Revolutionary Alpha-Emitters Radiotherapy: Brain Tumors

May 11, 2026

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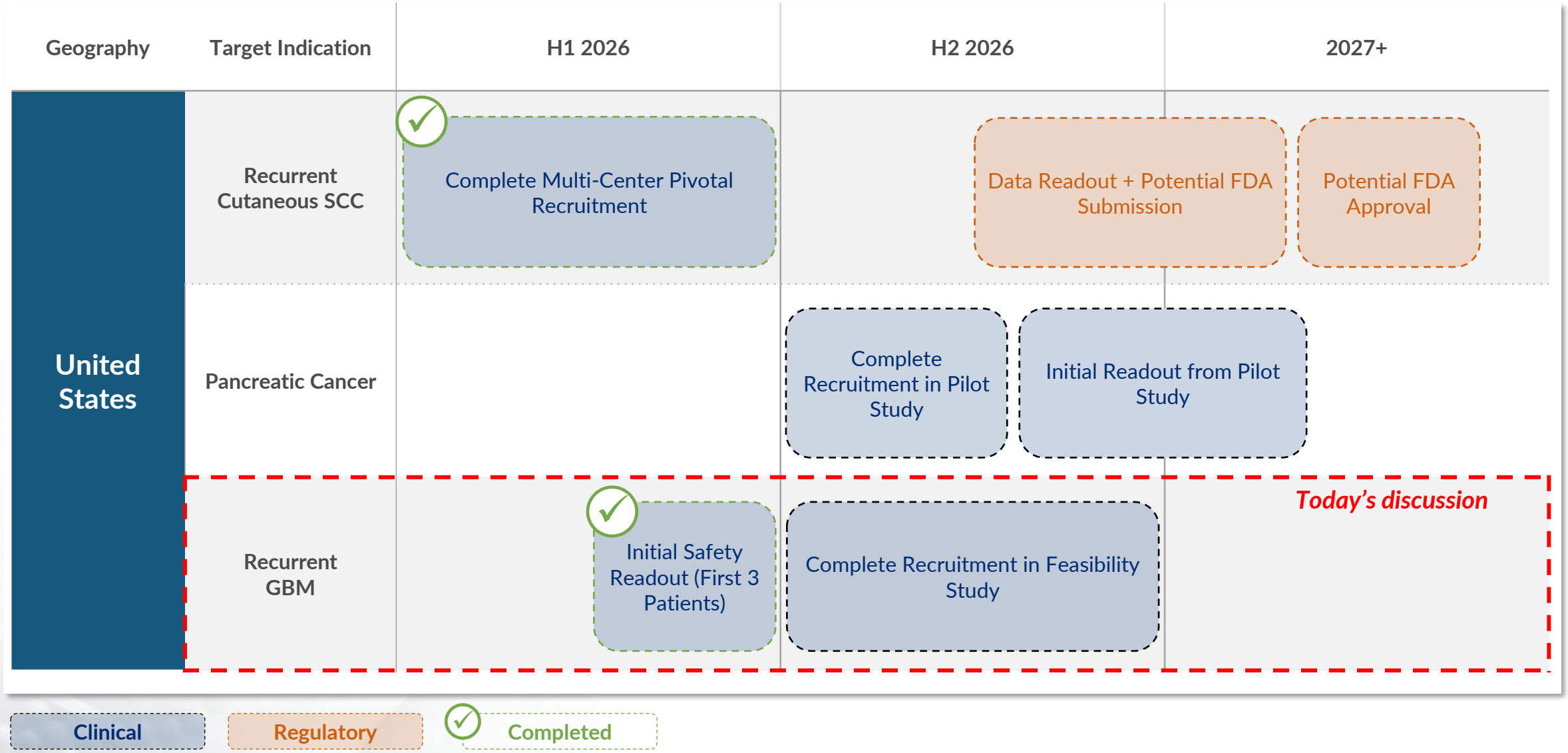
Agenda

- Alpha DaRT Mechanism of Action
- Preclinical Data
- Clinical Approach
- Clinical Trial

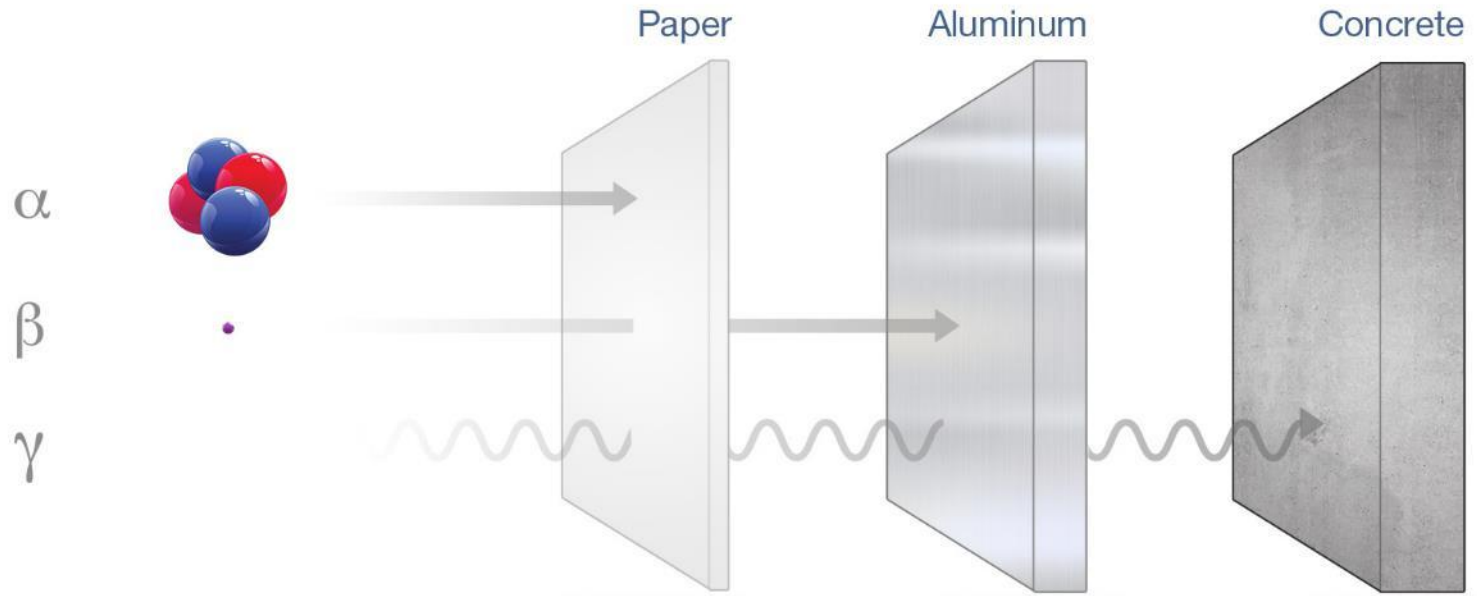
Anticipated Milestones



Alpha DaRT: Mechanism of Action

Types of Radioactive Decay

Due to the mass of the alpha particle, in comparison to beta particle, alpha has a low penetration power. This means that the outside layer of the human skin, for example, can block these particles.



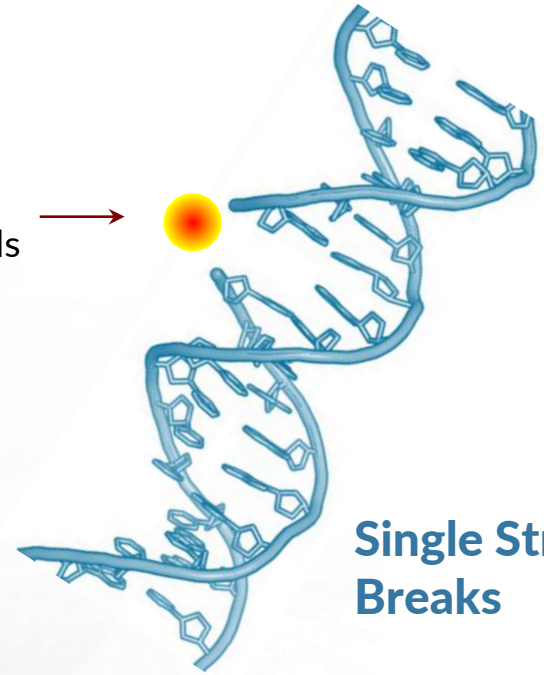
Why Use Alpha Radiation?

Conventional Gamma/Beta Radiation

- Indirectly damaging the DNA
- Dependent on oxygen presence
- **Repairable single strand breaks**

γ/β Radiation

O_2 → Free Radicals →

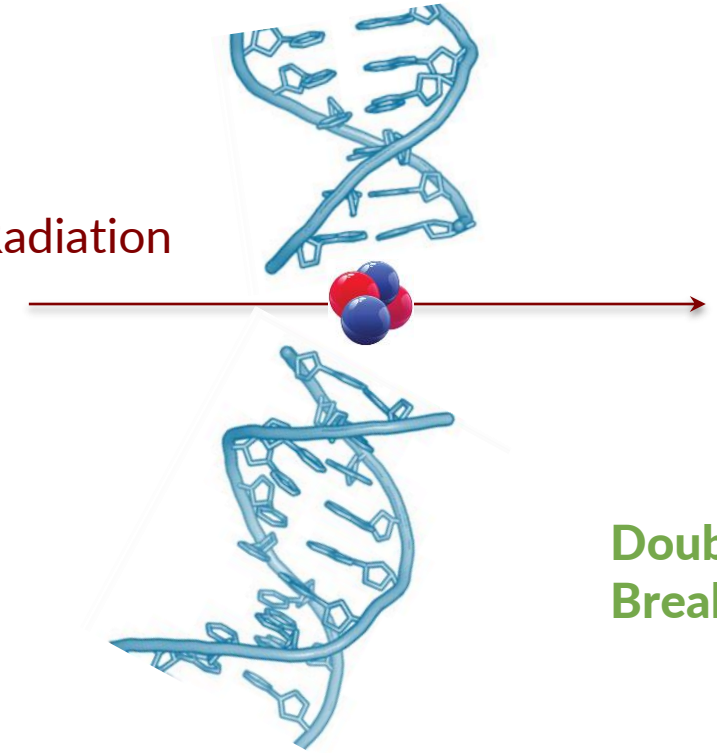


Single Strand Breaks

Alpha Radiation

- Directly damaging the DNA
- Independent of oxygen presence
- **Irreparable double strand breaks**

α Radiation



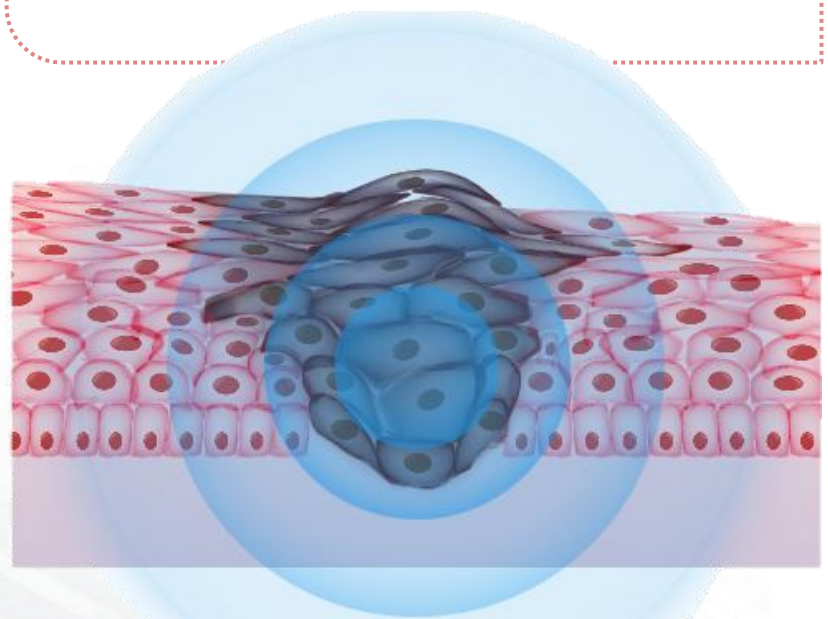
Double Strand Breaks

Why has alpha-based radiation not been integrated into clinical practice?

Alpha Radiation is Focal - Short Range Limits Clinical Use

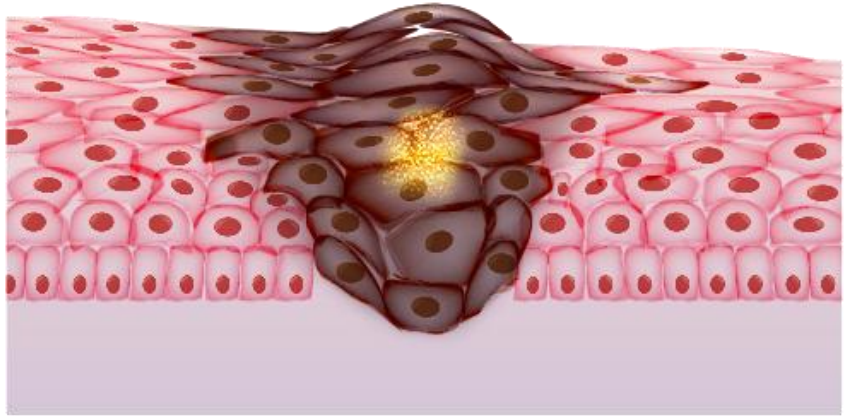
Beta/Gamma Radiation

Long therapeutic range with risk to surrounding organs



Alpha Radiation

Short range in tissue limits damage to surrounding organs but also limits coverage



What is the Alpha DaRT?

