10/28/2024

Oncolytic immuno-activation Clinical Trial in Glioblastoma: Preliminary Safety and Feasibility from Longitudinal Injections

E.A. Chiocca, MD PhD

Disclosures and Financial Support

Current Advisor to Insightec, Inc., DNAtrix Inc, Bionaut Therapeutics, Theriva, Inc

Equity interest in DNAtrix, Seneca Therapeutics, Ternalys Therapeutics

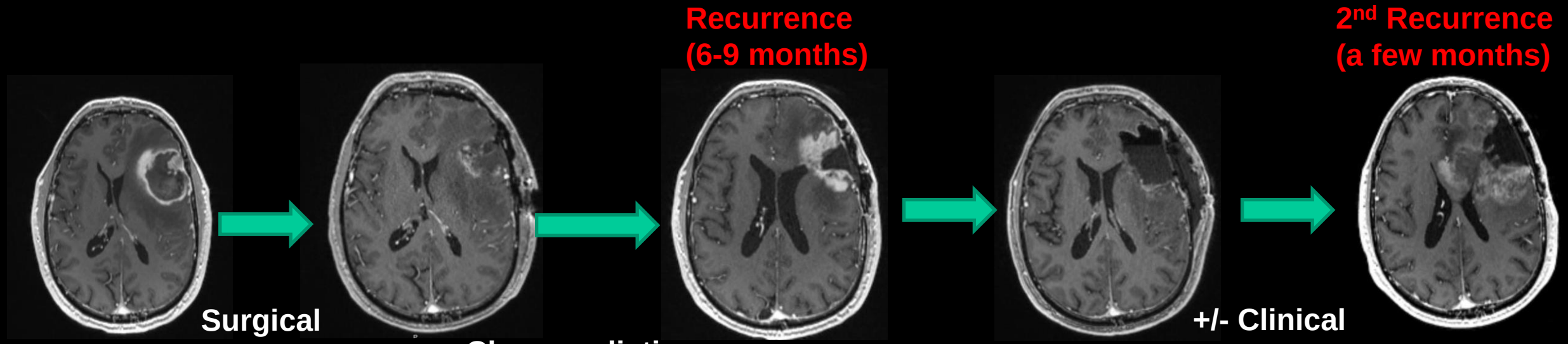
Royalties/ Milestones to MassGeneral Brigham from Candel Therapeutics

Research support from NIH, US Department of Defense, Alliance for Cancer Gene Therapy.

Named inventor on patents related to oncolytic HSV1 (licensed to Candel Therapeutics, Inc) and noncoding RNAs

Founder of Ternalys Therapeutics

Glioblastoma clinical timeline (2024)



Median survival time from initial dx = 15-20 months (but this varies based on genetic and demographic markers)

Clinical trials of targeted therapies and anti-angiogenic therapies have not been successful

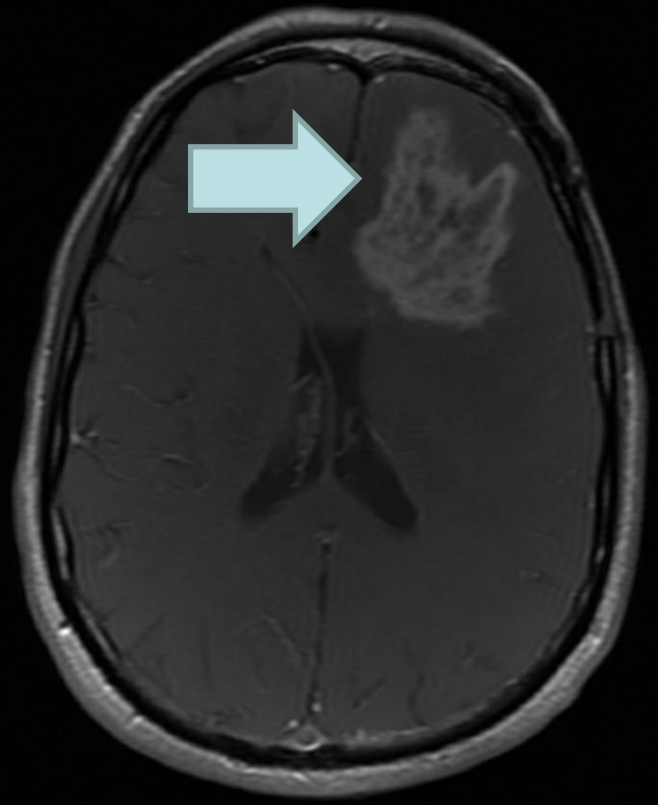
Clinical trials of immune therapy have also not been successful

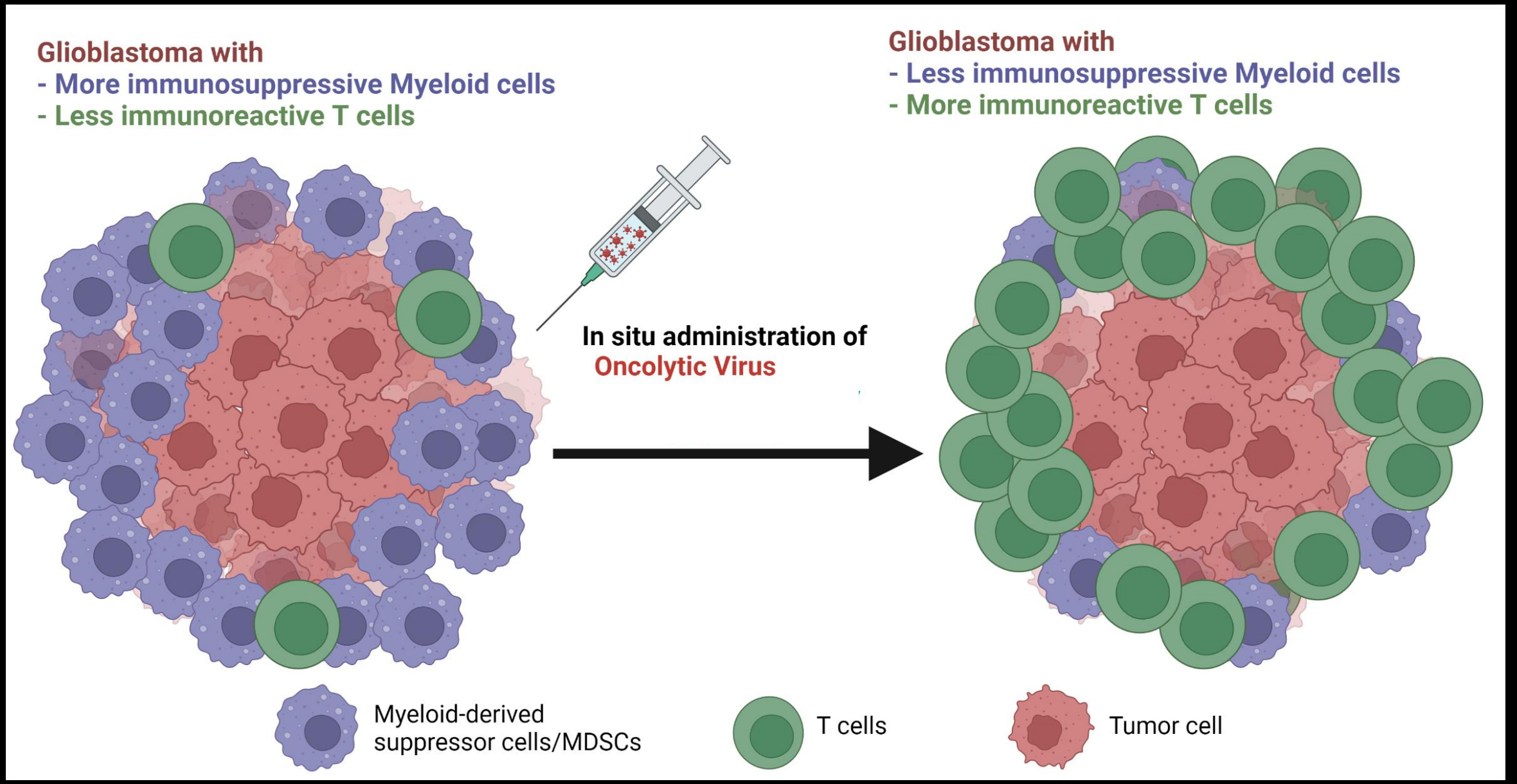
The Problem

For GBM, novel therapies (Immunotherapies) have not been Successful. Why?

