1-4 catheters were used per subject. Average absorbed radiation dose to the tumor (AARD) was 273 Gy (8.9-740 Gy) while exposure outside the brain was negligible. In cohorts 1-4, an AARD of >100 Gy was achieved in 5/12 (42%) subjects vs 8/10 (80%) subjects treated in cohorts 5-7. Tumor coverage or percent tumor volume (TuV) in the treated volume (TrV) [%TuV/TrV] was 71% (19.8%-100%) and correlated to AARD. In 5/23 subjects receiving prior bevacizumab therapy, the AARD was 149 Gy and the %TuV/TrV was 47.9% compared to 18 subjects not receiving prior bevacizumab therapy in which the AARD was 302 Gy and the %TuV/TrV was 77.7%. ^{186}RNL was safe and well tolerated with most AE's grade 1 or 2. The AE's with the highest incidence included fatigue (50%), muscular weakness (33.3%), headache (33.3%), and gait disturbance (27.8%). All SAE's were determined unrelated by investigator except for cerebral edema in 1 subject which was controlled with corticosteroids and did not require study discontinuation.





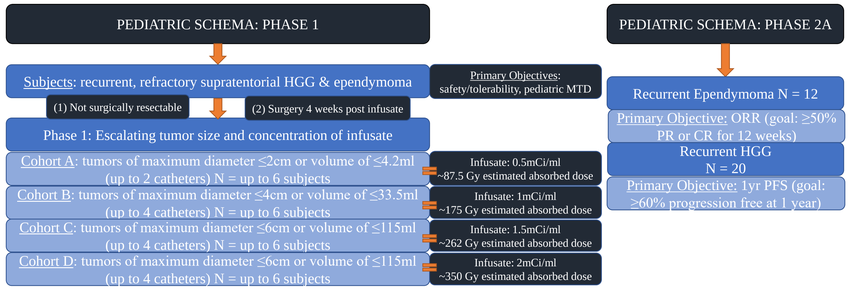
Dose (Gy)	Overall Survival (weeks)			Patients Remain Alive
	Median	95% CI	Mean ± SE	
<100	**22.3**	6.4, 45.3	24.6 ± 4.8	0
>100	**129.7**	35, 169.1	100.8 ± 19	4

Historical Control

By comparison, **median overall survival of 32.1 weeks** reported in 8 study meta-analysis of 694 recurrent GBM subjects treated with bevacizumab monotherapy

Pediatric Phase 1/2a Clinical Trial

PLUS Therapeutics in collaboration with Lurie Children's Hospital investigators is planning the first-in-pediatrics clinical trial with IND submission later this year. This is a Phase 1/2a clinical trial to determine the maximum tolerated dose, safety, and tolerability of ^{186}RNL delivered via CED in supratentorial recurrent or progressive pediatric ependymoma and high-grade glioma (HGG) and evaluate early efficacy.



Pediatric Dose Escalation Schema
Escalation based on Tumor Volume(s) + Concentration

Cohort	Tumor Diameter (cm)	Calculated Tumor Volume (ml)	Tumor Diameter plus 0.5cm margin (cm)	Calculated Vd (ml)	Est Drug Volume (ml) [Vi] (assume Vd/Vi = 3)	Concentration (mCi/ml)	Total Activity (mCi)	Estimated Absorbed Dose
A	1	0.5	2	4.2	1.4	0.5	0.7	87.5
	1.5	1.8	2.5	8.2	2.7	0.5	1.35	86.5
	2	4.2	3	14.1	4.7	0.5	2.35	87.5
B	2.5	8.2	3.5	22.4	7.5	1	7.5	175.8
	3	14.1	4	33.5	11.2	1	11.2	175.6
	3.5	22.4	4.5	47.7	15.9	1	15.9	175.1
	4	33.5	5	65.4	21.8	1	21.8	175.1
C	4.5	47.8	5.5	87.1	29	1.5	43.5	262.3
	5	65.7	6	113.1	37.7	1.5	56.55	262.6
	5.5	87.7	6.5	143.8	47.9	1.5	71.85	262.4
	6	114.1	7	179.6	59.9	1.5	89.85	262.7
D	4.5	47.8	5.5	87.1	29	2	58	349.7
	5	65.7	6	113.1	37.7	2	75.4	350.1
	5.5	87.7	6.5	143.8	47.9	2	95.8	349.9
	6	114.1	7	179.6	59.9	2	119.8	350.3

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