UPDATES ON IMMUNOTHERAPY FOR PRIMARY BRAIN TUMORS

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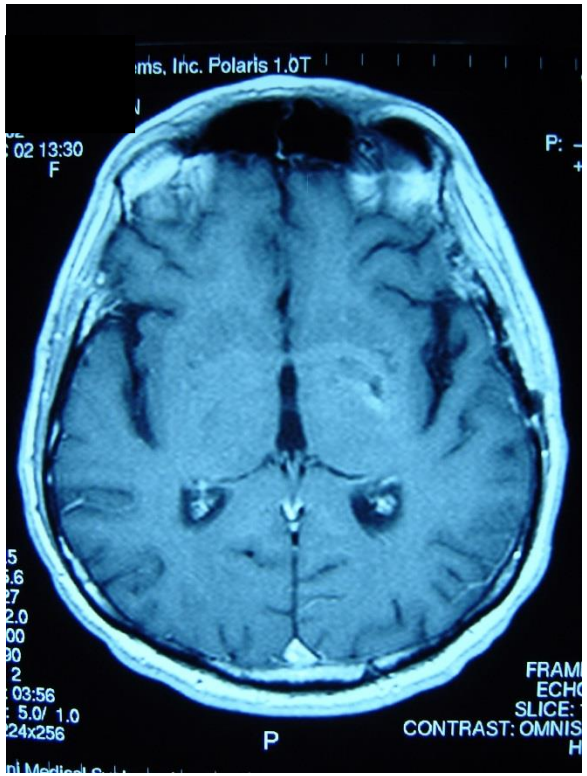
Disclosures

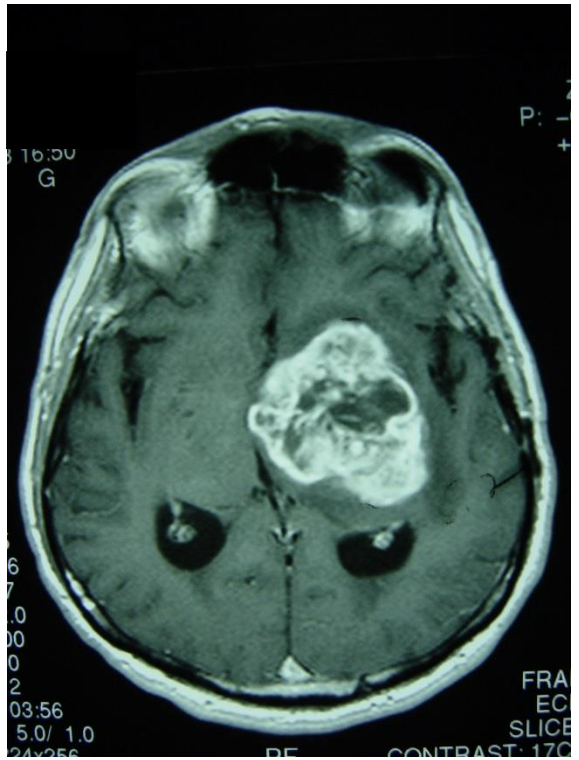
- I have nothing to disclose.

Glioblastoma (GBM)

- GBMs are aggressive gliomas, notoriously invasive, rendering complete surgical resection impossible.
- Remains the most common brain tumor in adults, less than 10% patients live beyond 5 years from diagnosis, with median survival less than 20 months.
    - With surgery, chemotherapy, alternating electrical fields, radiation (Alexander & Cloughesy, 2017; Stupp et al., 2017).
- Even in children and young adults, brain tumors remain the leading cause of cancer-related deaths (Pollack, Agnihotri, & Broniscer, 2019)
- Because the blood-brain barrier (BBB) precludes the transmission of many standard therapies, Neuro-oncologists are desperate for novel therapies.