Immunological “coldness”
Immune-deserted tumor

Glioblastoma (GBM)

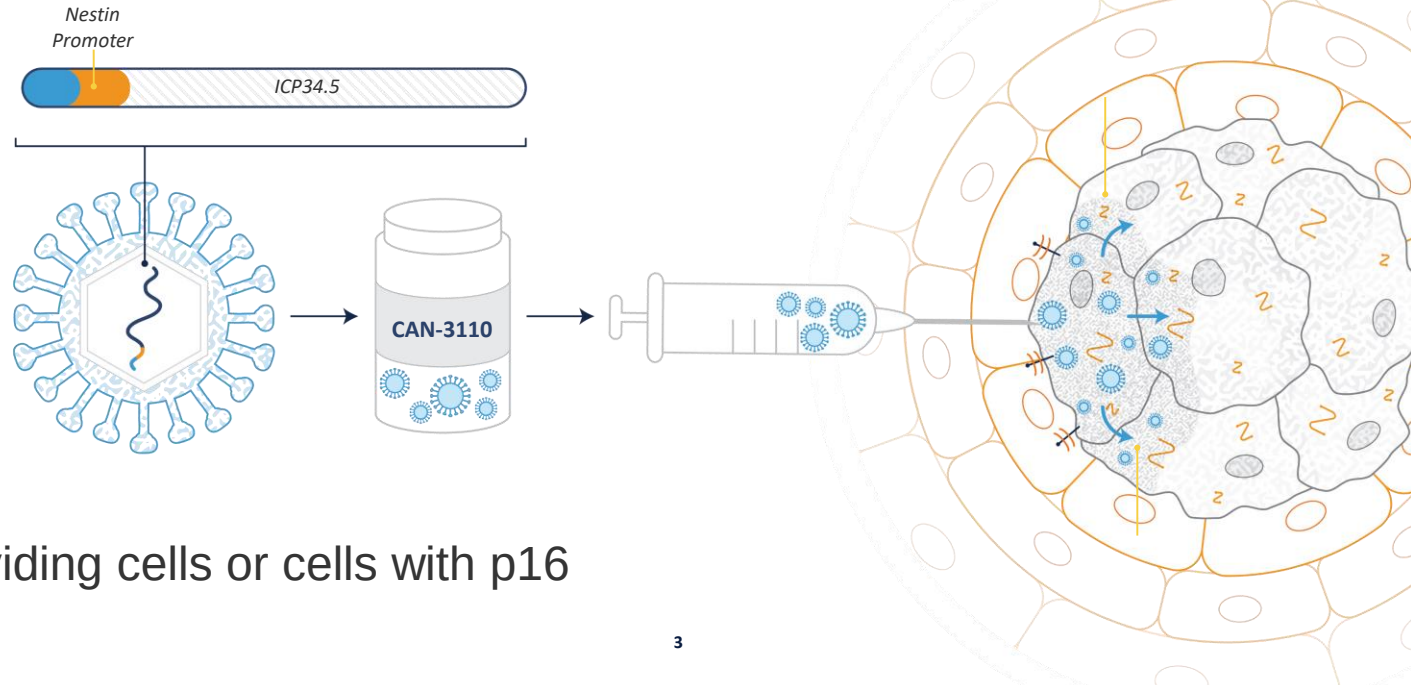



Glioblastoma with
- More immunosuppressive Myeloid cells
- Less immunoreactive T cells
In situ administration of
Oncolytic Virus
Glioblastoma with
- Less immunosuppressive Myeloid cells
- More immunoreactive T cells
Myeloid-derived
suppressor cells/MDSCs
T cells
Tumor cell

CAN-3110 (formerly known as rQNestin34.5v.2, Nakashima et al, 2020 Kambara et al, 2005)

HSV-1 engineered for immunogenic potency and specificity

- ICP34.5-null viruses have shown safety but replicate poorly
- CAN-3110: ICP34.5 expression under control of Nestin promoter
  - Nestin overexpressed in gliomas
  - Improves replication
  - Provides tumor-specific oncolytic activity



Designed for Safety

- Disruption of ICP6 limits virus replication to dividing cells or cells with p16 tumor suppressor pathway defects
- Remains sensitive to anti-herpetic drugs
- Nestin provides tumor specificity in a range of other indications

Steps towards clinical trial (rQnestin34.5v.2, now CAN-3110)

1999: Initial paper/IP on use of tumor-specific promoters to drive expression of ICP34.5 in oHSV

2000: Licensed to newCO/ oHSV GMP sub-contracted to Magenta, Inc.

2000-2001: Magenta “experts” cannot grow oHSV to required titers/ lose MVB

2002: newCO shuts down

2005: rQNestin34.5v.1 paper published/ new IP/meeting with FDA representatives

2005-2007: Re-engineering of rQNestin34.5 to remove FDA “undesirable” sequence (GFP)

2007-2010: Bioequivalency studies to show that rQNestin34.5v.2 is equivalent to rQNestin (FUNDED BY NIH and Alliance for Cancer Gene Therapy)

2010-2011: Production of preclinical/ clinical lots by Dyamid/Periphagen Inc/ preIND meeting with FDA to decide on final tox. Study (FUNDED BY NIH and Alliance for Cancer Gene Therapy

2012-2013: Tox/ BD study (FUNDED BY NIH and Alliance for Cancer Gene Therapy

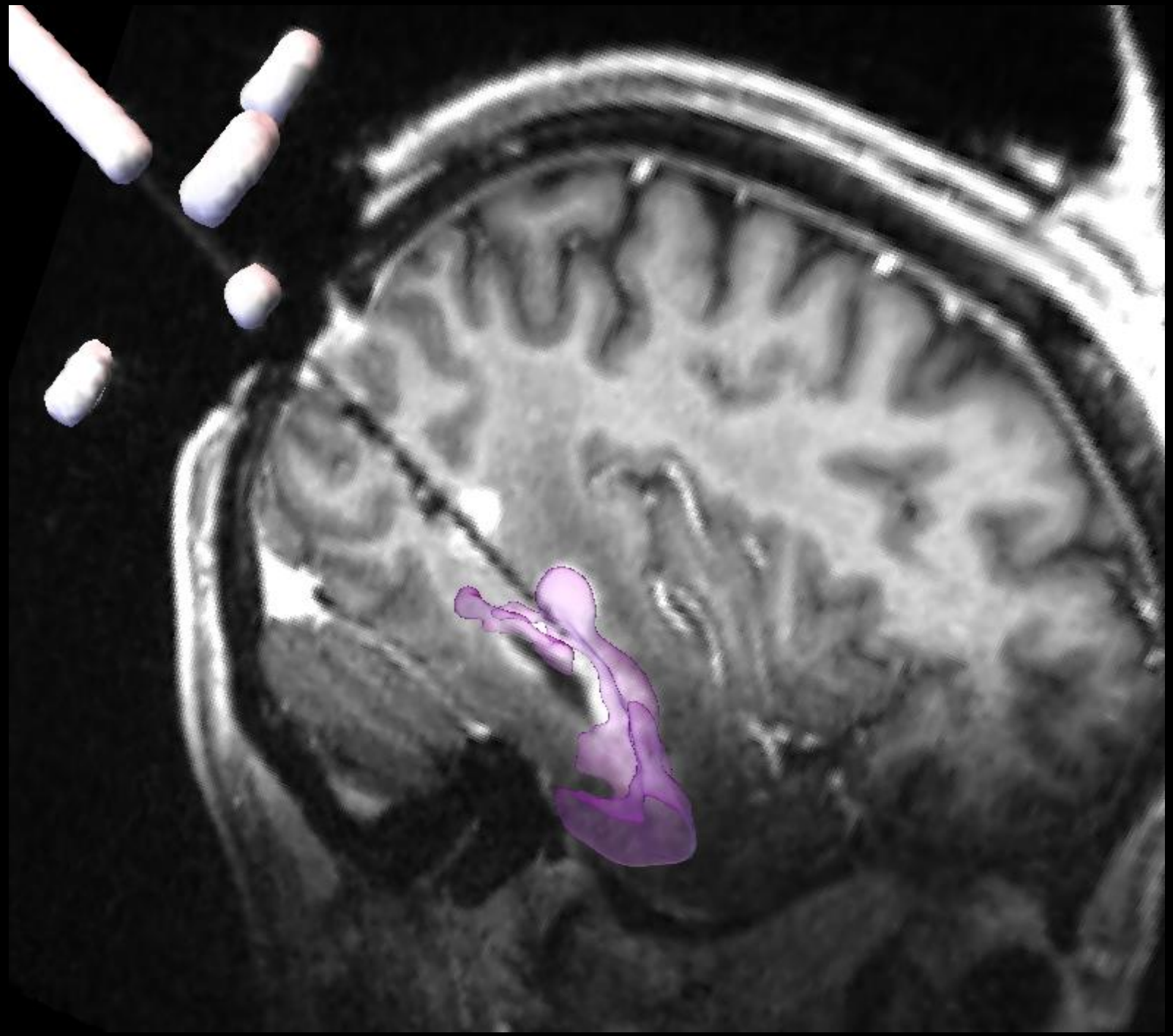
2011-2015: RAC/ file IND

2015-2016: CMC hold on IND/Preclinical and Clinical part of iND approved

2016: Revised IND refiled with answers to hold.