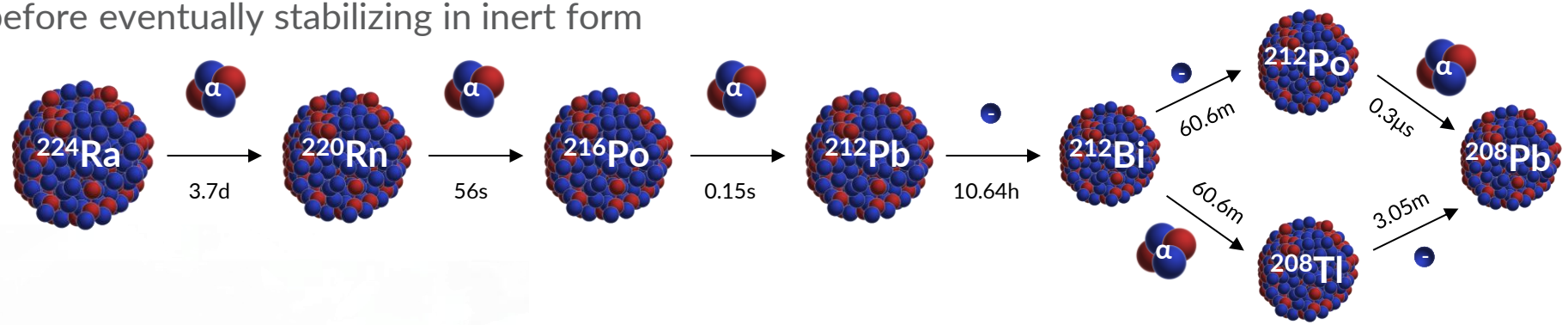
Alpha DaRT - Diffusing Alpha-emitters Radiation Therapy

https://www.youtube.com/watch?v=nwfzJHm0fTQ

Mechanism of Action of the Alpha DaRT Technology

^{224}Ra Decay Chain

- Alpha DaRT leverages the innate decay chain of Radium-224
- The decay chain of Radium-224 includes four alpha particles
- Radium-224 has a half-life of ~3.7 days, while the remaining decay chain has a total half-life of approximately 12 hours, before eventually stabilizing in inert form



Alpha DaRT

- The Alpha DaRT utilizes stainless steel sources that are impregnated with Radium-224
- The source is designed such that when injected into the tumor, the radium remains attached to the source while its daughter atoms detach, emitting cytotoxic alpha particle payloads as they move deeper into the tumor until stabilizing

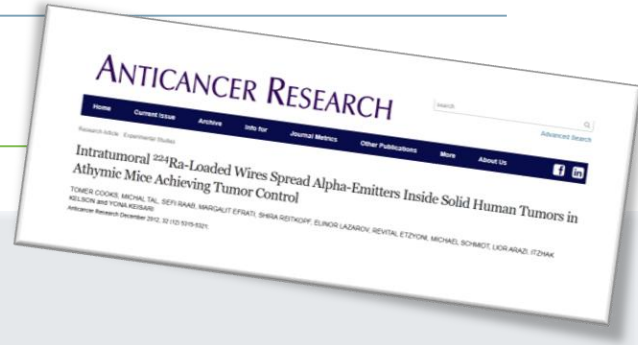
Alpha DaRT is designed to overcome the range limitations of alpha particles through precise release of alpha emitters into the tumor, generating a potent and tight distribution of alpha radiation

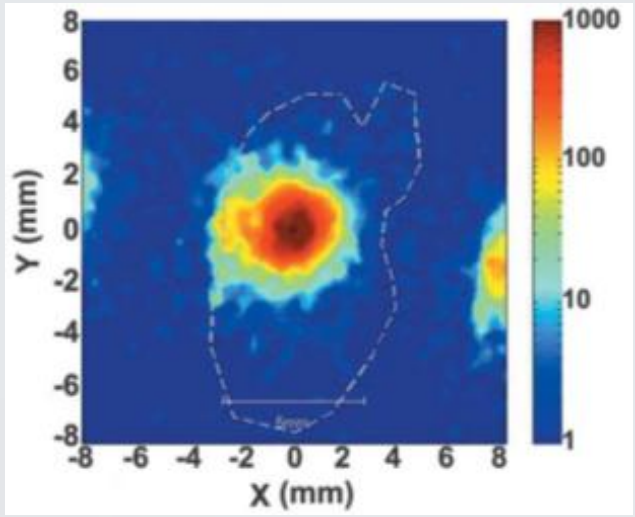
Brain

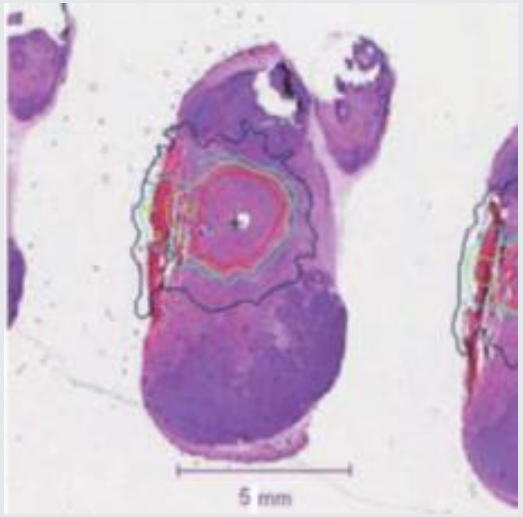
Preclinical Studies – Small Animal

Alpha DaRT is Designed to be Highly Potent and Conformal

Alpha DaRT observed activity range (U87 GBM s.c. tumors):





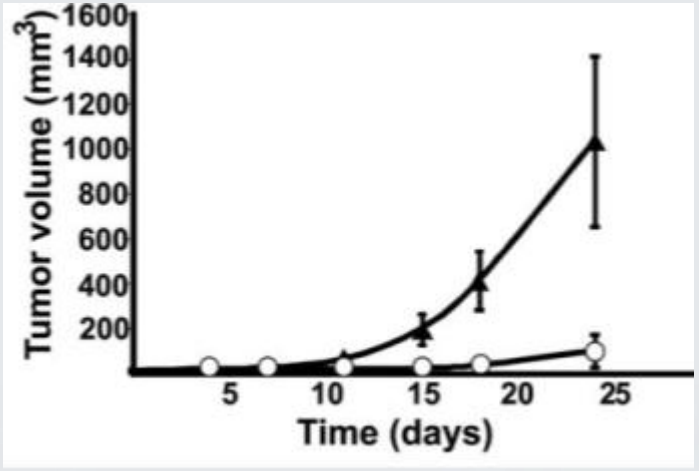


A representative tumor section demonstrating (left) normalized asymptotic dose according to high-resolution autoradiography analysis, and (right) correlating necrotic domains following H&E staining

- "Death zone" of ~4-5 mm in diameter (>16 Gy)
- The dose drops down sharply
- No damage was caused to the adjacent tissue

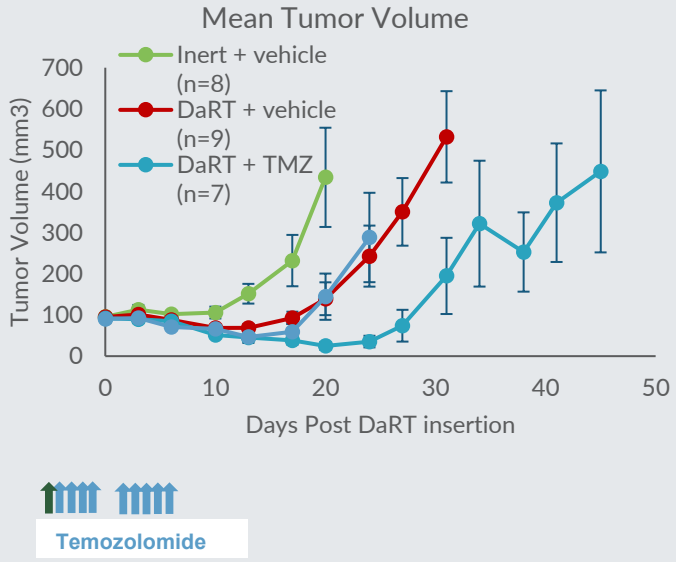
Cooks, Tomer et al. "Intratumoral 224Ra-loaded wires spread alpha-emitters inside solid human tumors in athymic mice achieving tumor control." Anticancer research vol. 32,12 (2012): 5315-21.
Note: "Gy" = Gray

In Vivo Impact of Alpha DaRT Monotherapy and in Combination with Temozolomide



Growth of U87 tumors (4 mm length) treated with a single 21.3-24.3 kBq Alpha DaRT source or inert control.

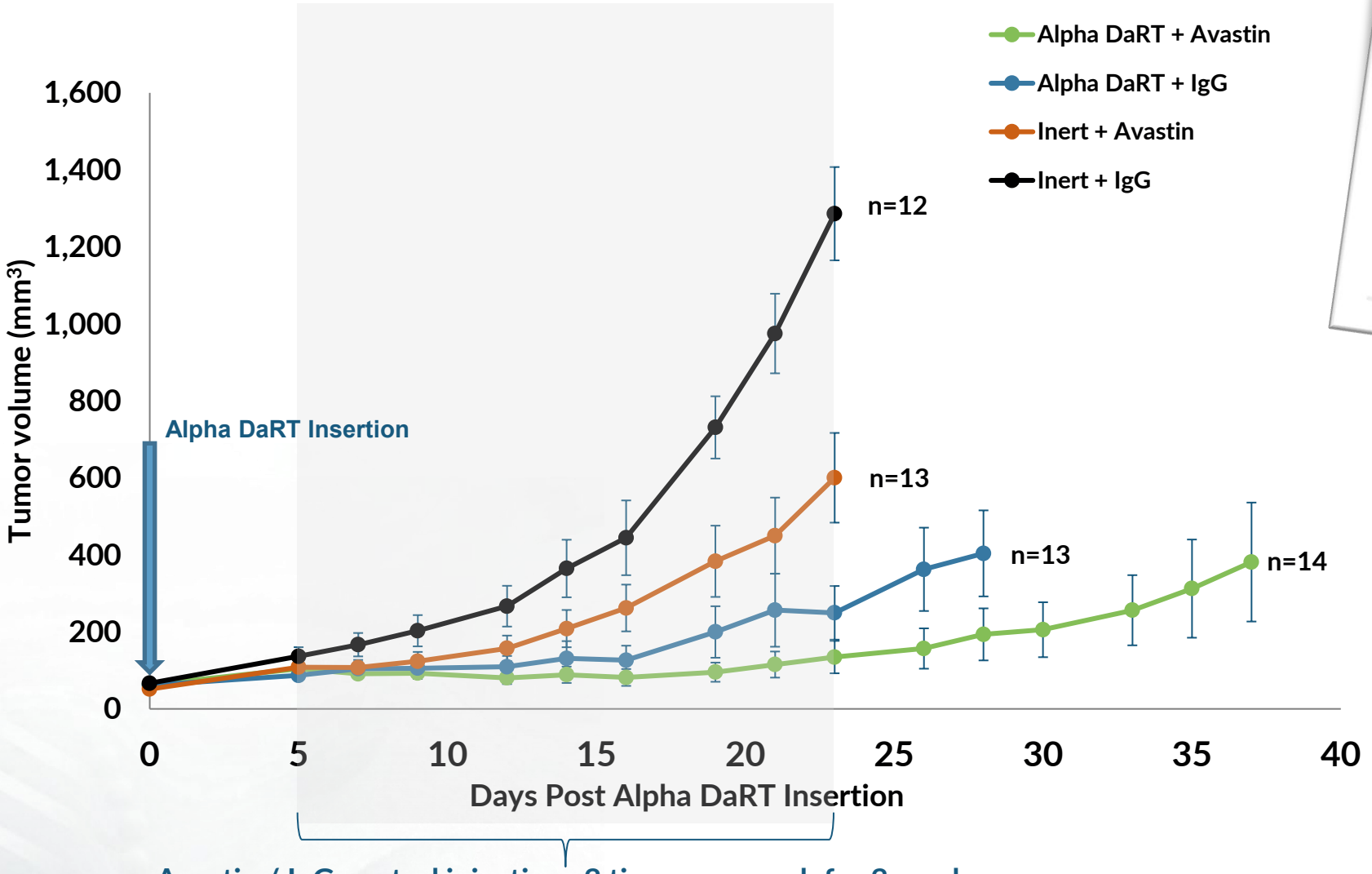
Alpha radiation reduced the growth in vivo in U87 cells

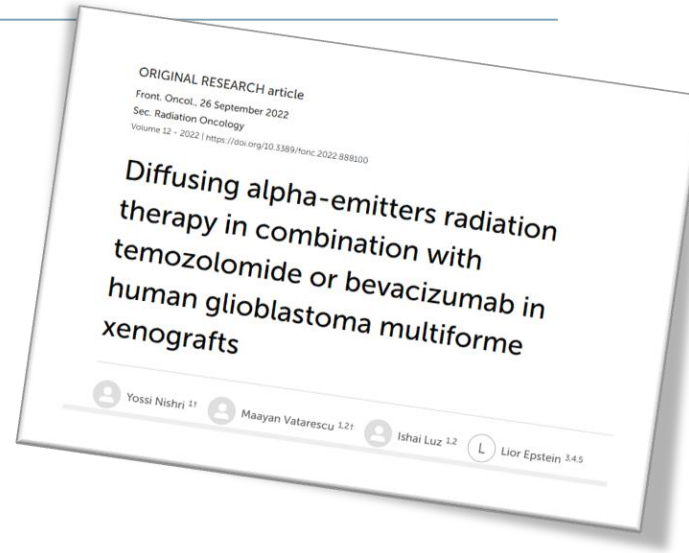


Growth delay of U87 tumors treated with Alpha DaRT in combination with temozolomide vs. monotherapies and control

Nishri, Yossi et al. "Diffusing alpha-emitters radiation therapy in combination with temozolomide or bevacizumab in human glioblastoma multiforme xenografts." Frontiers in oncology vol. 12 888100. 27 Sep. 2022, doi:10.3389/fonc.2022.888100

Alpha DaRT + Avastin Combo Showed Attenuated Growth of GBM Xenografts



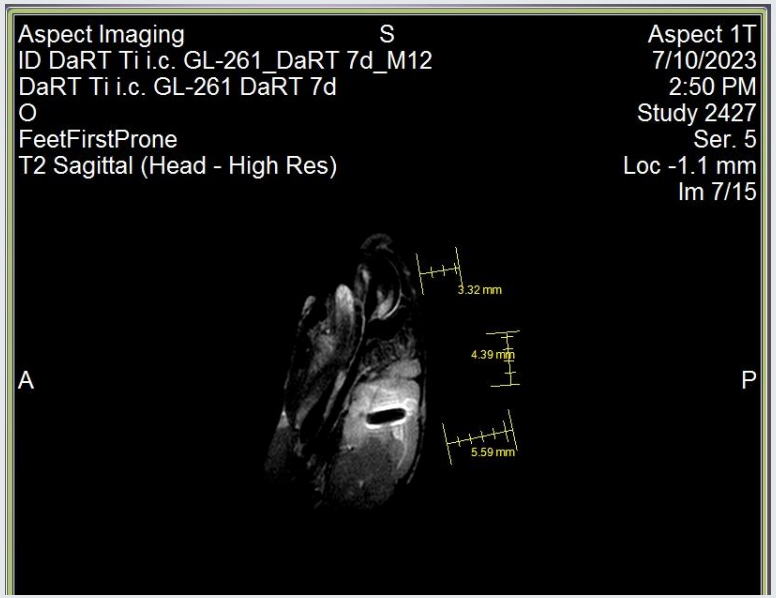

ORIGINAL RESEARCH article
Front. Oncol., 26 September 2022
Sec. Radiation Oncology
Volume 12 - 2022 | https://doi.org/10.3389/fonc.2022.888100