GBM





Dec 2002

March 2003

Estimated % of deaths and new cases 2020

Estimated Deaths

Male			Female		
Lung & bronchus	72,500	23%	Lung & bronchus	63,220	22%
Prostate	33,330	10%	Breast	42,170	15%
Colon & rectum	28,630	9%	Colon & rectum	24,570	9%
Pancreas	24,640	8%	Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%	Ovary	13,940	5%
Leukemia	13,420	4%	Uterine corpus	12,590	4%
Esophagus	13,100	4%	Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%	Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%	Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%	Brain & other nervous system	7,830	3%
All sites	**321,160**		**All sites**	**285,360**	

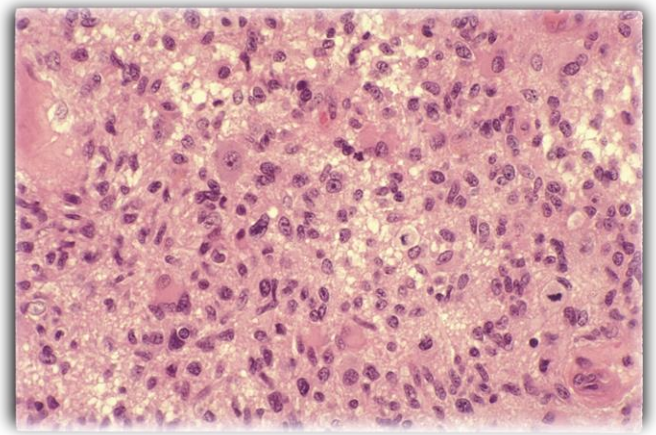
Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

According to the Central **Brain Tumor** Registry of the United States (CBTRUS), in **2019**, it is **estimated** that 84,170 **new** cases of **primary malignant** and non-**malignant brain** and other CNS **tumors** will be **diagnosed** in the United States in 2021.

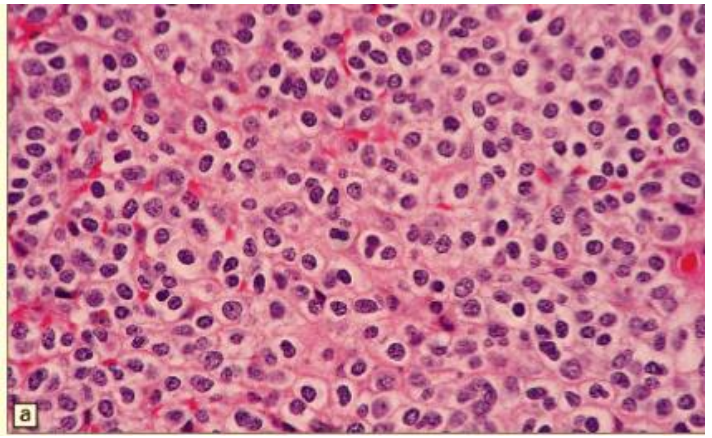
(CBTRUS, 2020)

Gliomas: W.H.O. Grading System

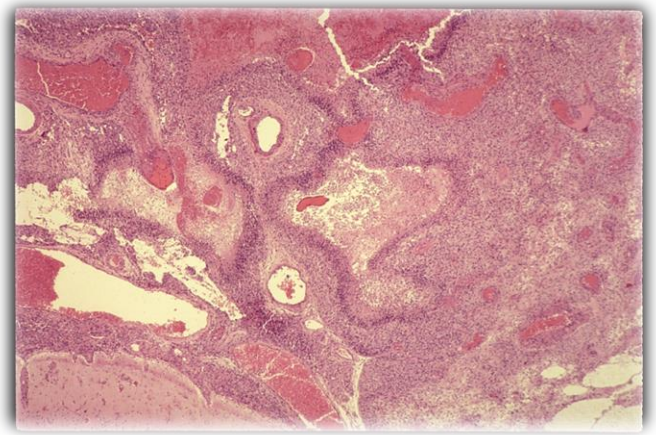
Anaplastic Features	Grade	Incidence
None	I	Rare
Nuclear atypia	II	~15%
Mitosis	III	~30%
Vascular endothelial proliferation	IV	50-60%
Necrosis	IV	