2017: First patient

February 20: 57th Patient treated/ middle of arm C



Ongoing phase 1 clinical trial of CAN-3110 in patients with recurrent high-grade glioma

Patients with recurrent high-grade glioma

Completed →

Dose escalation
Single stereotactic injection of CAN-3110
3+3 dose escalation
1x10⁶ to 1x10¹⁰ PFU in half-log increments

Completed:
30 patients dosed
No dose-limiting toxicity observed
Maximum administered dose: 1x10¹⁰ PFU

Completed →

Dose expansion
1x10⁹ PFU
12 patients dosed as of 30 April 2021

Completed →

Pre Administration of Cytoxan
+1x10⁸ PFU
3 patients dosed
+ 1 x 10⁹ PFU
6 patients dosed

→ Manuscript in preparation

Clinical trial links oncolytic immunoactivation to survival in glioblastoma

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BREAK THROUGH CANCER →

Repeat Dosing (x6)
+1x10⁸ PFU x 6 doses

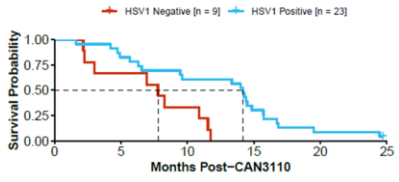
+ 1 x 10⁹ PFU x 6 doses
Multi-institutional

→ Accrual ongoing (6/12)

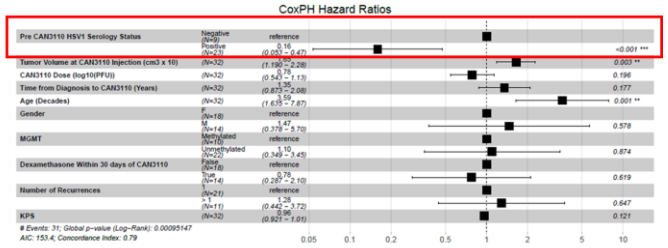
Summary of Arm A from Ling et al, 2023

1. Well tolerated. No DLT up to 10e10 PFUs or with single timepoint injection in up TO 5 regions in tumor

2. Unexpected post-hoc analysis shows that mOS significantly linked to HSV1 serology, which was also a significant independent predictor of response

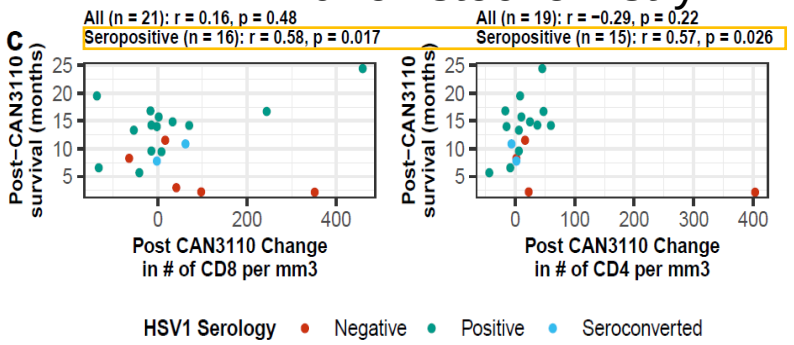


p = 0.007 (likelihood ratio test)

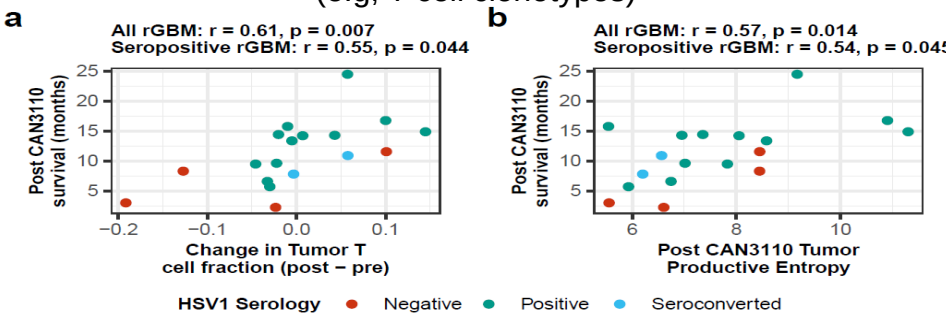


3. OS significantly links in post-CAN3110 tumors to changes in CD4+/CD8+ T cells (IHC), in T cell clonotype frequency and diversity, tumor immune transcriptomic signatures. HSV1 serology links to clearance of CAN-3110 in tumors

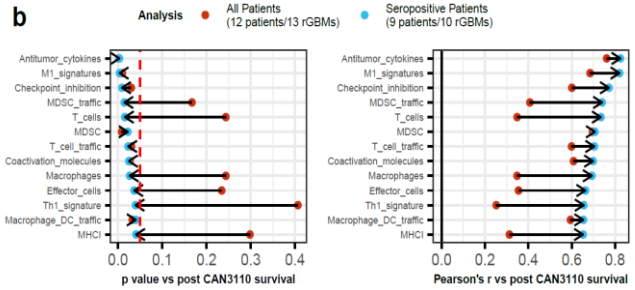
Immunohistochemistry

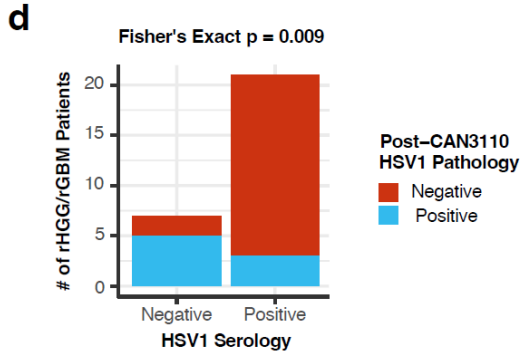


Tumor T cell receptor sequence (e.g, T cell clonotypes)



Tumor Immune Transcriptomic Signatures





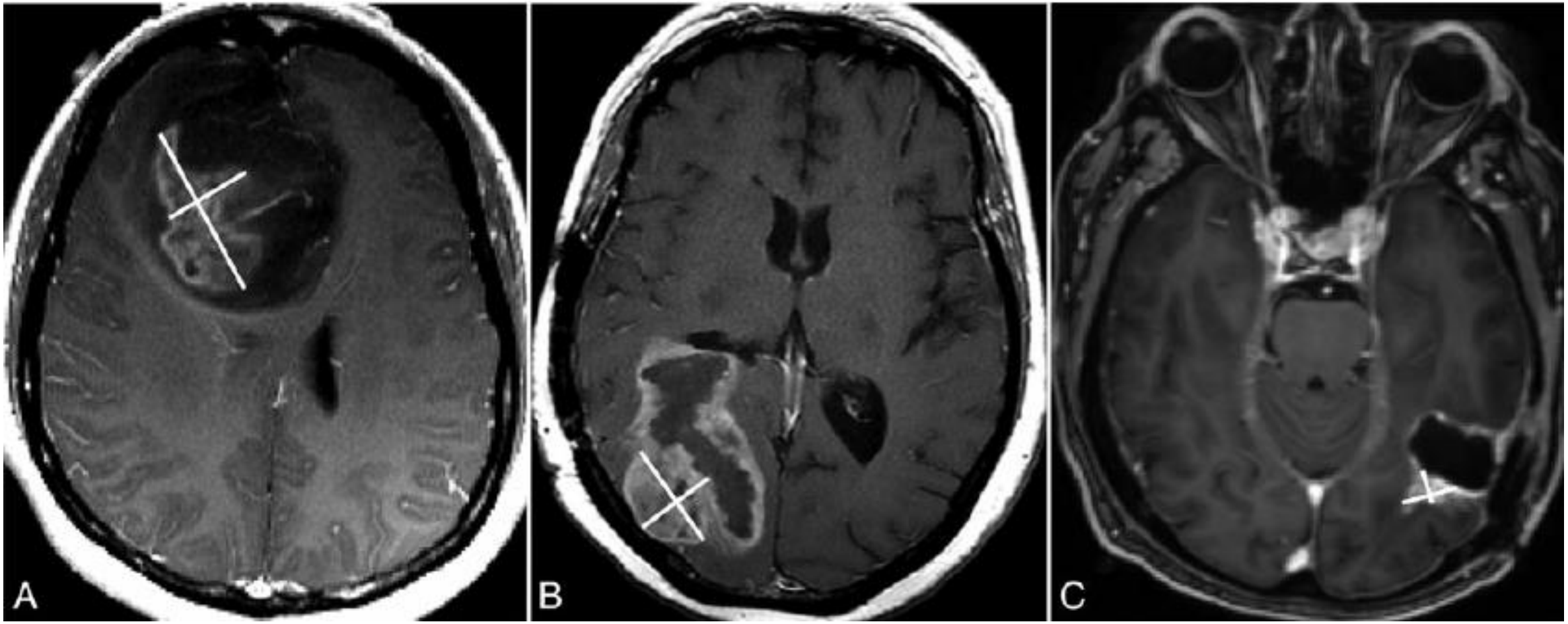
How do we measure responses in clinical trials of cancers like glioblastoma (GBM) ?