Diffusing alpha-emitters radiation therapy in combination with temozolomide or bevacizumab in human glioblastoma multiforme xenografts

Yossi Nishri [1†] Maayan Vatarescu [1,2†] Ishai Luz [1,2] Lior Epstein [3,4,5]

Nishri, Yossi et al. "Diffusing alpha-emitters radiation therapy in combination with temozolomide or bevacizumab in human glioblastoma multiforme xenografts." Frontiers in oncology vol. 12 888100. 27 Sep. 2022, doi:10.3389/fonc.2022.888100

Alpha DaRT Can be Implanted Orthotopically



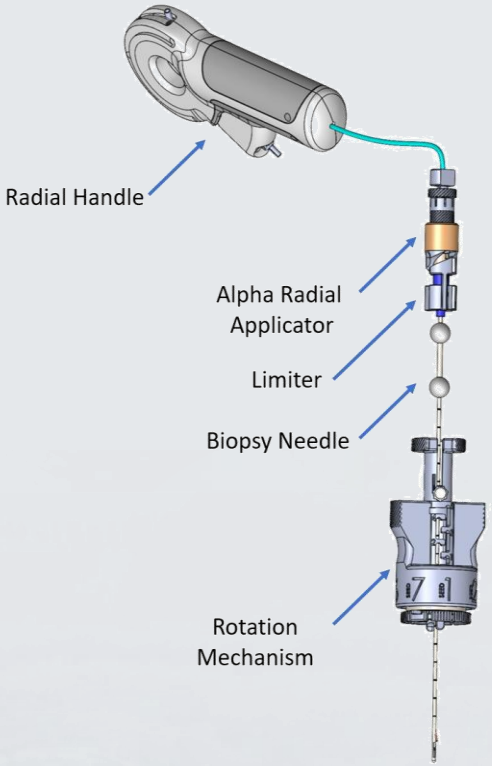
Brain

Preclinical Studies – Large Animal

Alpha Radial Applicator

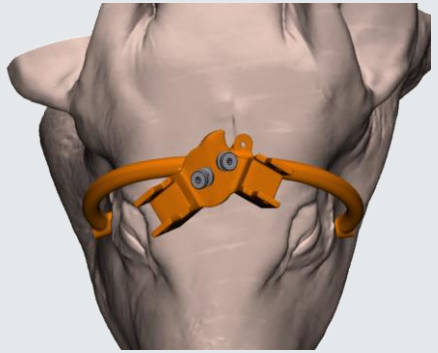
https://www.youtube.com/watch?v=IJY965J0xMk

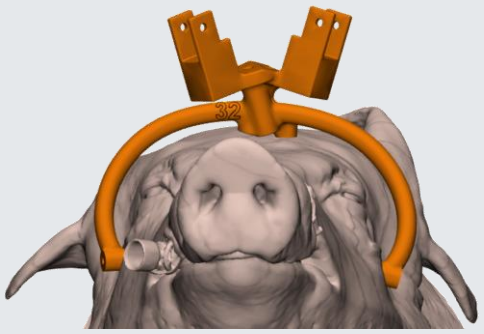
MR Image of an Alpha DaRT Source in a Phantom Model

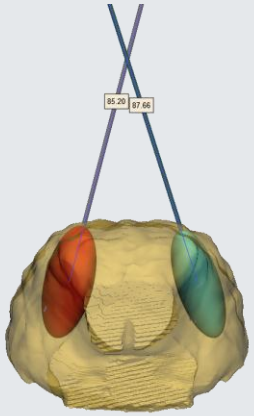


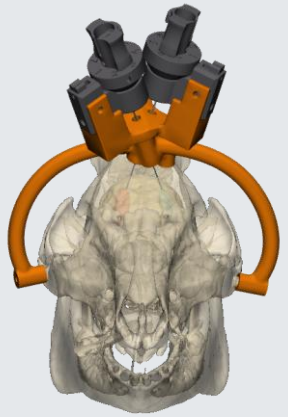
Full Cluster
2 Layers

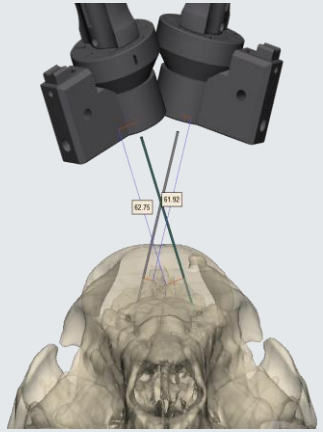
Full Cluster
2 Layers (Top View)







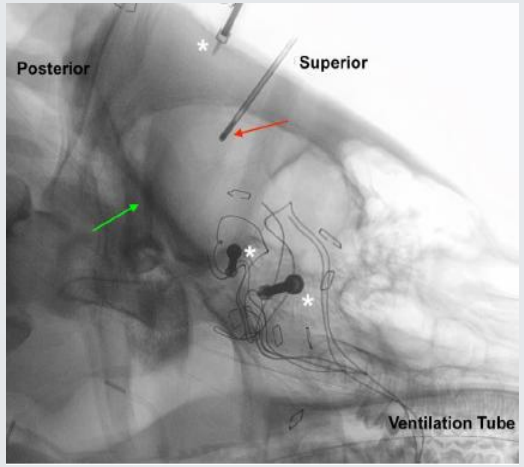




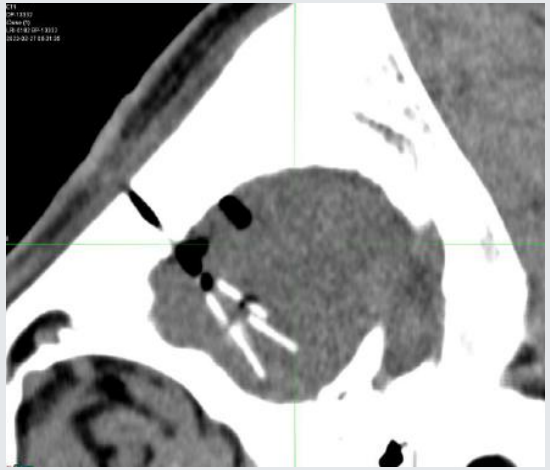
A designated applicator allowed the delivery of 1-3 clusters of 7 sources in each hemisphere

Large Animal Pre-Clinical Trial of Brain Applicator

Surgical Insertion



Intra-op Fluoroscope



Post – Insertion CT

Post – Coronal MRI

Shushan, Yigal et al. “Stereotactic implantation of diffusing alpha-emitters radiation therapy sources in the swine brain: a potential new focal therapy for brain tumors.” Journal of Neuro-Oncology vol. 172. 2 January 2025, doi:10.1007/s11060-024-04919-5

Highlights from Pre-Clinical Brain Studies

- Image-guided stereotactic Alpha DaRT **deployment and implantation in the swine brain was demonstrated to be feasible and safe**.
- The configuration required by the treatment plan was **efficiently implemented** using a **designated applicator**.
- In contrast to other radiotherapies, **no tissue changes** in distant sites were observed. This is a major potential advantage of the suggested therapy, especially for patients who were previously treated with radiation and cannot receive additional external radiation treatments.
- Based on these safety findings, Alpha DaRT is being studied in clinical trials for patients with **recurrent brain tumors**.

Alpha DaRT

Interim Data
First 3 Patients in CTP-GBM-01

REGAIN Clinical Trial Design

Recurrent GBM

Key Eligibility Criteria:

1. Age 18-85
2. Single gadolinium-enhancing lesion ≤ 3 cm
3. 6 month interval since completion of prior XRT
4. Disease Progression per RANO criteria
5. 4 week interval from any prior therapy

AlphaDaRT Insertion →

Primary Endpoints:

Feasibility and Safety

Secondary Endpoints:

MRI Response and Overall Survival

Feasibility: Defined as placement of Alpha DaRT in 7 out of 10 patients

Safety: Incidence of any Grade 3 or higher CNS adverse event

MRI Response: Local radiographic tumor control

Overall Survival: Time from treatment until death

Treatment Protocol:

- One-time treatment with Alpha DaRT using the Alpha radial applicator
- The patients will receive steroids to prevent edema or increase intracranial pressure, but no other treatments are specified in the protocol
- No additional requirements beyond standard of care
- Neurosurgical monitoring, all patients discharged within 36 hours

Patient Enrollment:

- 3 patients enrolled and treated to date
- Planning to enroll 10 patients total

FDA Review:

- The FDA requested first 3 patients treated at a maximum of 1 per month
- Initial treated patients followed by an interim safety analysis for FDA review before treating remaining 7 patients

Baseline Characteristics of First Three Patients Treated

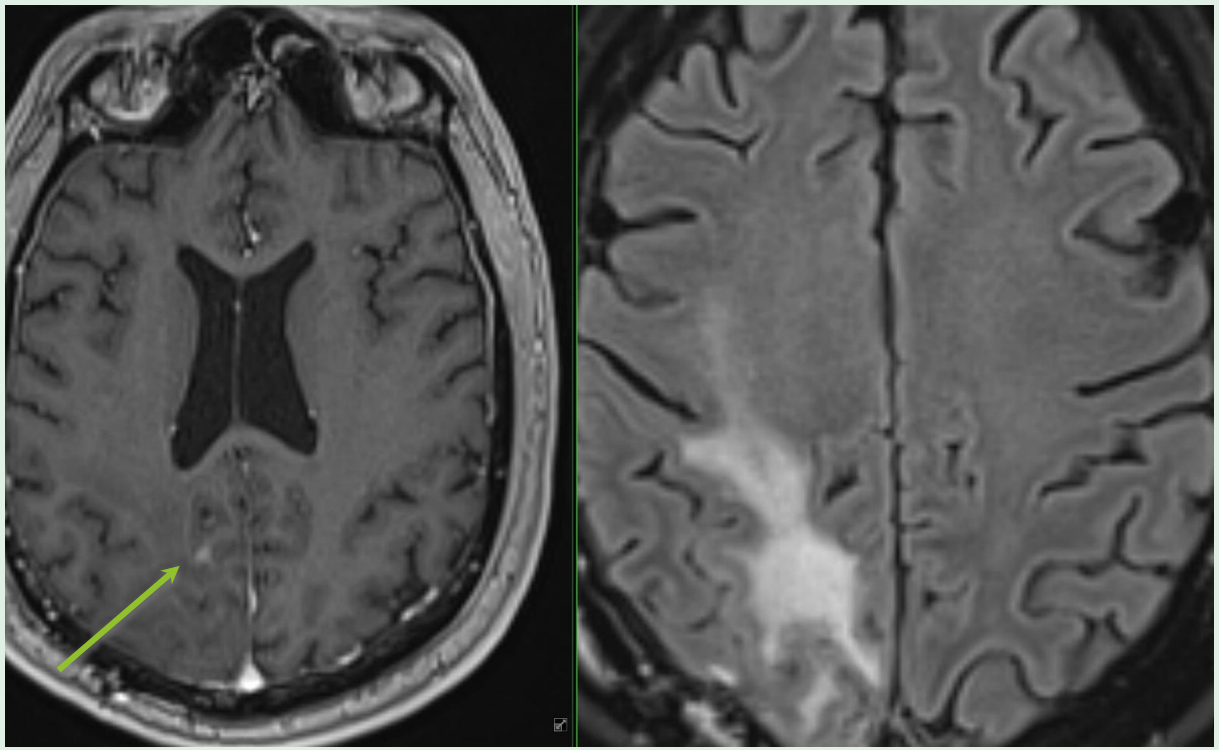
	Patient 1	Patient 2	Patient 3
Age	56	71	56
Sex	Male	Male	Male
Initial Diagnosis	WHO grade 4 glioma IDH wild type, MGMT unmethylated with FGFR:TACC fusion	Right frontal WHO grade 4 glioma IDH wild type	WHO grade 4 glioma IDH wild type, MGMT hypermethylated
Date of Initial Diagnosis	Feb 2024	May 2021	Feb 2025
Number of Recurrences	3	2	1

Patient 1

- 56-year-old male with a WHO grade 4 glioma IDH wild type, MGMT unmethylated with FGFR:TACC fusion
- Initial Diagnosis was in 2/2024, Gross Total Resection in 2/11/24
- Post operative course:
- 60 Gy in 30 fractions with temozolomide completed 3/19/24-4/30/24
- 1st recurrence 10/24 underwent LITT and Gallium Maltolate trial
- 2nd recurrence underwent surgery revealing recurrent GBM
- 3rd recurrence led to Alpha DaRT trial
- He has baseline left homonymous hemianopsia