Grade III Astrocytoma



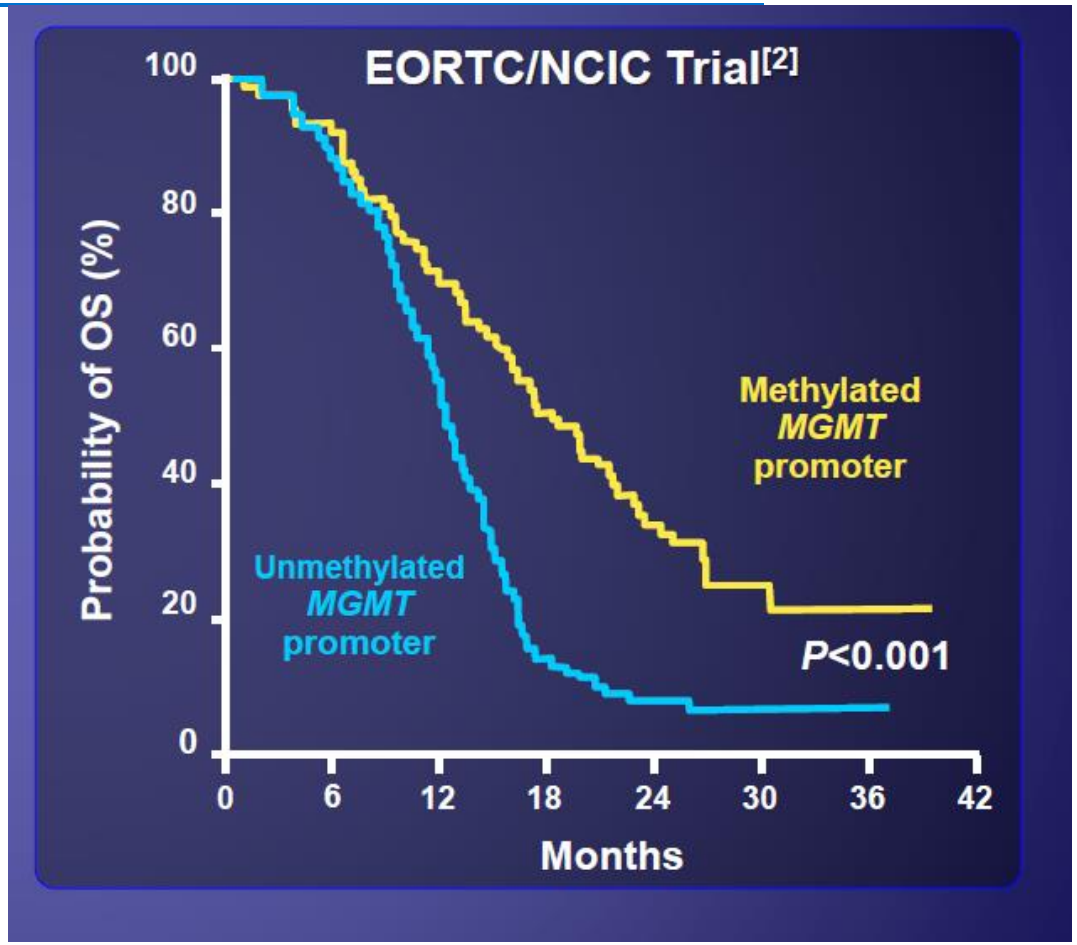
Anaplastic Oligodendroglioma



Grade IV Astrocytoma
Glioblastoma (GBM)

MGMT (O^6-Methylguanine-DNA Methyl Transferase)

- MGMT is an enzyme that repairs damage to DNA from alkylating agents.
- Methylation (inactivation) of the MGMT gene results in lower levels of MGMT in tumor.
- **Methylated MGMT** occurs in 50% of GBM pts
  - A prognostic factor for GBM patients
  - A predictive factor for response to treatment with an alkylating agent (temozolomide, BCNU)



(Hegi et al., 2005)