- The only accepted “biomarker” of response is imaging by MRI

Criterion	RECIST	MacDonald	RANO
Measurement	1D contrast enhancement	2D contrast enhancement	2D contrast enhancement + T2/FLAIR
Progression	≥20% increase in sum of lesions	≥25% increase in product of perpendicular diameter	≥25% increase in product of perpendicular diameter
Response	≥30% decrease in sum of lesions	≥50% decrease in product of perpendicular diameter	≥50% decrease in product of perpendicular diameter
Durability of response	Optional	Yes (at least 4 week)	Yes (at least 4 week)
Definition of measurability	Yes	No	Yes
Number of target lesions	Up to 5	None specified	Up to 5
T2/FLAIR	Not evaluated	Not evaluated	Evaluated
Corticosteroids considered	No	Yes	Yes
Clinical status considered	No	Yes	Yes
Pseudo-progression considered	No	No	Yes

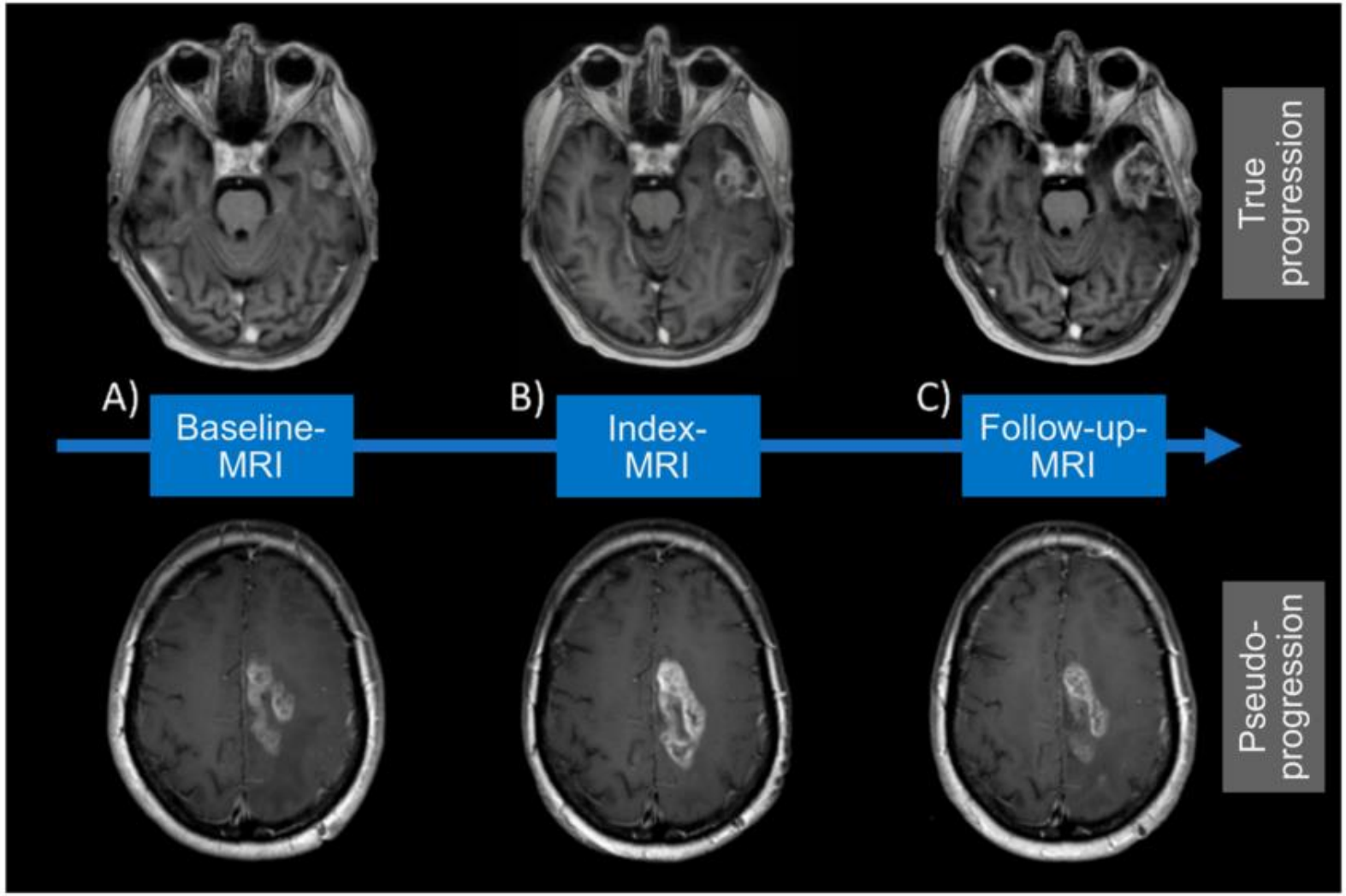
RANO: Response Assessment in Neuro-Oncology; RECIST: Response Evaluation Criteria in Solid Tumors.

Manual 2D measurement in operator-selected MRI slice



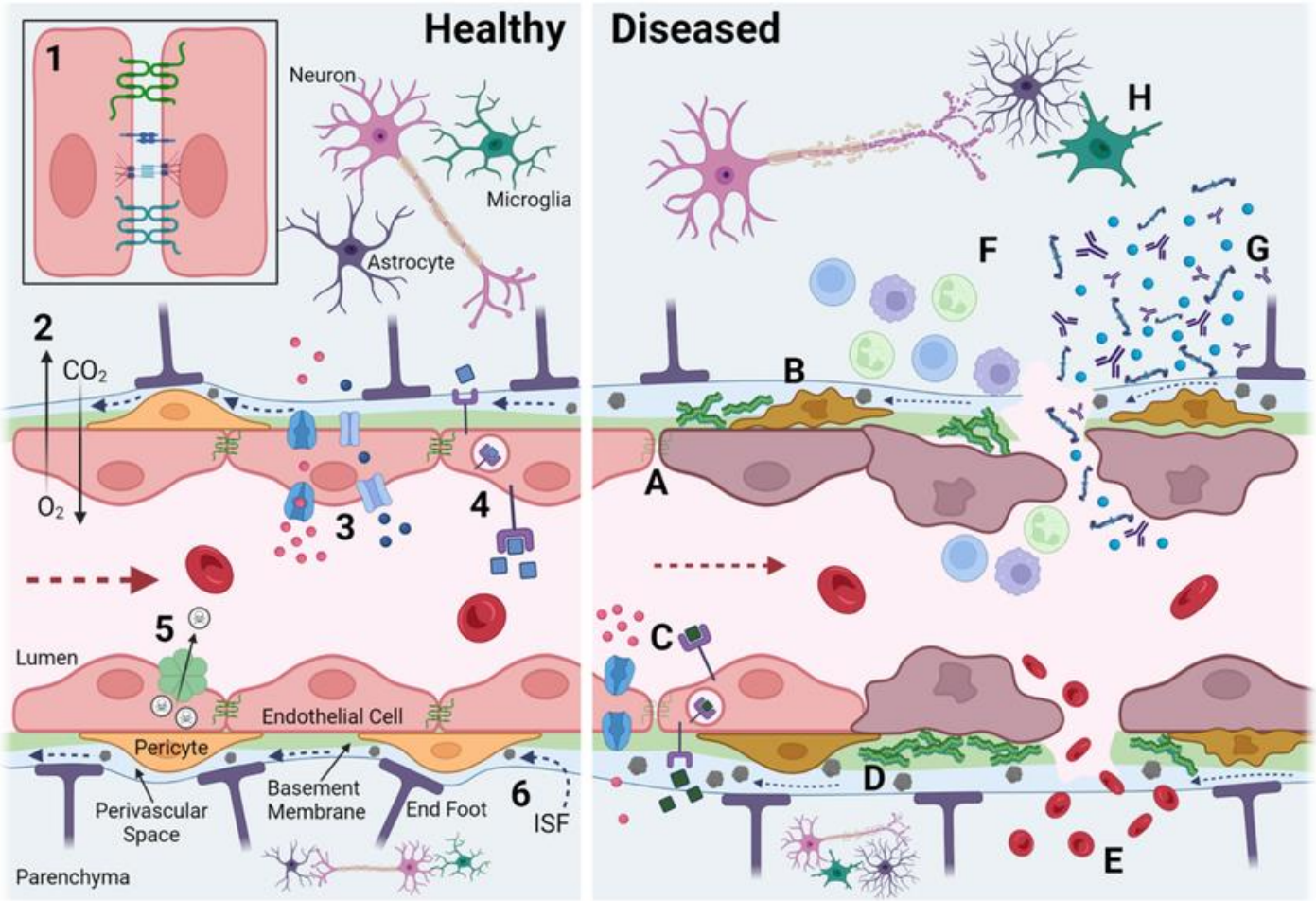
Yang et al, 2015

Limitations of current methods of using gadolinium contrast extravasation in MRI as “biomarker” of response in GBM clinical trials: BBB disruption can occur after radiation



Kebir et al, 2020

Limitations of current methods of using gadolinium contrast extravasation in MRI as “biomarker” of response in GBM oncolytic virus trials: BBB disruption occurs also during inflammation!

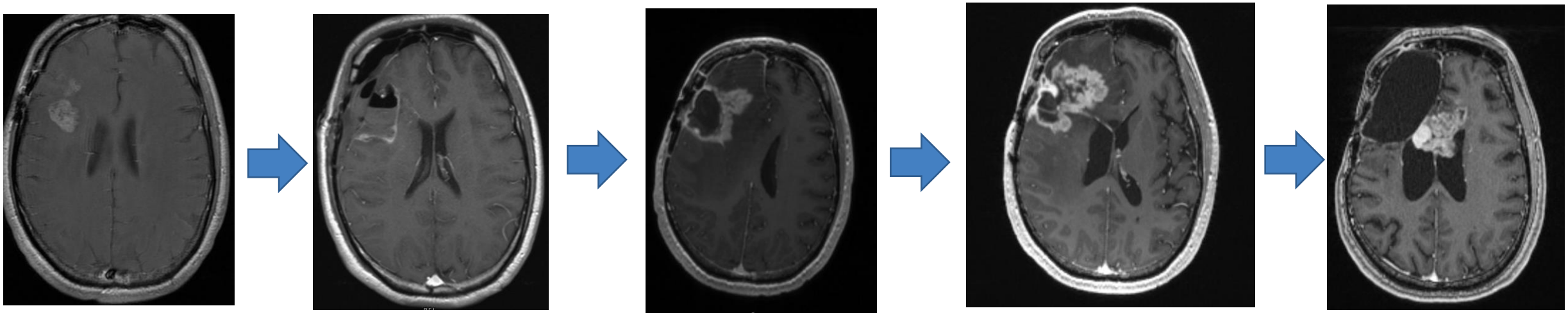


(Frederick et al, 2022)

Why are so many GBM clinical trials failing?
What is the problem?