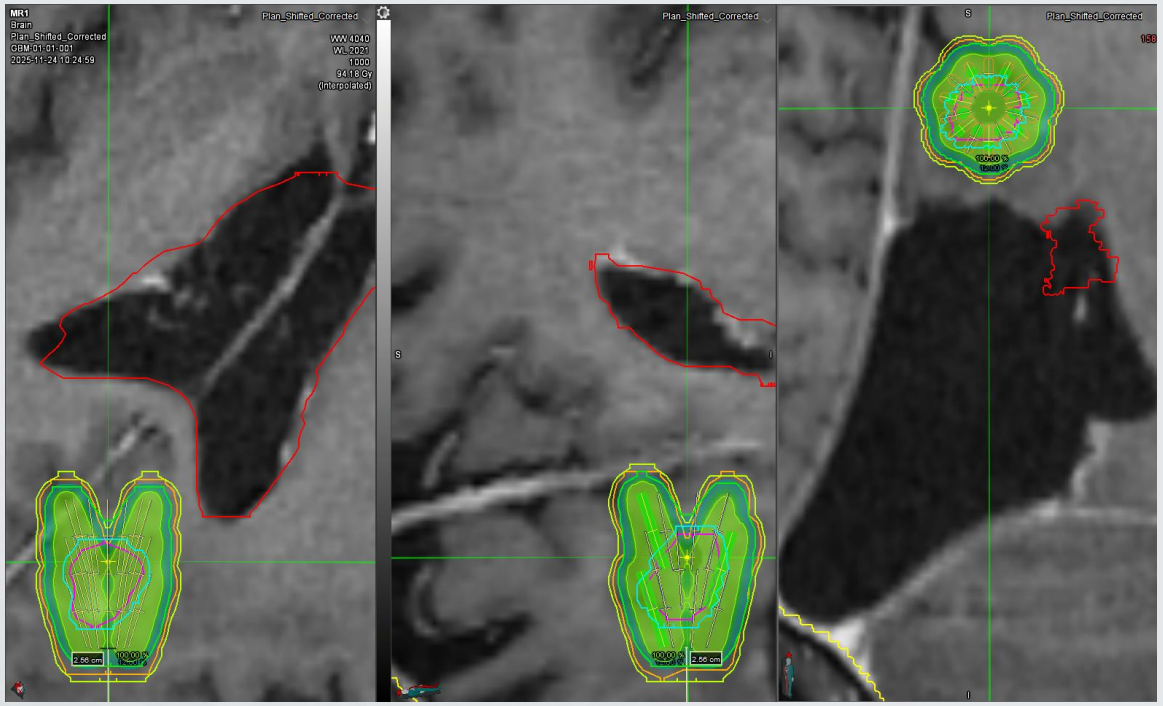
Pre-Alpha DaRT MRI

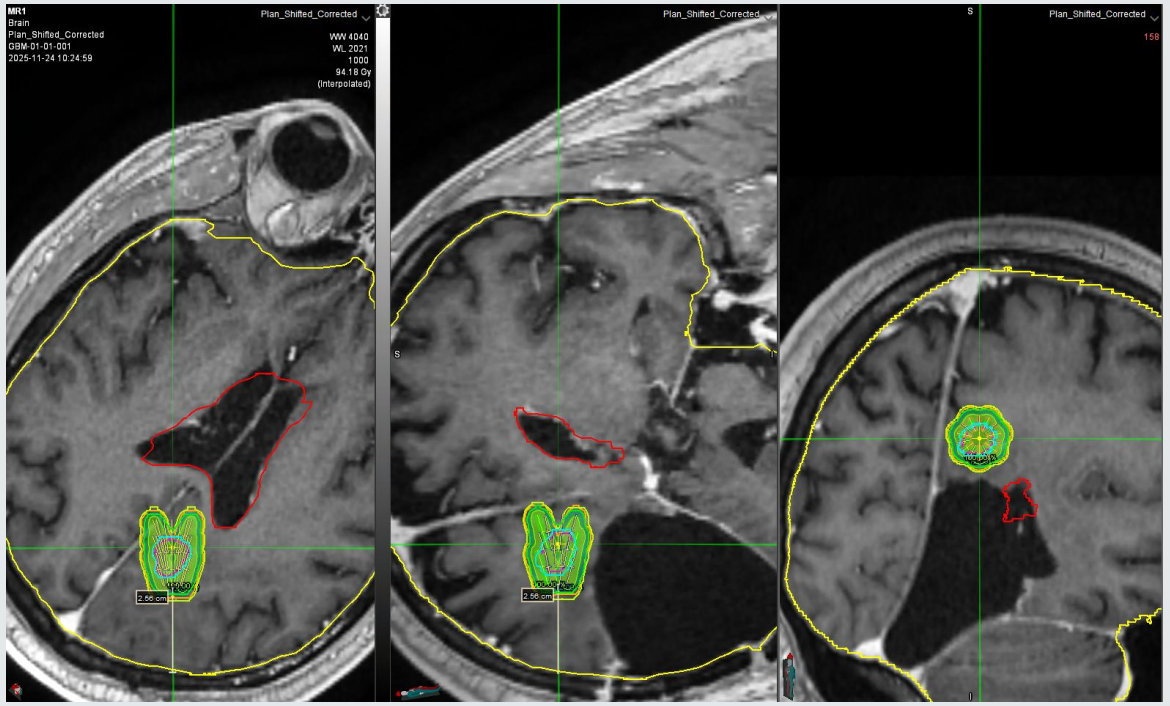
- New focal enhancement in the right parieto-occipital lobe with surrounding FLAIR
- Amino Acid PET performed and focal activity seen at these lesion only



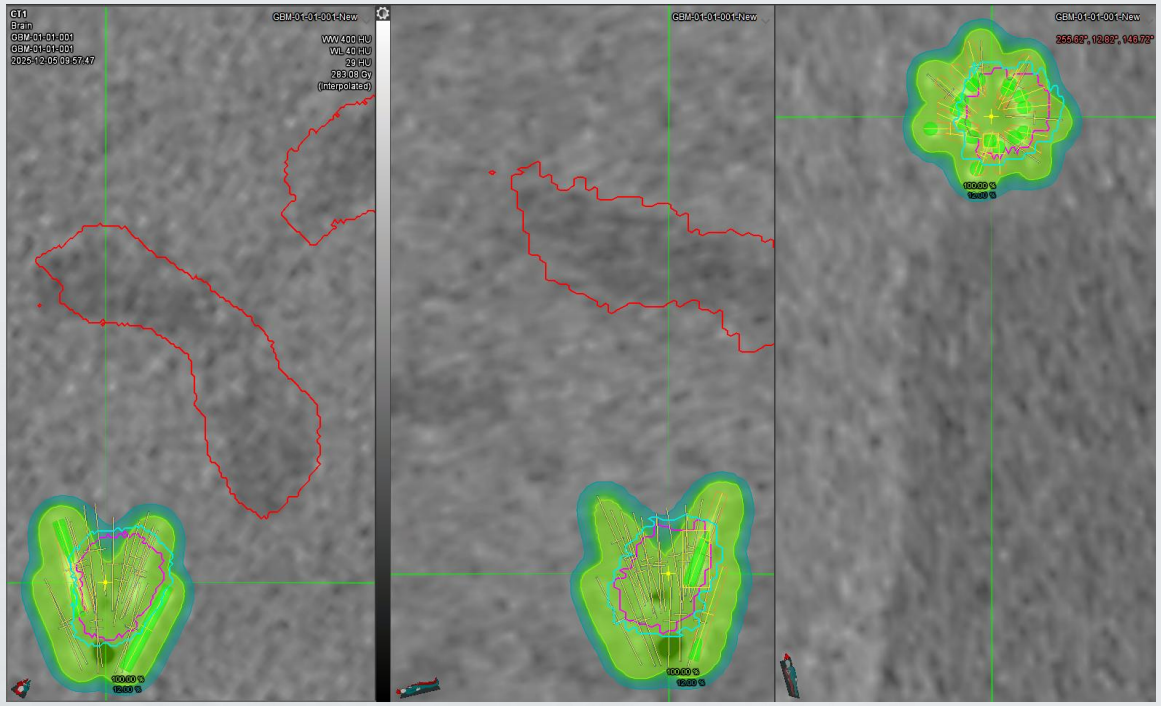
Ax T1 C+ | Ax T2 FLAIR

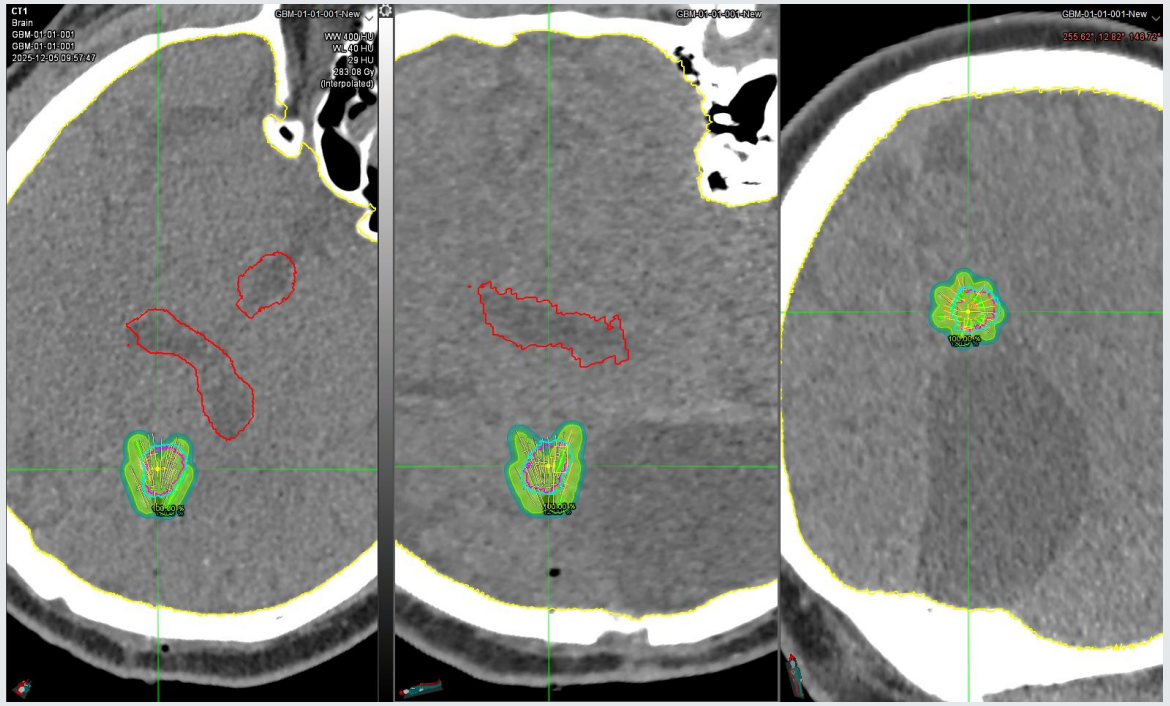
Treatment Plan

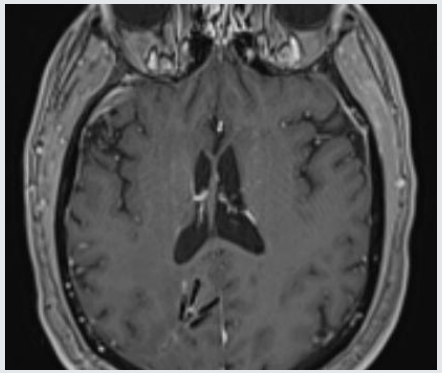




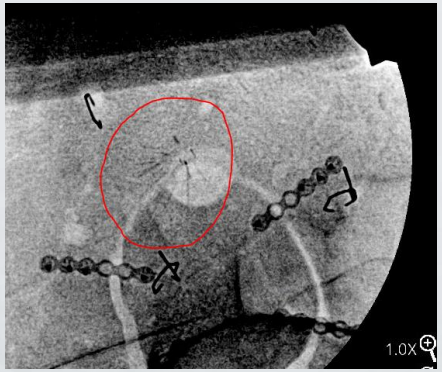
Post Insertion Dosimetry



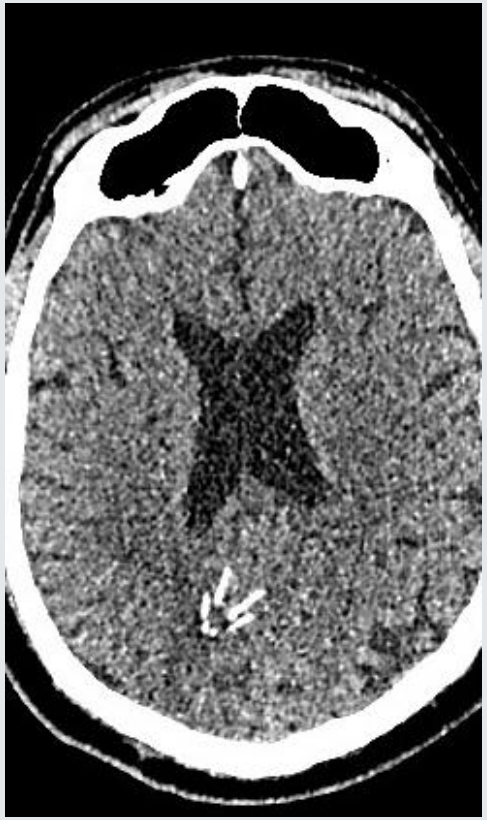




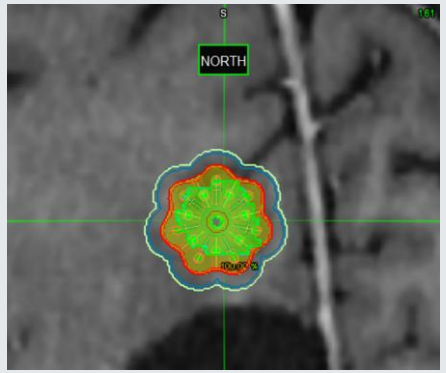
Post Implant MRI - Same Day showing accurate placement of sources



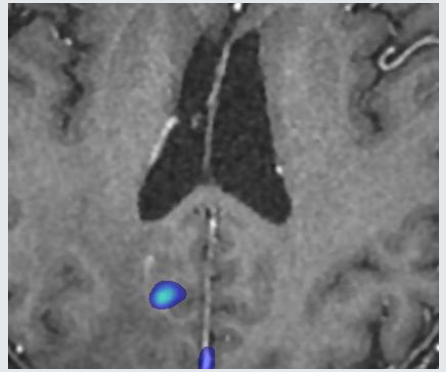
Post Implant XR - During surgery showing deployment of sources



Post Implant CT - Same Day showing accurate placement of sources, no bleed



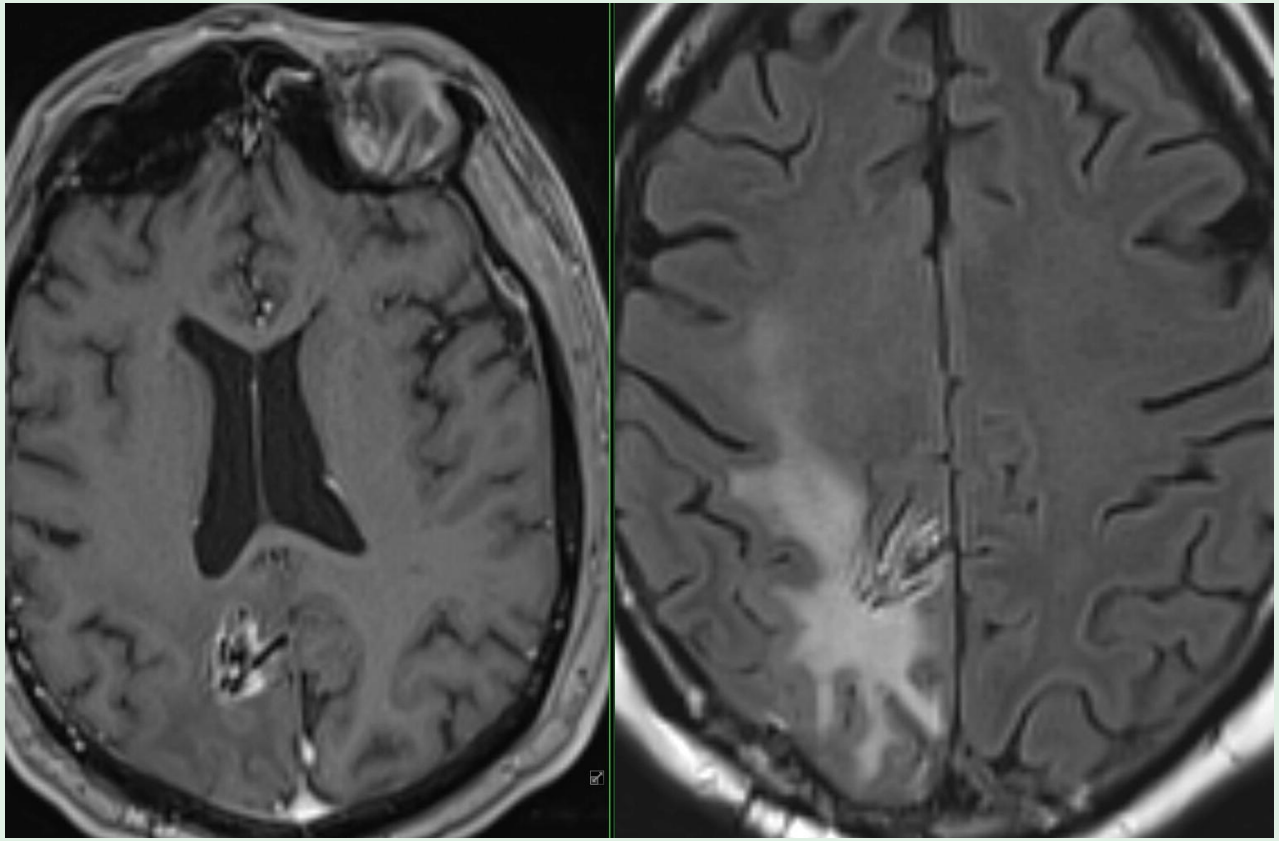
Post Implant MRI - Dosimetry confirming appropriate coverage