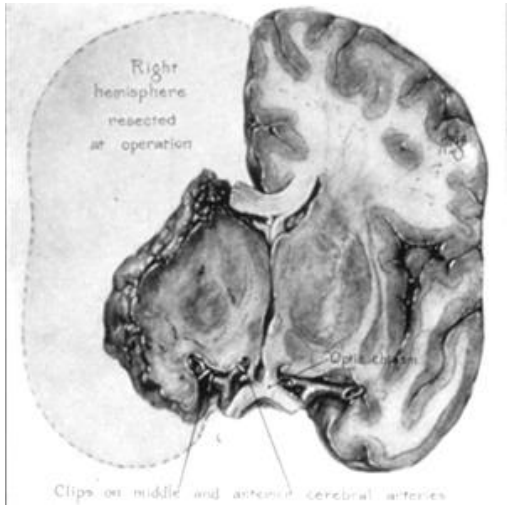
Select Biomarkers in Glioblastoma

Biomarker	Prognostic Indication	Prognostic Association: Favorable	Prognostic Association: Poor
MGMT methylation[1]	• Methylated in 30%–60% of cases • Methylated *MGMT* increases response to chemotherapy • Unmethylated *MGMT* decreases response to chemotherapy	✓	
IDH1/2 mutations[2,3]	• More common in lower grade glial tumors • IDH1/2 mutation occurs in approximately 3.7% of primary GBMs versus 73.3% in secondary GBM	✓	
EGFR amplification[4,5]	Observed in ~50% of primary glioblastomas		✓
EGFRvIII mutation[4]	• *EGFR*-amplified cells often contain *EGFRvIII* mutation, which confers constitutive activity • 30% glioblastoma tumors express *EGFRvIII*		✓

(Johnson et al., 2012; McNamara, Sahebjam, & Mason, 2013; Nobusawa, Watanabe, Kleihues, & Ohgaki, 2009; Preusser et al., 2011; Stupp et al., 2014; Yan et al., 2009)

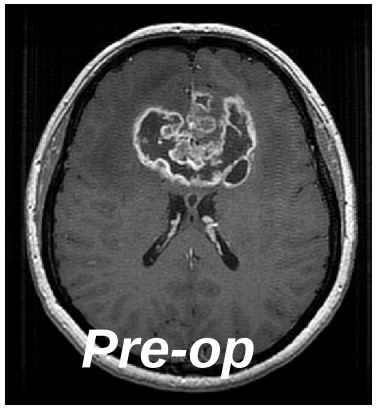
Standard Treatments for Glioblastoma

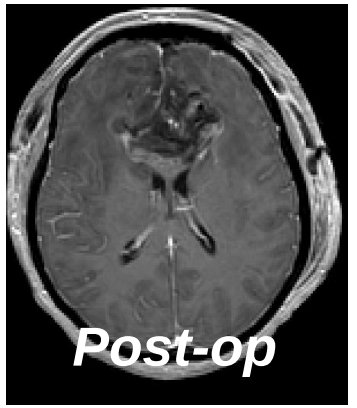
- **No curative options!**
  - **Goal: Preserve QOL, neuro function and extending survival** (Henriksson, Asklund, & Poulsen, 2011)



(Dandy, 1928)

- **Surgery**
  - Pathological diagnosis
  - Maximal safe resection can increase survival
  - Alleviation of mass effect (pressure)
  - Reverse or prevent neurological deficit
  - Avoid causing neurological deficits