We never know if the promising therapy actually does what it is supposed to do in patients because we use MRI as the biomarker of response

SOC surgery/ Radiochemotx Clinical Trial 1 Clinical Trial 2 Surgery and Clinical Trial 3



BREAK THROUGH CANCER

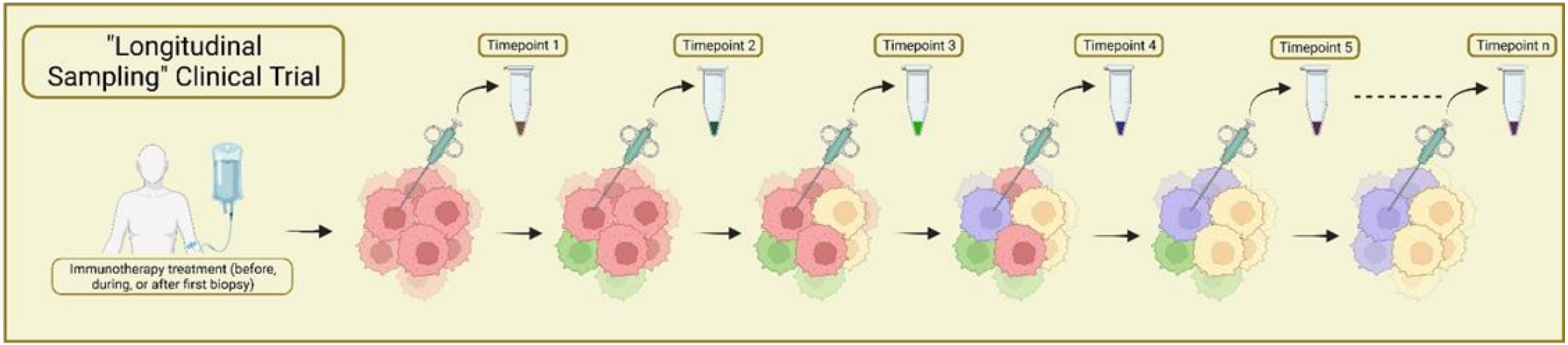
Longitudinal Sampling Platform to Accelerate Development of Therapeutics for Glioblastoma (GBM)

A new clinical trial approach:

GBM TeamLab (MIT, DFCI, BWH, MSKCC, JHU, MDA)

RADICAL**COLLABORATION**

Longitudinal Sampling Clinical Trial for GBM



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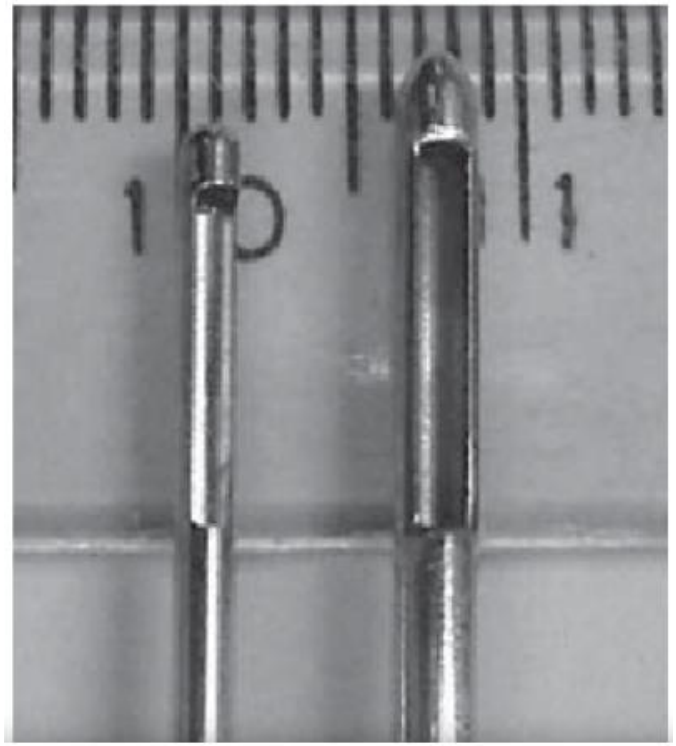
26(2), 211–225, 2024 | https://doi.org/10.1093/neuonc/noad211 | Advance Access date 23 November 2023

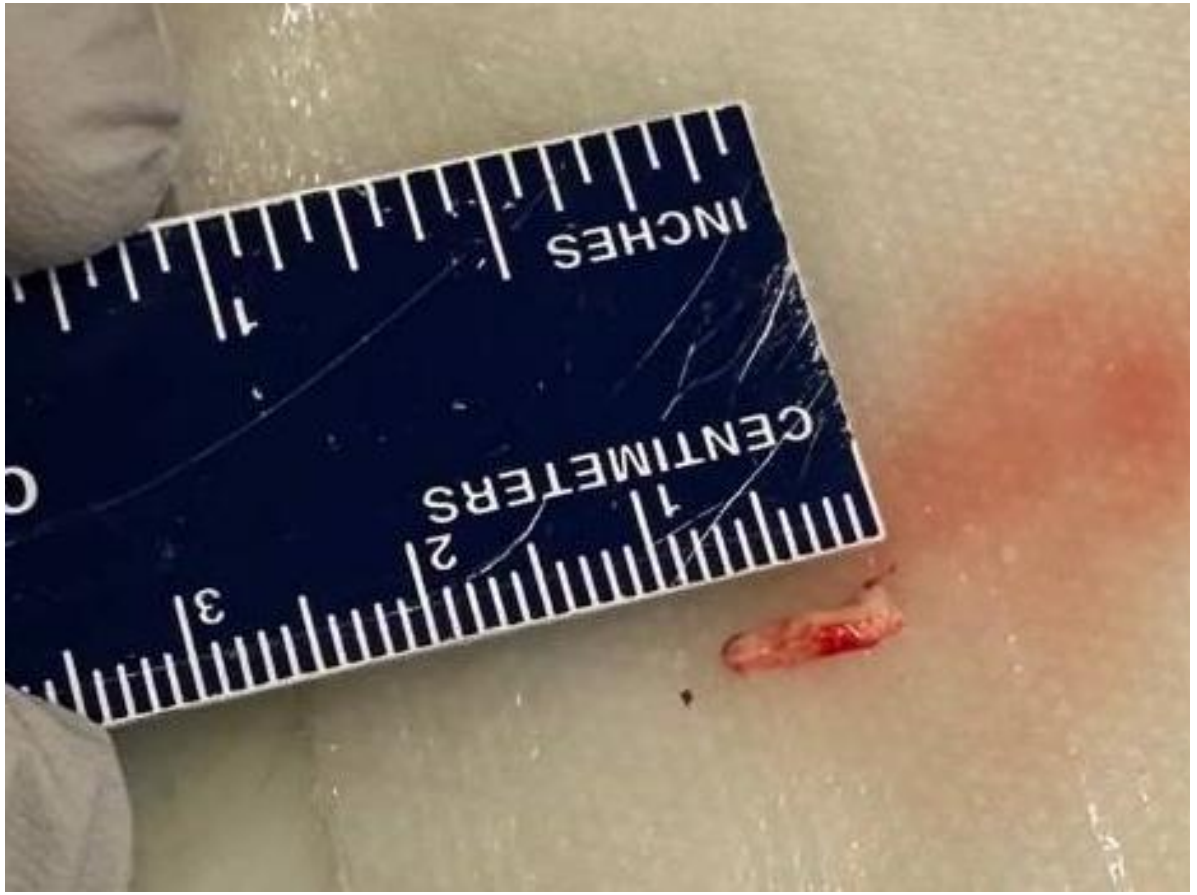
Lessons learned from phase 3 trials of immunotherapy for glioblastoma: Time for longitudinal sampling?