Pre-treatment PET demonstrating activity only in the new focal lesion

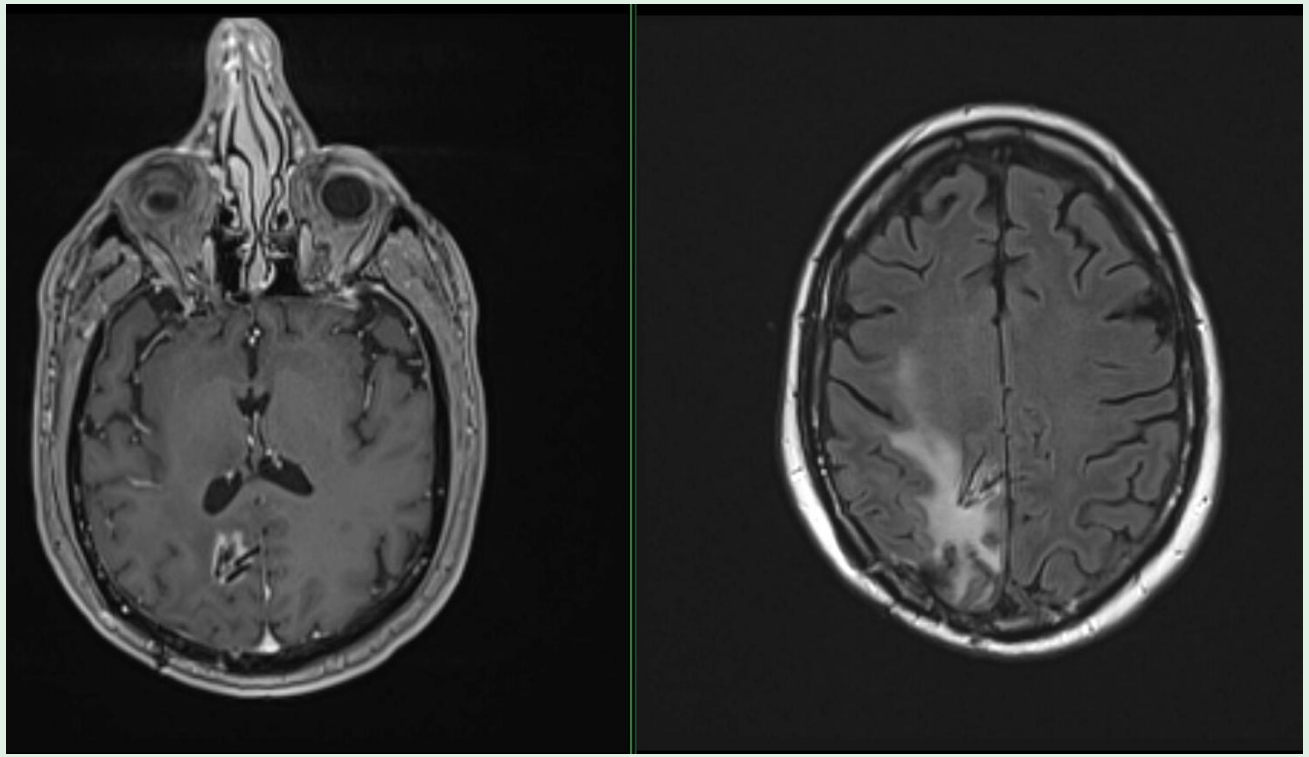
MRI 1 Month Post Alpha DaRT

- There was a focal enhancement around each Alpha DaRT
- No discernable lesion remained
- Confirmed on central neuroradiology review with 2 neuroradiologists
- No new edema around implant



MRI 3 Months Post Alpha DaRT

- No progression of disease
- Continued to be in CR
- No new radiation treatment changes or injury
- Alpha DaRT sources continued to have linear enhancement



Adverse Events and Current Status*

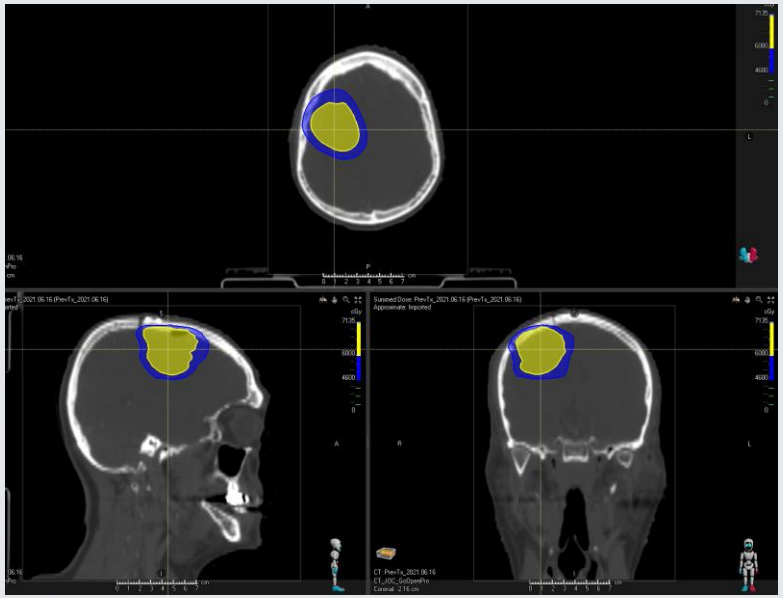
- He developed no dose limiting toxicities, no symptoms from treatment
- NED (no evidence of disease), with complete response (CR) in the lesion

* Interim Data as of 3-May-2026

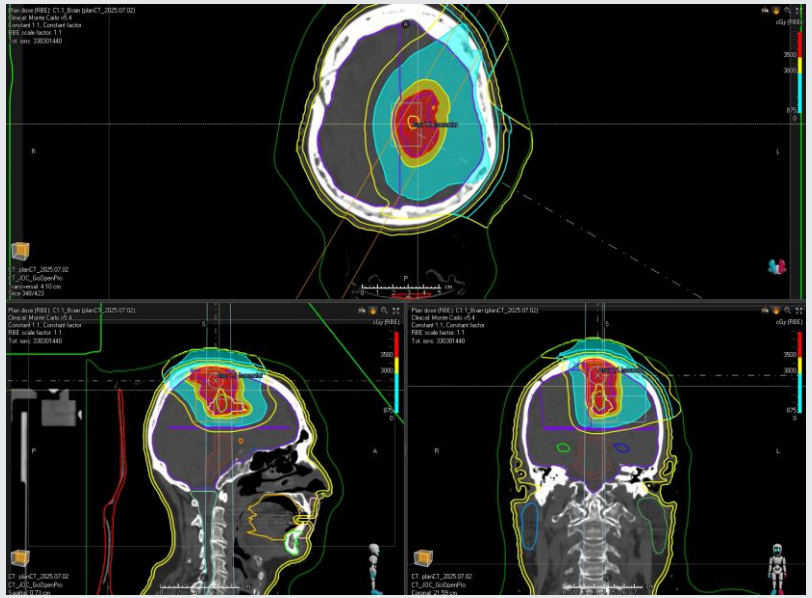
Patient 2

- 71-year-old male with an initial diagnosis in 5/2021 of a right frontal WHO grade 4 glioma IDH wild type, who underwent gross total resection and completed chemo-RT with 60 Gy in 30 fractions 6/21-8/11/21 and temozolomide
- The patient had seizures post surgery
- This right frontal was stable.
- He developed a left frontal lesion in 5/2025 and underwent gross total resection on 5/20/25 demonstrating a WHO grade 4 glioma IDH wild type
- He underwent 35 GyE in 10 fractions intensity modulated proton therapy completed on 7/22/25
- On 2/2/26 he developed a local recurrence in the right frontal lobe

Prior Radiation Therapy Courses



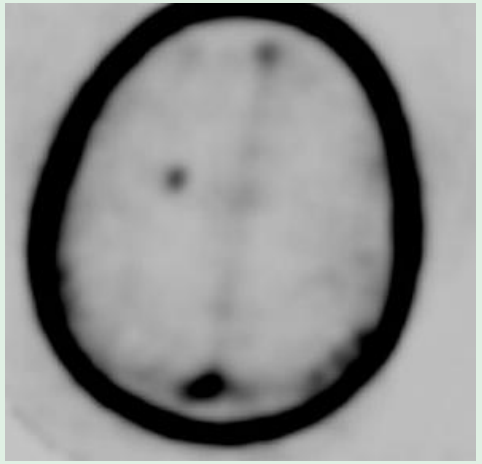
46 Gy with 14 Gy boost (60Gy) total



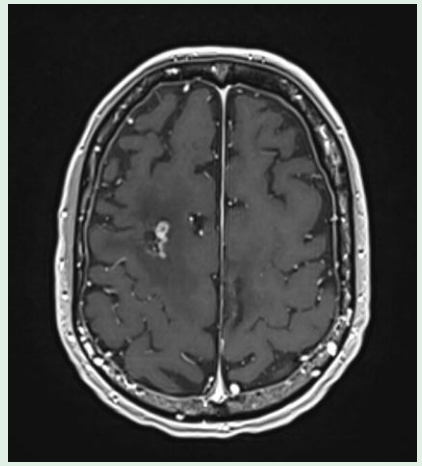
35 GyE in 10 fractions focal protons IMPT

Pre-Alpha DaRT MRI

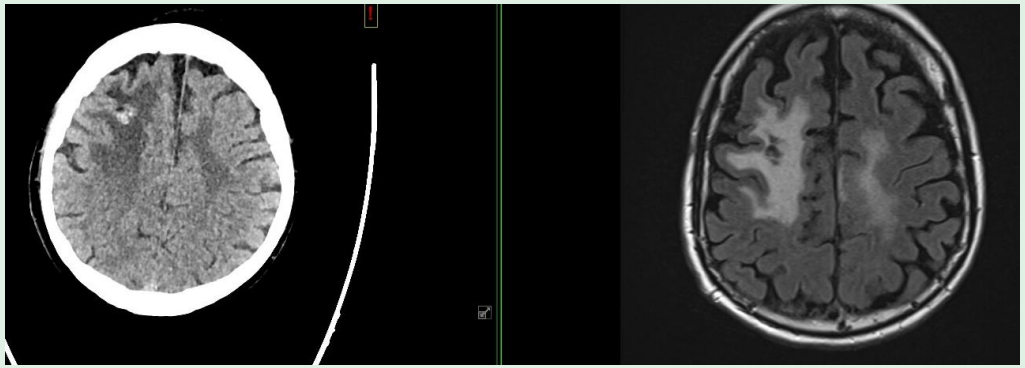
- New focal enhancement in the right frontal lobe with surrounding FLAIR
- Amino Acid PET performed and focal activity seen at these lesion only