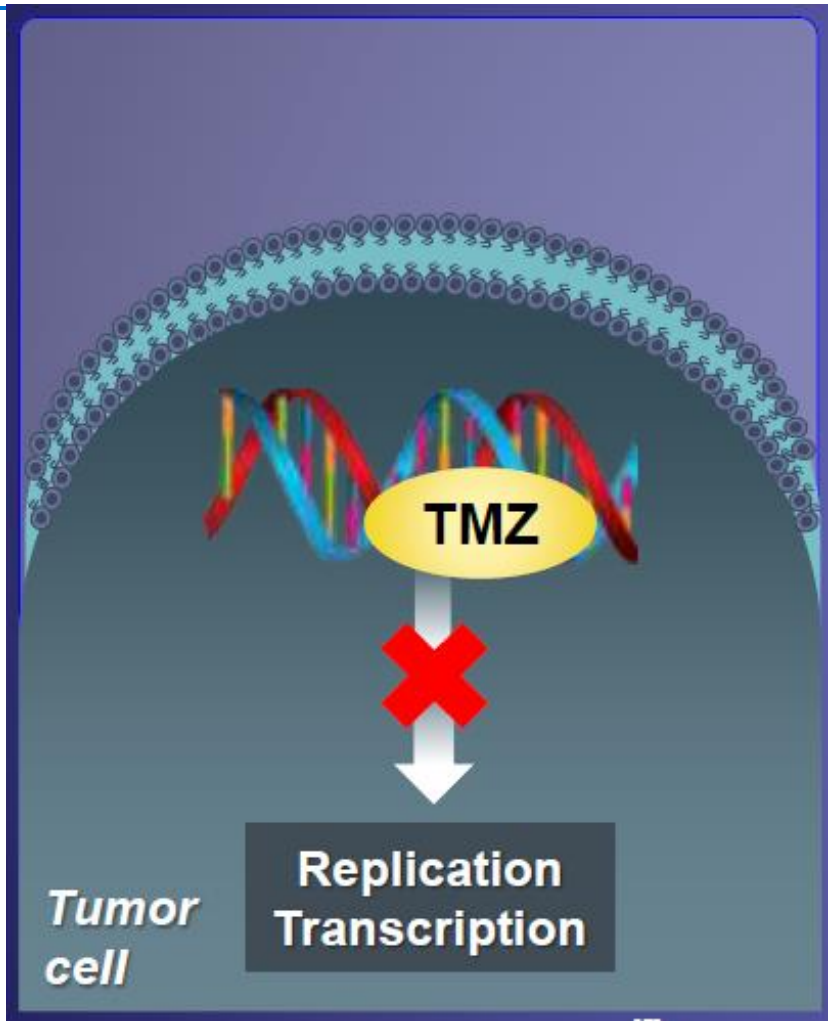


Standard Treatments for Glioblastoma

- **Radiation**
  - For 6 weeks, focal brain RT
  - Side effects: hair loss, fatigue, cognitive decline

- **Chemotherapy**
  - **Temozolomide (TMZ):** oral and IV alkylating agent (during RT and for at least 6 months afterwards)
  - Alkylating agents bind to DNA, impair replication/transcription → cell death (Fu, Calvo, & Samson, 2012)
  - TMZ crosses BBB and is spontaneously converted into active metabolite in CNS (Agarwala & Kirkwood, 2000)

  - **Toxicity**
    - Most common: constipation, nausea
    - Dose-limiting: neutropenia (14%), thrombocytopenia (19%)



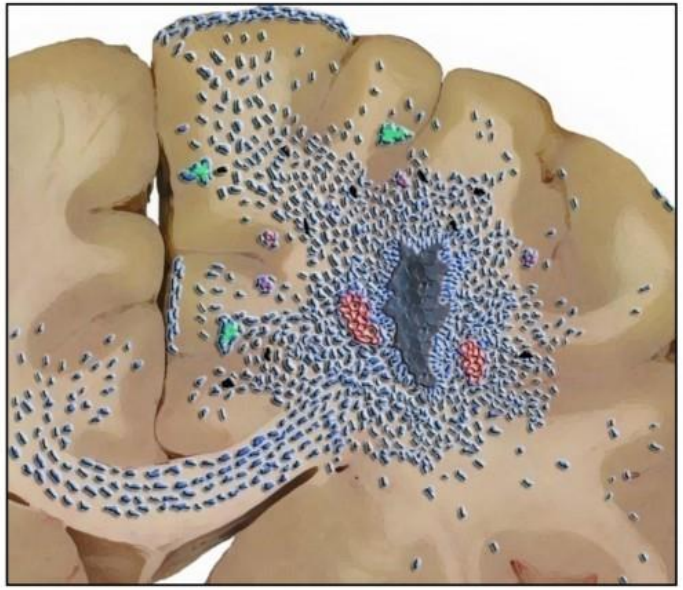
(Wesolowski, Rajdev, & Mukherji, 2010)

Treatment Challenges

Median Survival

1980:	**9 → 12 months (BCNU)**
2012:	**12 → 15 months (Temozolomide)**
2014:	**17 → 17 months (Avastin)**
2015:	**17 → 19 months (NovoTTF)***

1. Brain tumors are invasive
2. Standard therapies (surgery, radiation, and chemotherapy) may cause brain injury
3. The blood-brain barrier prevents penetration of most chemotherapies into the brain
4. Tumor heterogeneity
5. Immunosuppressive microenvironment




better Must do better
better Must do better
better Must do better
better Must do better