Ethan Chen, Alexander L. Ling, David A. Reardon, and E. Antonio Chiocca*
All author affiliations are listed at the end of the article

Biopsy size

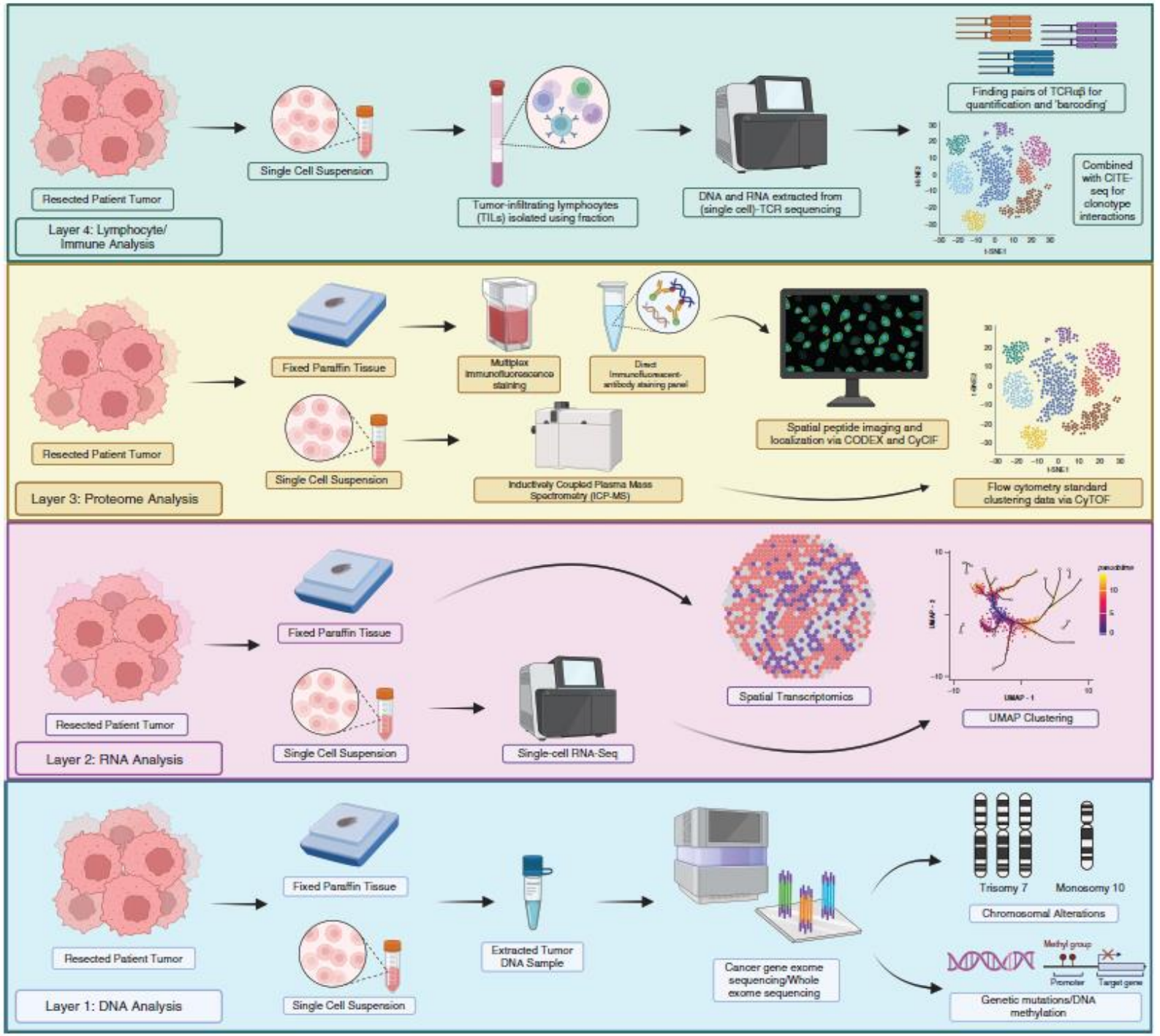


Stereotactic needle has cut window ~ 10 mm x 3 mm.



Stereotactic needle GBM biopsy

What can you do with serially biopsied GBMs?



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Lessons learned from phase 3 trials of immunotherapy for glioblastoma: Time for longitudinal sampling?

Ethan Chen, Alexander L. Ling, David A. Reardon, and E. Antonio Chiocca*
All author affiliations are listed at the end of the article

For the first longitudinal biopsy clinical trial in USA, there is a need to justify the serial procedures

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01897-x

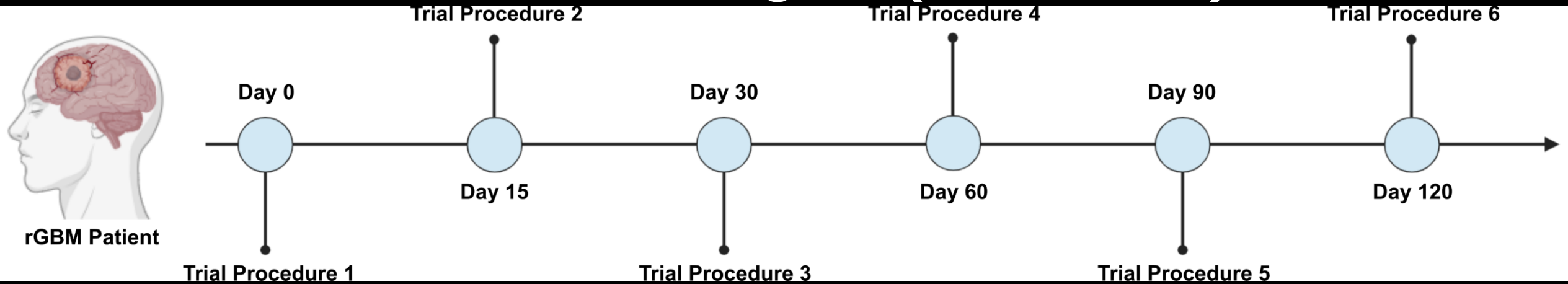
Check for updates

OPEN

Intratumoral oncolytic herpes virus G47Δ for residual or recurrent glioblastoma: a phase 2 trial

Tomoki Todo[1]✉, Hirotaka Ito[1], Yasushi Ino[1], Hiroshi Ohtsu[2,3], Yasunori Ota[4], Junji Shibahara[5] and Minoru Tanaka[1]

Instead of a systemic agent/drug, administer an Intratumoral agent (like an OV)!



Questions

- Can we accrue/ consent patients to undergo multiple serial procedures?
- Can patients tolerate multiple serial procedures without serious adverse events/ dose-limiting toxicities and/or “serial procedure” limiting toxicity?
- Can we obtain biopsies from multiple sites in tumor?
- How many biopsies can be obtained?
- Will be each biopsy be of sufficient quality and quantity to obtain useful scientific data via “omics” approaches?

DF/HCC Trial #16-557 Arm C Status

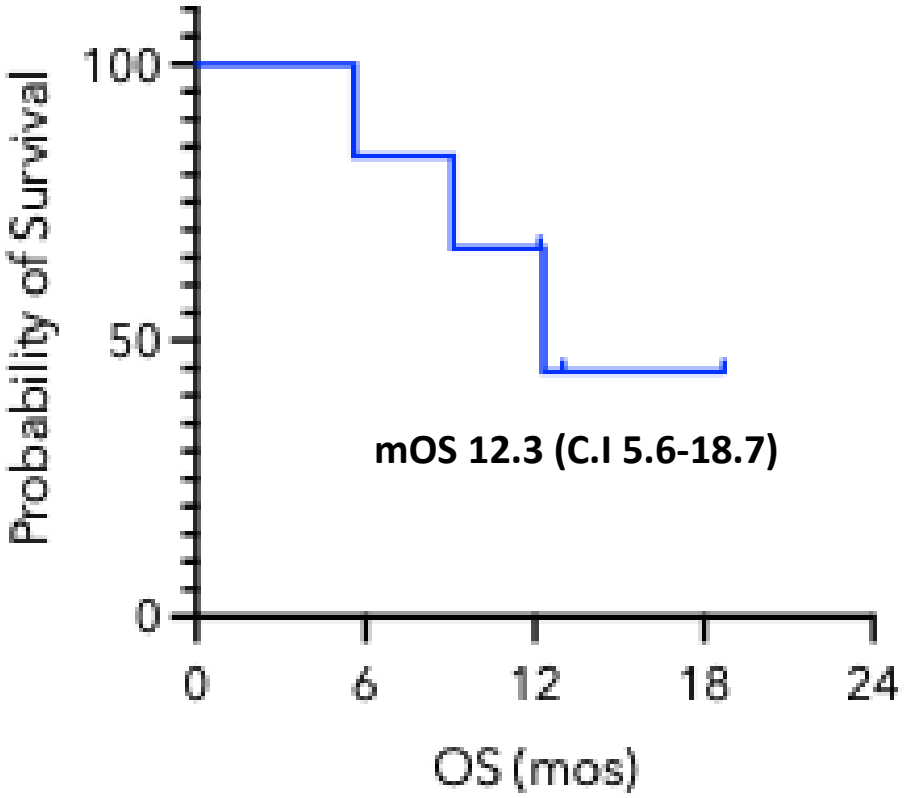
	Day 0	Day 15	Day 30	Day 60	Day 90	Day 120	
Patient 1	6 biopsies 1 Location ✓	6 biopsies 1 Location ✓	8 biopsies 1 Location ✓	6 biopsies 1 Location ✓	✗	✗	Completed
Patient 2	9 biopsies 1 Location ✓	6 biopsies 1 Location ✓	5 biopsies 1 Location ✓	13 biopsies 2 Locations ✓	12 biopsies 2 Locations ✓	12 biopsies 2 Locations ✓	Completed
Patient 3	16 biopsies 2 Locations ✓	14 biopsies 2 Locations ✓	18 biopsies 4 Locations ✓	26 biopsies 4 Locations ✓	18 biopsies 2 Locations ✓	16 biopsies 2 Locations ✓	Completed
Patient 4	8 biopsies 1 Location ✓	8 biopsies 1 Location ✓	16 biopsies 2 Locations ✓	14 biopsies 2 Locations ✓	21 biopsies 2 Locations ✓	✗	Completed
Patient 5	10 biopsies 1 Location ✓	10 biopsies 1 Location ✓	10 biopsies 1 Location ✓	20 biopsies 2 Locations ✓	✗	✗	Completed
Patient 6	8 biopsies 1 Location ✓	6 biopsies 1 Location ✓	7 biopsies 1 Location ✓	6 biopsies 1 Location ✓	✗	✗	Completed