F18 Fluciclivine PET

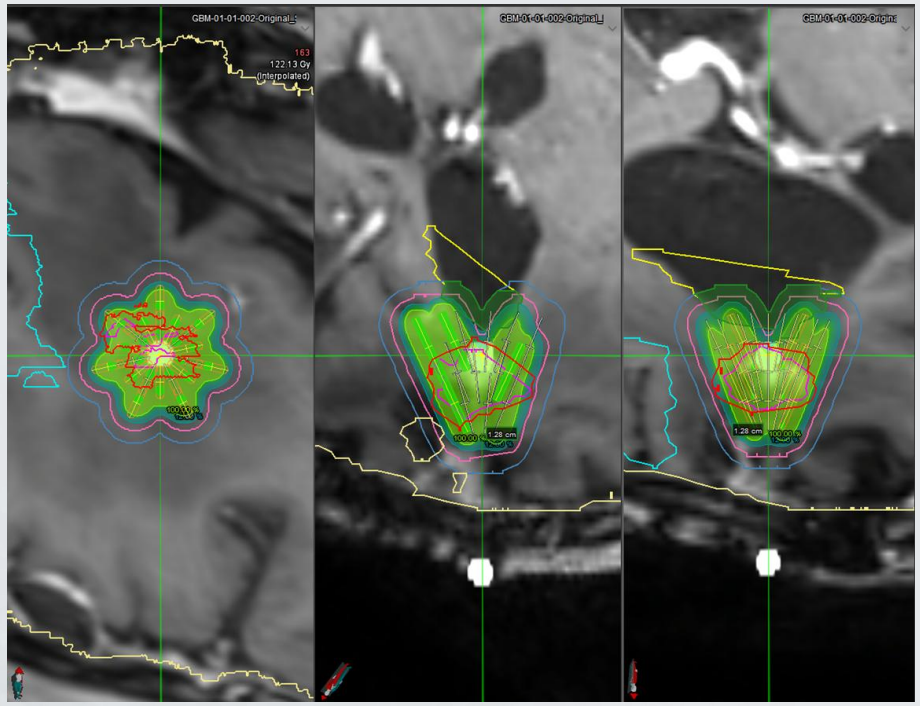


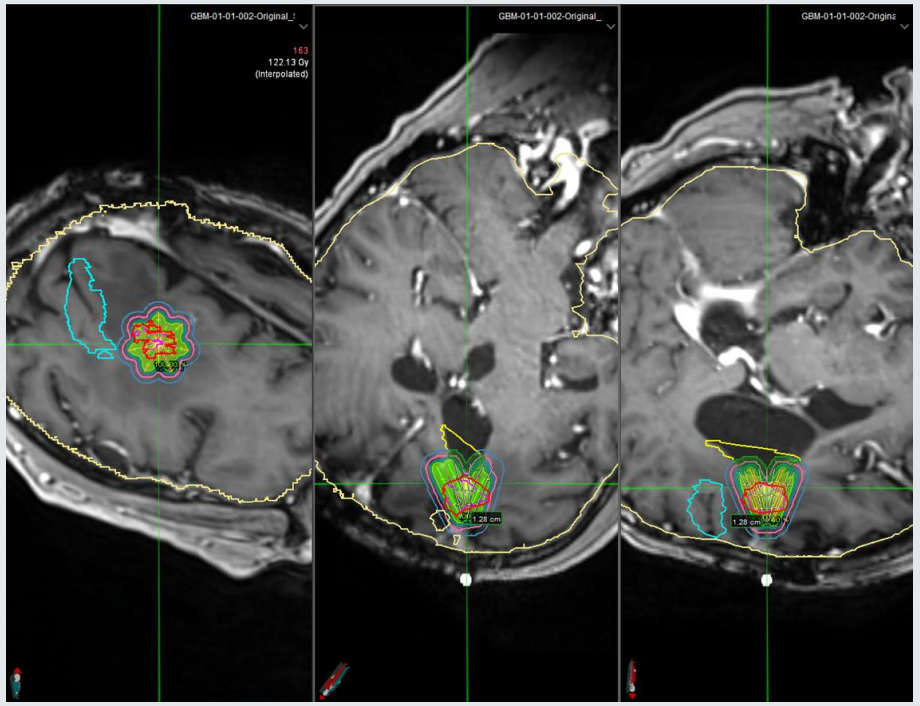
Ax T1 C+



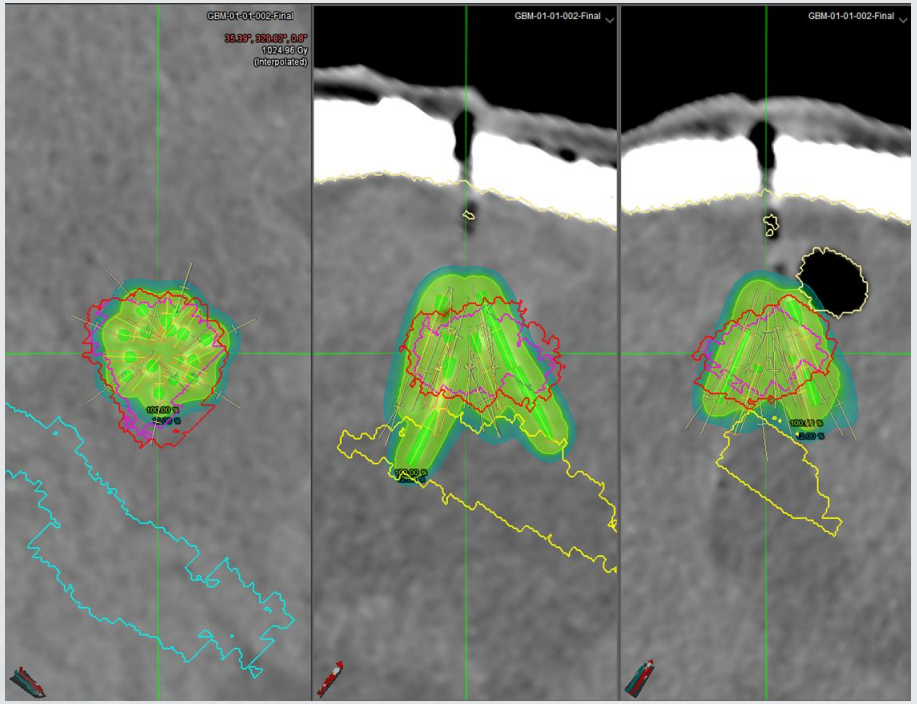
CT head no contrast | Ax T2 FLAIR

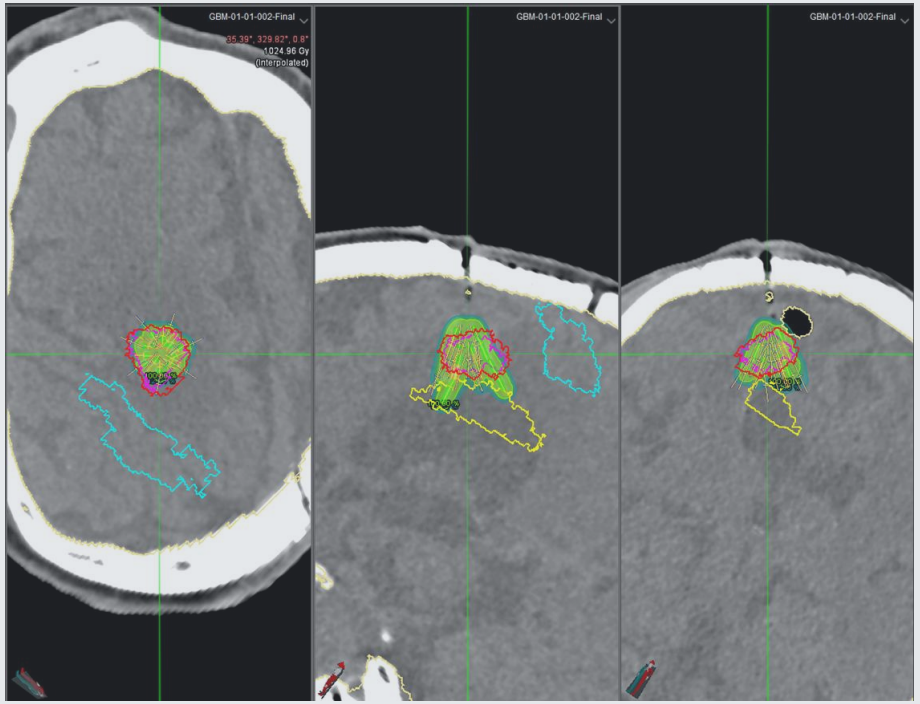
Treatment Plan



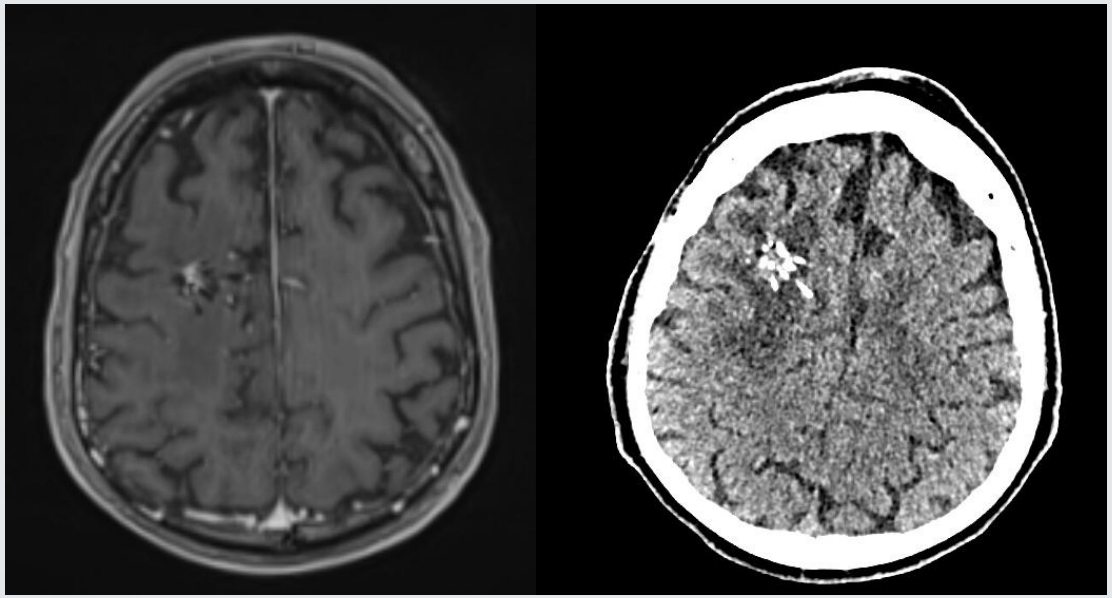


Post Insertion Dosimetry





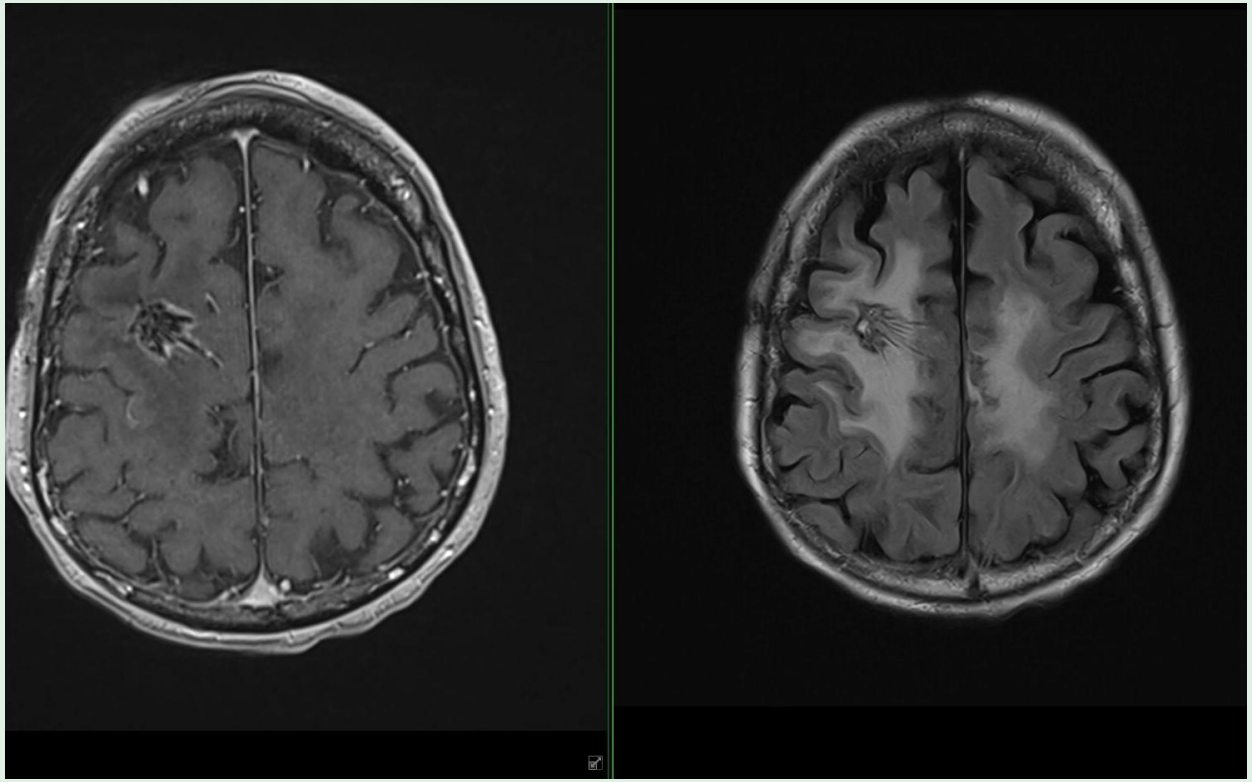
Alpha DaRT Deployment



Post-op Day 0 MRI and CT demonstrating accurate deployment

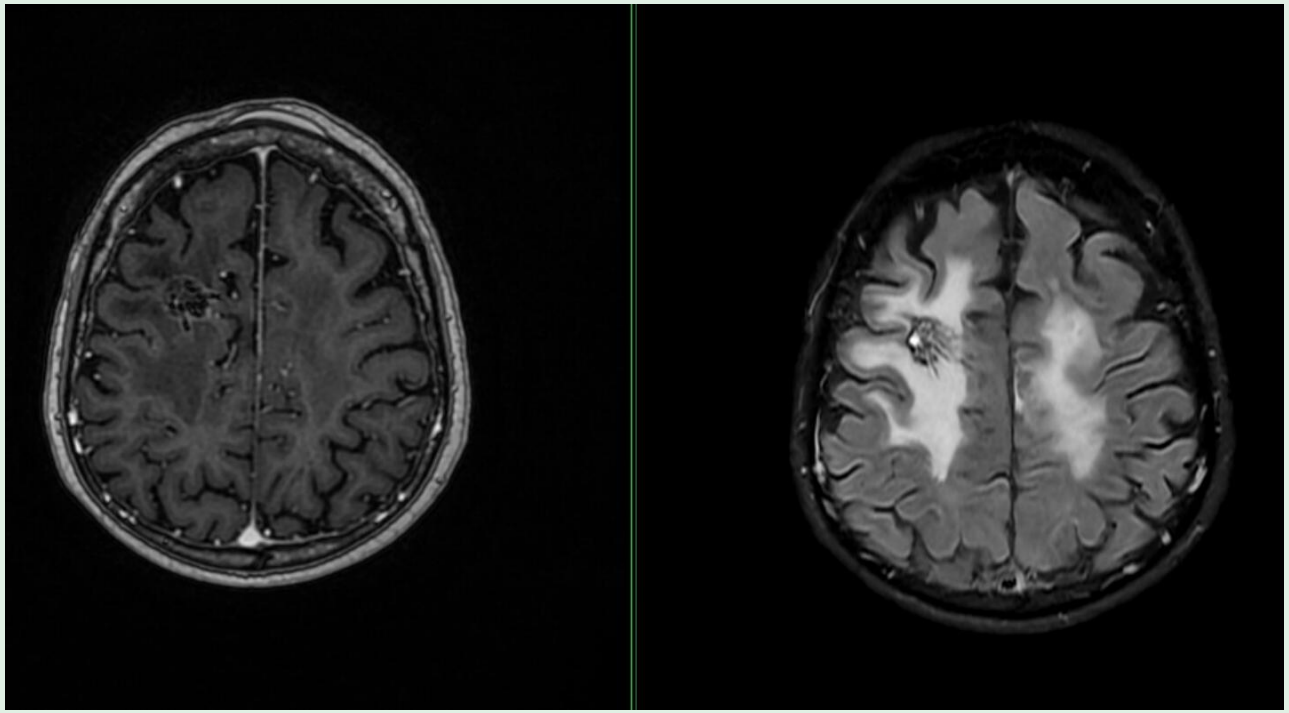
MRI 1 Month Post Alpha DaRT

- There was a focal enhancement around each Alpha DaRT
- No discernable lesion remained
- Confirmed on central neuroradiology review with 2 neuroradiologists
- No new edema around implant



MRI 3 Months Post Alpha DaRT

- No progression of disease
- Continued to be in complete response
- No new radiation treatment changes or injury
- Alpha DaRT with continued but diminishing enhancement



Adverse Events

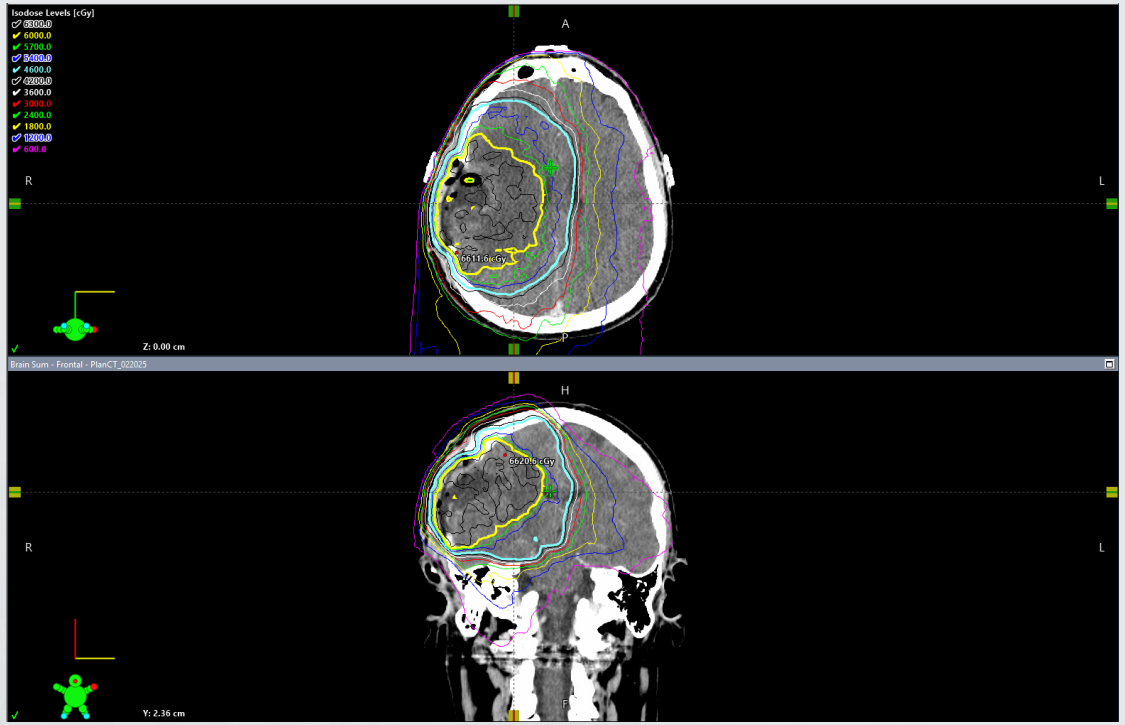
- He developed a grade 3 seizure with Todd's paralysis 10 days post Alpha DaRT, this occurred during his steroid taper
  - This required a 48-hour hospitalization
  - As previously noted, the patient had a history of seizures
- Symptoms improved to baseline on steroids and additional imaging showed normalizing edema to pretreatment extent
- Doing well and returned to his neurologic baseline*

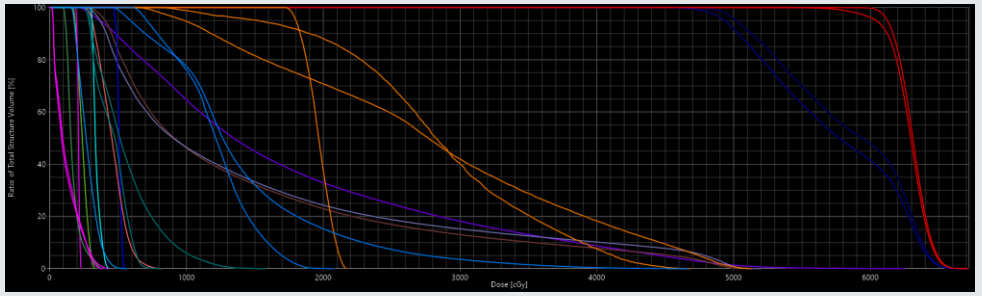
* Interim Data as of 3-May-2026

Patient 3

- 56 yo M with WHO grade 4 glioma IDH wt, MGMT hypermethylated, Ki67-40%, DL1 0%
- He underwent a subtotal resection and underwent a reoperation (gross total resection) 1 month later due to early progression noted on imaging, and developed post op empyema with klebsiella
- He has a history of seizures since his first surgery
- He underwent post op Chemo RT with 60 Gy and temozolomide
- During adjuvant temozolomide noted to have progressive enhancement in the prior surgical resection
- Amino Acid PET positive and RANO progressive based on size and consensus review

Prior Radiation Treatment Plan

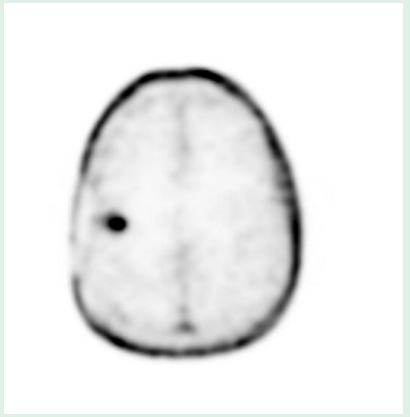




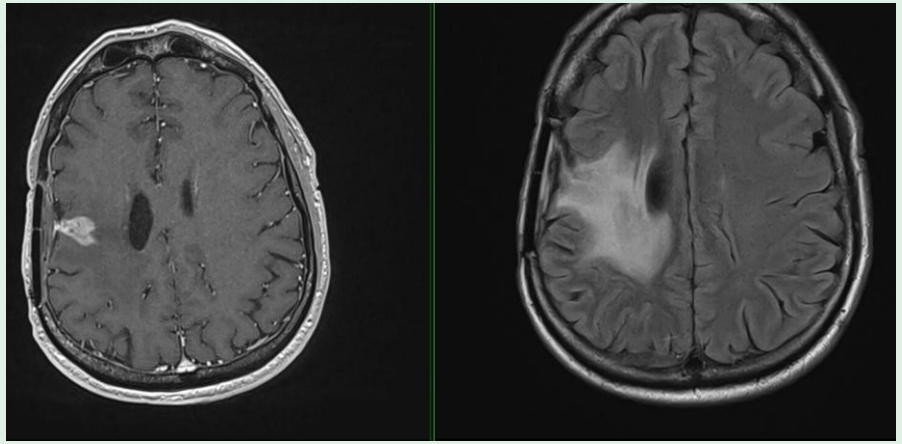
	Template	Plan					
1	PTV	PTV_6000	Target	**6000: 6000cGy**	D95% ≥	100%	100.704%
2	PTV	PTV_6000	Target	**6000: 6000cGy**	CI using External 100% ≤	1.05	1.221
3	**PTVlo**	**PTV_4600**	**Target**	**4600: 4600cGy**	**D95% ≥**	**100%**	107.257%
4	External	External	OAR	**6000: 6000cGy**	Max ≤	115%	112.016%
5	Brainstem	Brainstem	OAR		D1cc ≤	5400-6000cGy	4758.2cGy
6	Brainstem	Brainstem	OAR		D0.03cc ≤	6000cGy	5016.4cGy
7	BrainStem_PRV03	Brainstem_PRV03	OAR		D1cc ≤	5400-6000cGy	4948.2cGy
8	BrainStem_PRV03	Brainstem_PRV03	OAR		D0.03cc ≤	6000cGy	5107.6cGy
9	OpticChiasm	OpticChiasm	OAR		D0.03cc ≤	5400cGy	4021cGy
10	OpticChiasm_PRV3	OpticChiasm_PRV3	OAR		D0.03cc ≤	5400-5600cGy	4996.6cGy
11	OpticNrv_L	OpticNrv_L	OAR		D0.03cc ≤	5400cGy	647.2cGy
12	OpticNrv_PRV03_L	OpticNrv_PRV03_L	OAR		D0.03cc ≤	5400-5500cGy	1316.2cGy
13	OpticNrv_R	OpticNrv_R	OAR		D0.03cc ≤	5400cGy	1739.3cGy
14	OpticNrv_PRV03_R	OpticNrv_PRV03_R	OAR		D0.03cc ≤	5400-5500cGy	3902.6cGy
15	Retina_L	Retina_L	OAR		D0.03cc ≤	4500-5400cGy	N/A
16	Retina_R	Retina_R	OAR		D0.03cc ≤	4500-5400cGy	N/A
17	Eye_L	Eye_L	OAR		D0.03cc ≤	3000-3500cGy	325.2cGy
18	Eye_L	Eye_L	OAR		D5% ≤	3500cGy	303.5cGy
19	Eye_R	Eye_R	OAR		D0.03cc ≤	3000-3500cGy	763.9cGy
20	Eye_R	Eye_R	OAR		D5% ≤	3500cGy	627.2cGy
21	Cochlea_L	Cochlea_L	OAR		Mean ≤	2000-3600cGy	507.8cGy
22	Cochlea_L	Cochlea_L	OAR		D0.03cc (D0.03cc<2500cGy)	cGy	513.4cGy
23	Cochlea_R	Cochlea_R	OAR		Mean ≤	2000-3600cGy	1964.5cGy
24	Cochlea_R	Cochlea_R	OAR		D0.03cc (D0.03cc<2500cGy)	cGy	2003.4cGy
25	SpinalCord	SpinalCord	OAR		D0.03cc ≤	4500cGy	369.5cGy
26	SpinalCord_PRV03	SpinalCord_PRV03	OAR		D0.03cc ≤	4500cGy	418.7cGy
27	Brain-PTV	Brain-PTV	OAR		V3000cGy ≤	50%	18.174%
28	Glnd_Lacrimal_L	Glnd_Lacrimal_L	OAR		Mean ≤	1000-2500cGy	N/A
29	Glnd_Lacrimal_R	Glnd_Lacrimal_R	OAR		Mean ≤	1000-2500cGy	N/A
30	Lens_L	Lens_L	OAR		D0.03cc ≤	700cGy	219.9cGy
31	Lens_R	Lens_R	OAR		D0.03cc ≤	700cGy	377.4cGy

Pre-Alpha DaRT MRI

- New focal enhancement in the right frontal lobe with surrounding FLAIR
- Amino Acid PET performed and focal activity seen at these lesion only