No Serious Adverse Events or DLTs from serial biopsies or serial CAN-3110 injections

Treatment with multiple injections of CAN-3110 is associated with survival that exceeds 12 months in 3/6 rGBM subjects

Francesca Barone, MD PhD (Candel Therapeutics)

Six out of 12 patients have been treated in arm C with 1x10^8 pfu



Patient	Sex	Age	MTMG status	#injections	OS in months	Status
1	54	M	unmet	4	12.3	D
2	66	F	unmet	6	18.7	A
3	75	F	meth	6	9.1	D
4	64	M	unmet	5	13.0	A
5	61	F	unmet	4	12.2	A
6	69	F	unmet	4	5.6	D

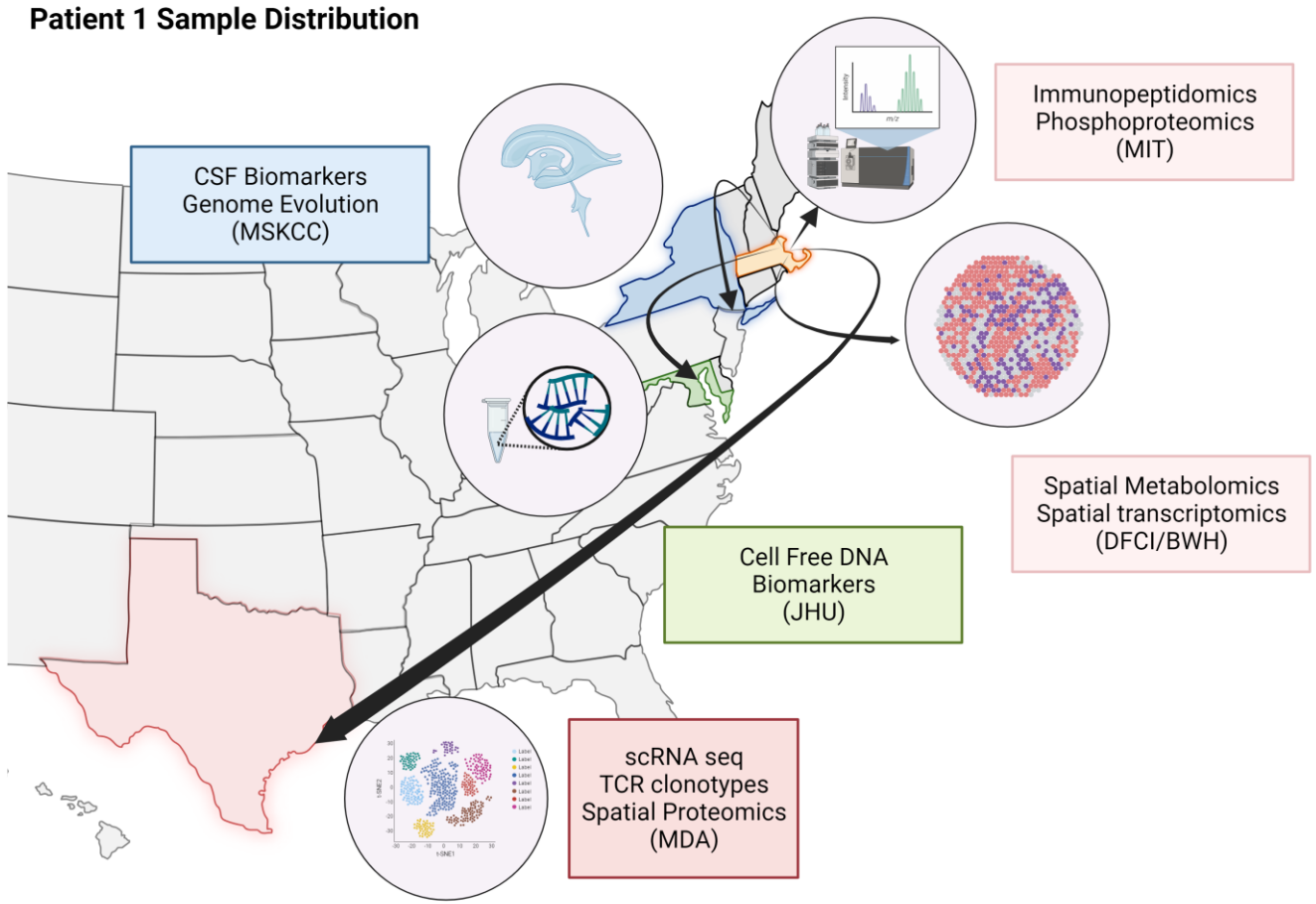
MTMG = O6-methylguanine-DNA methyltransferase
methylation status: unmet=unmethylated, met=methylated

Data cutoff October 24th 2024

How do we make it work? “It takes a village”!

IND/ Clinical trial protocols/clinical data acquisition
Agent storage and maintenance/ FDA/
rgeries and patient care/ Sample collection: tumor, csf, pbmcs)
(Brigham)
Nafisa Masud; Dan Triggs; Jen Gantchev, PhD; Mike Regan;
Mike Prabhu; Brigham research pharmacy group

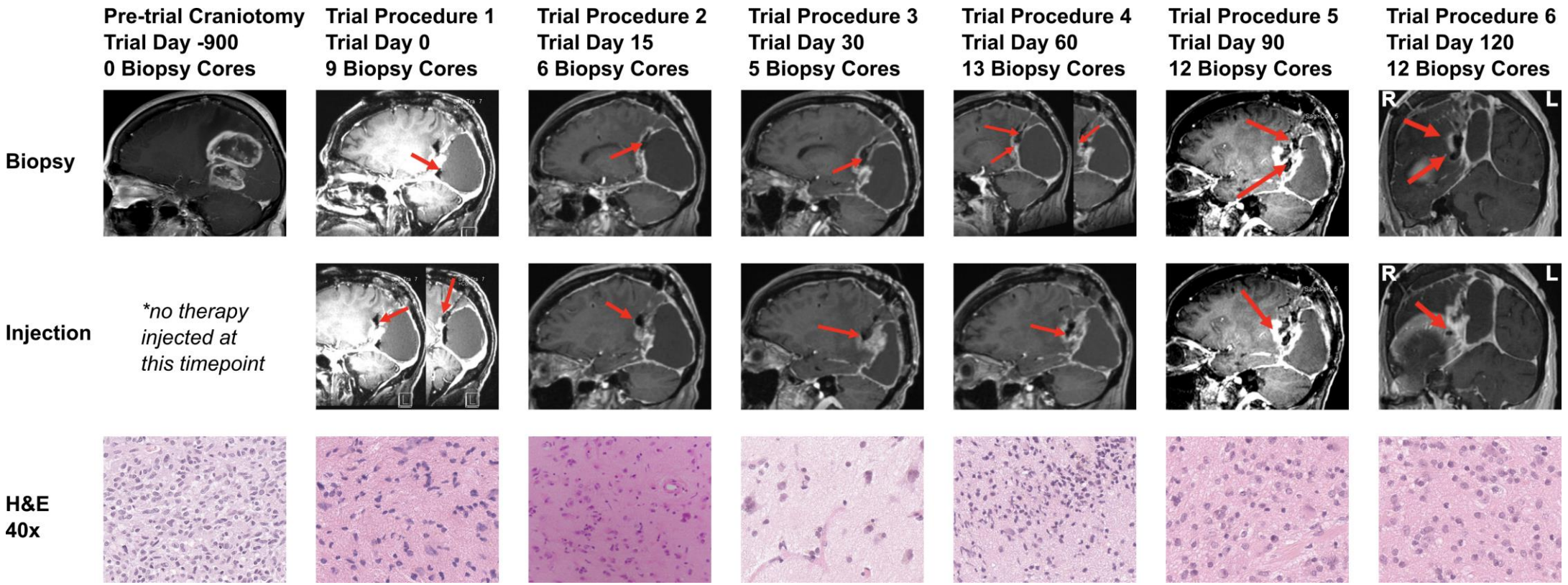
IND/IRB/ Multi-institutional regulatory/ audit/ monitoring
(DFCI)
Jen Willey; Maria Lavalee; Kathy Partridge



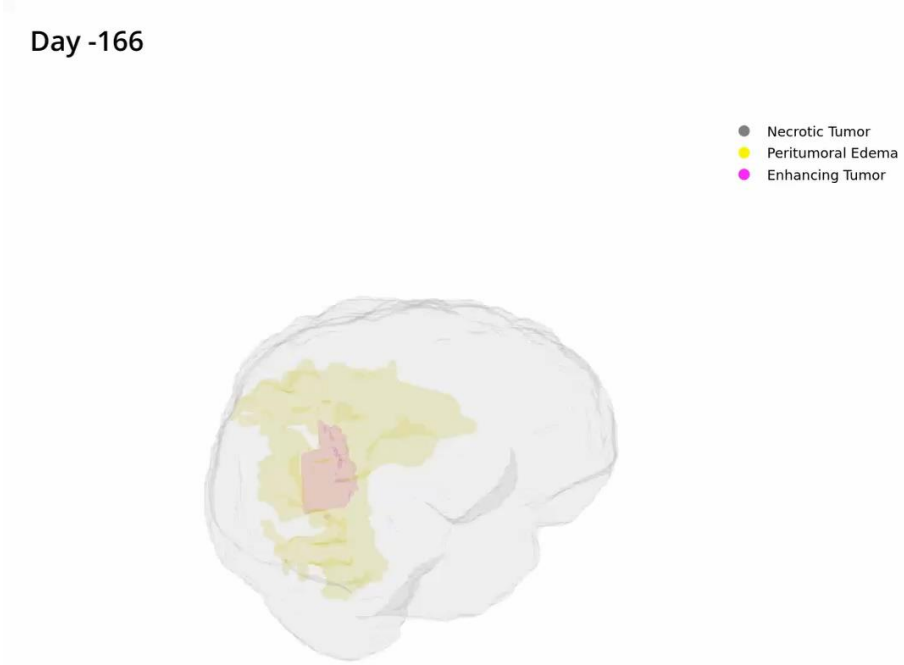
BTC GBM biospecimen allocation flow chart

Core 1	Permanent QC H&E and FFPE
	DNA/RNA Extraction for eventual bulk RNA/DNA seq from FFPE sections
	Digital Pathology analysis (Dr. Huse MDACC)
	CODEX Spatial Protein Imaging IF (TBD)
Core 2	Single Cell RNA Sorting and Sequencing (Sharma lab MDACC) T/BCR Sequencing (Sharma lab MDACC)
Core 3	
Core 4	QC H&E, IF and Spatial Metabolomics (Agar lab DFCI)
	RT-PCR for virus detection (Chiocca lab DFCI)
	Phosphoproteomic Analysis (White lab MIT)
	DNA/RNA Bulk Sequencing (Cima/Koch Core Lab MIT)
Core 5	Immunopeptidomics (White lab MIT)
Core 6	S1: Patient-Derived Model Generation (CPDM/Ligon lab DFCI) for central characterization (seq and QC) S2-S6: Banked for Backup Assays (Ligon lab DFCI)
CSF	Cell counting, separation and collection of cellular and acellular material CITE-Seq Analysis Metabolomics ctDNA Sequencing (Boire lab MSKCC)
Blood	Collection of plasma and PBMCs ctDNA Sequencing TCRβ DNA Sequencing (Bettegowda lab JHM)

Although MRI scans show increased enhancement with each timepoint (tumor progression?), traditional histology shows increased inflammatory reaction at each timepoint

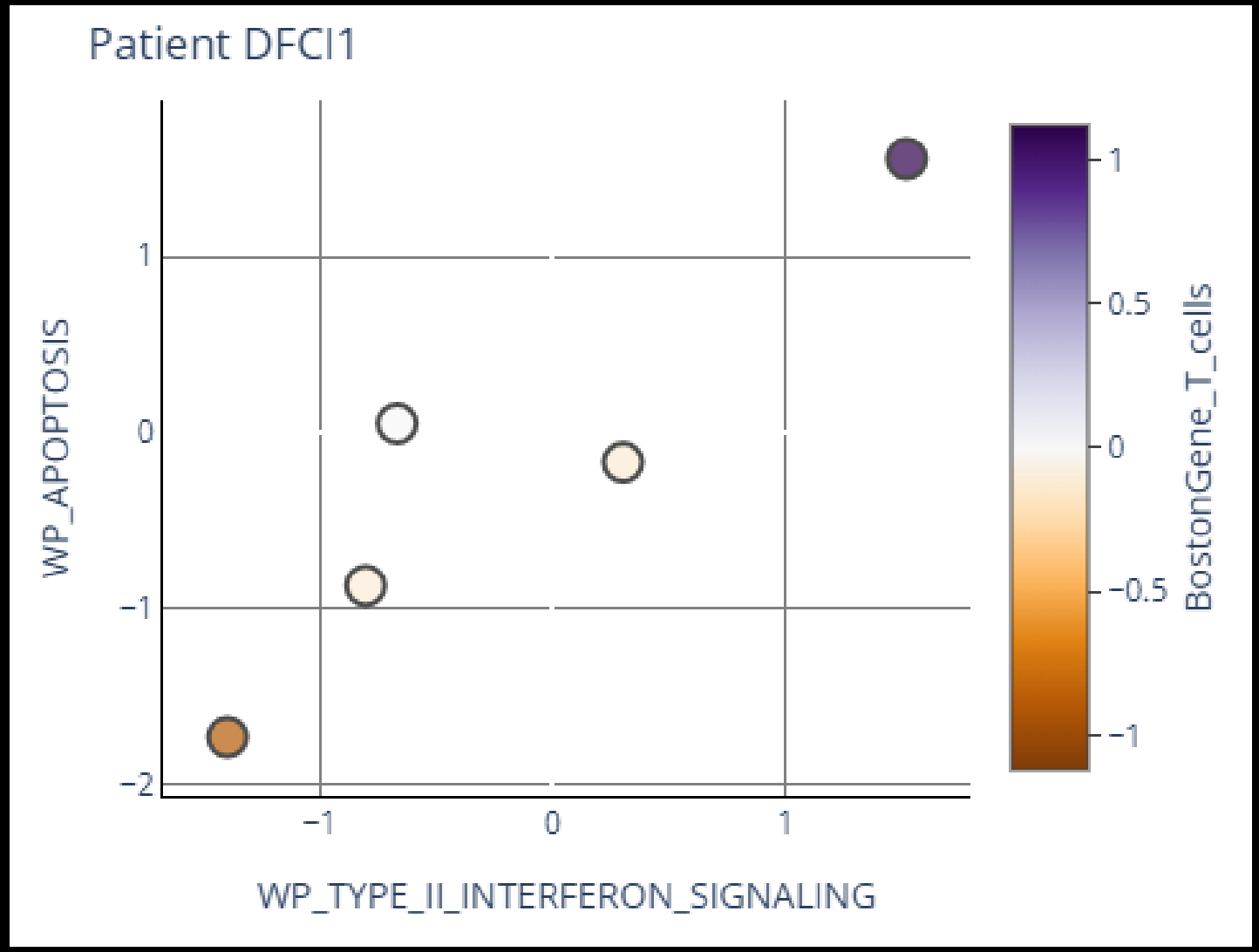


How do we spatially and longitudinally localize each biopsy site with the MRI?



Alex L. Ling PhD
(BWH Neurosurgery)

Integrated multimodal spatial and longitudinal analyses of collected serial biopsies



Alex L. Ling PhD
(BWH Neurosurgery)

Questions

- Can we accrue/ consent patients to undergo multiple serial procedures? YES
- Can patients tolerate multiple serial procedures without serious adverse events/ dose-limiting toxicities and/or “serial procedure” limiting toxicity? YES
- Can we obtain biopsies from multiple sites in tumor? YES
- How many biopsies can be obtained? 6-26 (total > 300)
- Will be each biopsy be of sufficient quality and quantity to obtain useful scientific data via “omics” approaches? Yes

Summary

- Longitudinal injections of CAN-3110 with serial biopsies are well tolerated. Preliminarily mOS is 12.3 months with 3/6 patients alive
- Concomitant serial MRIs show increased enhancement (Progression?), but traditional histology shows increased inflammation
- Serial biopsies currently being analyzed by integrated multimodal -omics (single cell RANseq, proteomics, clonal evolution, spatial transcriptomics and proteomics)
- The integrated –omics studies are being super-imposed onto the spatial and longitudinal MRI data

Current GBM TeamLab Members

...likely addition of new members in years ahead

Zaki Abou Mrad
Nathalie Agar
Ryuhjin Ahn
Kadir Akdemir
Tejus Bale
Anna Ball
Gerard Baquer
Sreyashi Basu
Rameen Beroukhim
Chetan Bettegowda
Adrienne Boire
Cameron Brennan
Gregory Buchold
Qun Cao
Xiao-hua Chen
E. Antonio Chiocca
Kate Cho
Ugonma Chukueke
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Christopher Douville
Dina Elharouni
Sarah Frisken
Jennifer Gantchev
Alexandra Giantini
Sangeeta Goswami
JongHoon Ha
Matthias Holdhoff
Kelsey Hopland
Amin Hossain
Jian Hu
Harry Huo
Jason Huse
Wen Jiang
Sonali Jindal
Kathy Judge
Betty Kim
Frederick Lang
Stuart Levine
Jiyong Liang
Keith Ligon
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Calixto-Hope Lucas
Nafisa Masud
Ingo Mellinghoff
Franzisca Michor
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Hiroshi Nakashima
Subhiksha Nandakumar
Michal Oskar Nowicki
Shahiba Ogilvie
Brittany Parker Kerrigan
Kathryn Partridge
Raziye Piranlioglu
Marla Polk
Michael Prabhu
Antoinette Price
Vinay Puduvalli
David Reardon
Michael Regan
Jordina Rincon Torroella
Nikki Schultz
Sohrab Shah
Padmanee Sharma
Pratibha Sharma
Isaac Solomon
Himanshu Soni
Amanda Spearman
Sylwia Stopka
Viviane Tabar
Daniel Triggs
Logan Tritto
Jayne Vogelzang
Xinjun Wang
Chetna Wathoo
Shiao-Pei Weathers
Jeffrey Webb
Forest White
Jennifer Wiley
Jessica Wollett
Jihong Xu
Lingqun Ye
Kenny Yu
Ying Yuan