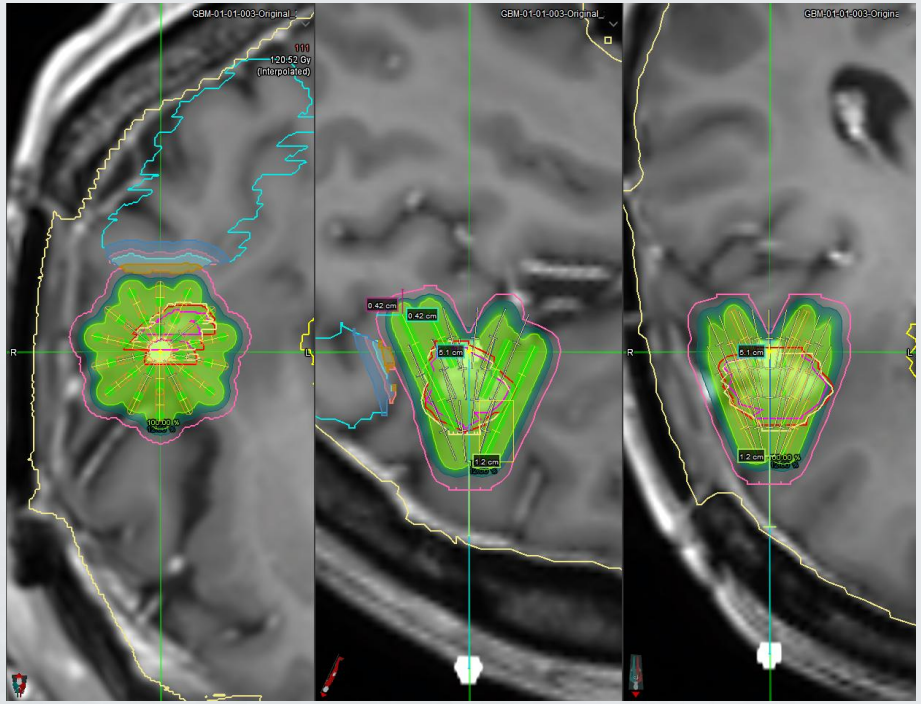


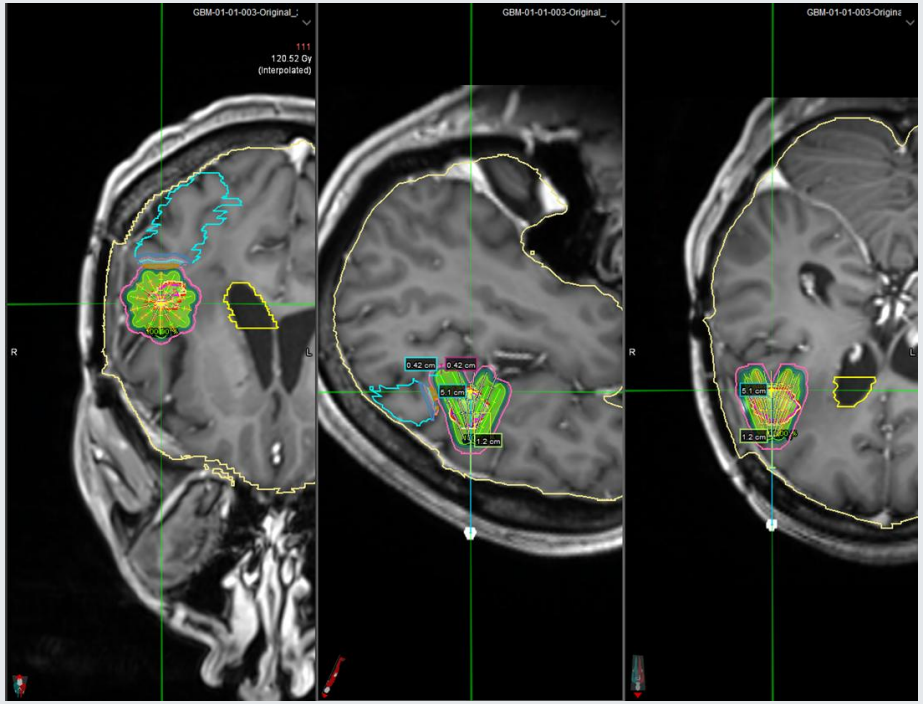
F18 Fluciclivine PET



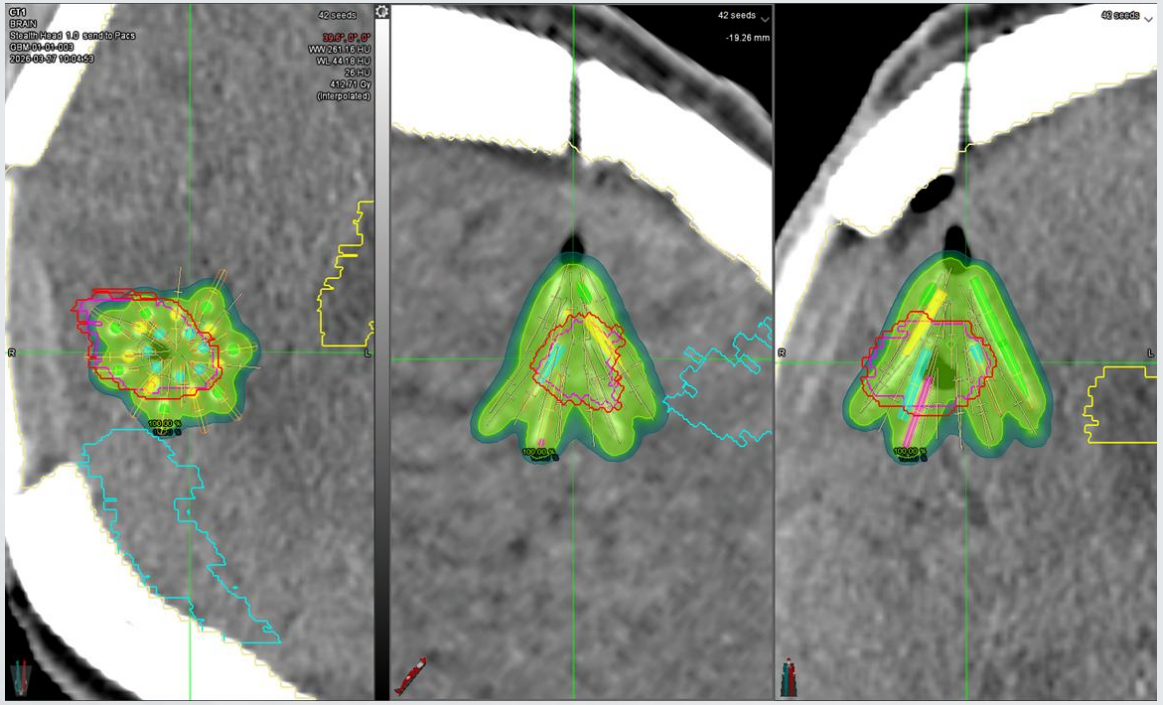
Ax T1 C+ | Ax T2 FLAIR

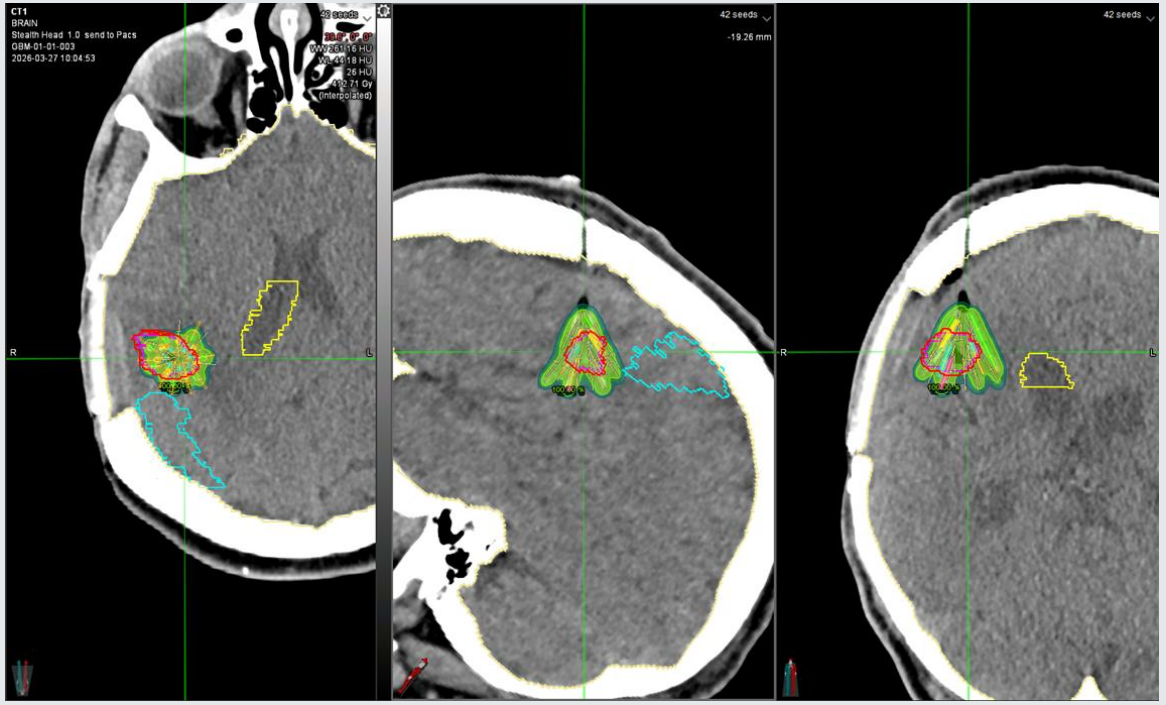
Treatment Plan



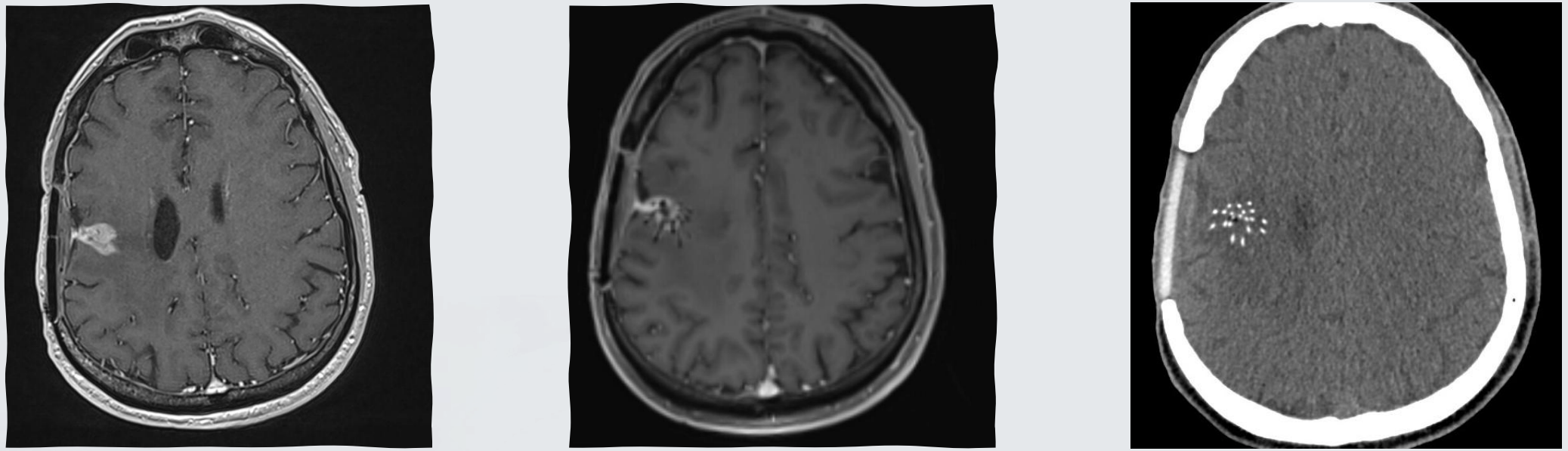


Post Insertion Dosimetry





Alpha DaRT Deployment

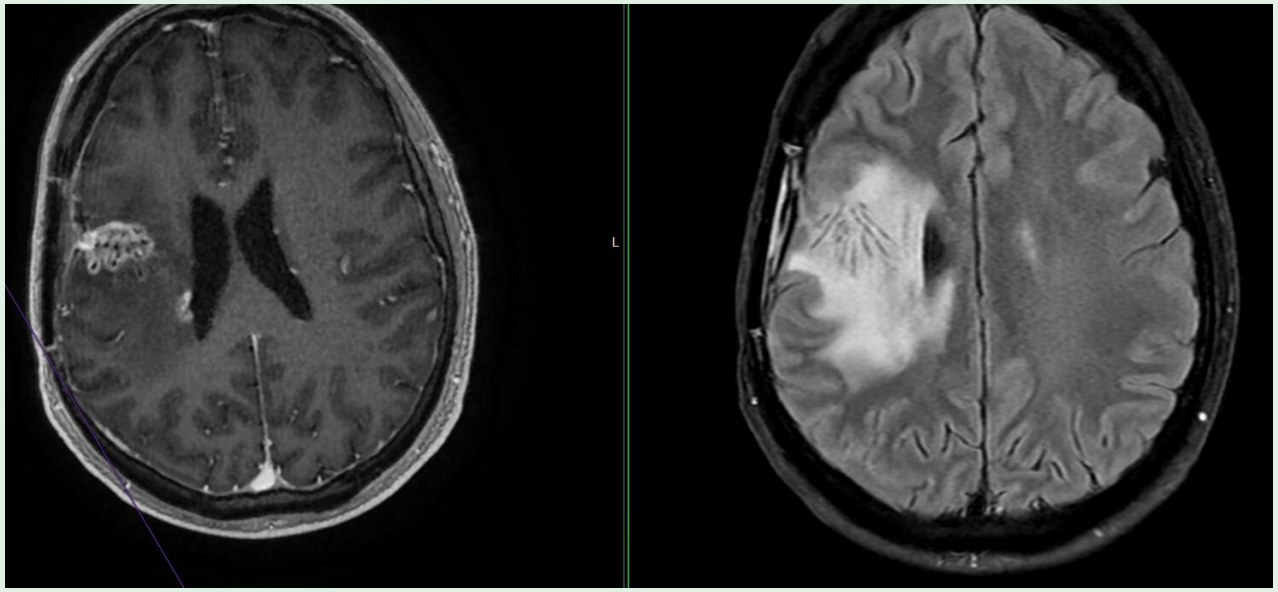


Post-op Day 0 MRI and CT demonstrating accurate deployment

Post Implant Day 3 MRI

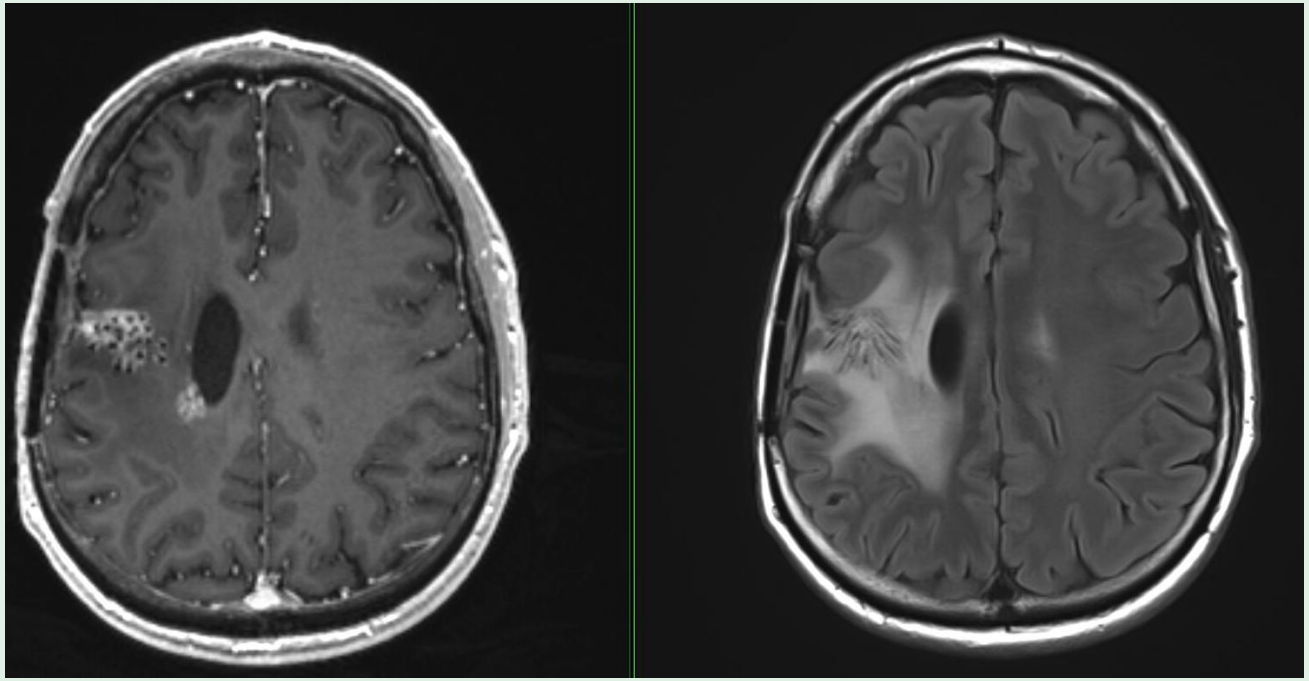
- 3 days post procedure and steroids patient had breakthrough seizure

- MRI showed pseudoprogression with edema and enhancement slightly larger



MRI 1 Month Post Alpha DaRT

- There was a focal enhancement around each Alpha DaRT
- 30% decrease in size
- Confirmed on central neuroradiology review with 2 neuroradiologists
- No new edema around Alpha DaRT



Adverse Events*

- He developed a grade 2 seizure
- His symptoms improved to baseline on steroids and additional imaging showed normalizing edema to pretreatment extent
- Doing well and back to his neurologic baseline
- His most recent response was Stable Disease per RANO criteria with a 30% reduction in size on 1 month MRI

* Interim Data as of 3-May-2026

Summary*

- Three patients have been treated
- There were no unanticipated associated side effects noted
- All patients' tumors have responded with 2 complete responses and one stable disease (30% size reduction)
- Plan for completion of enrollment of 10 patients on this pilot study pending FDA review

* Interim Data as of 3-May-2026

Questions?