Immunotherapy

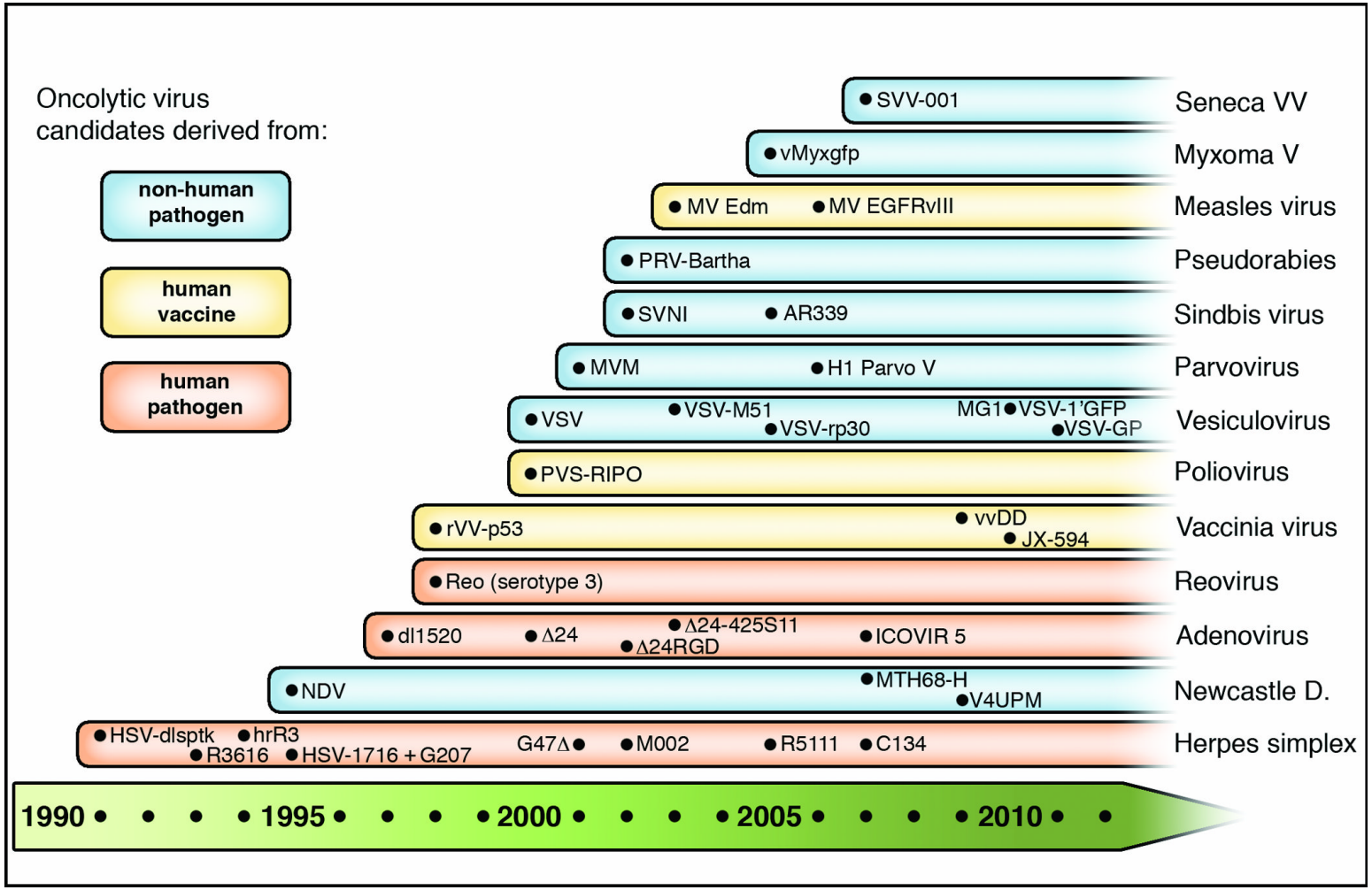
- Tumor cells have cleverly evolved to evade their destruction by the host immune system.

- Immunotherapy (AKA biological therapy, biotherapy or biological response modifier therapy) stimulates the immune system to recognize and target cancer cells and/or lessen treatment-related side effects.

- Current immunotherapies are available for breast, hematological, kidney, lung, melanoma, mesothelioma, ovarian, pancreatic, prostate cancers….

Timeline of oncolytic virus development from glioblastoma therapy

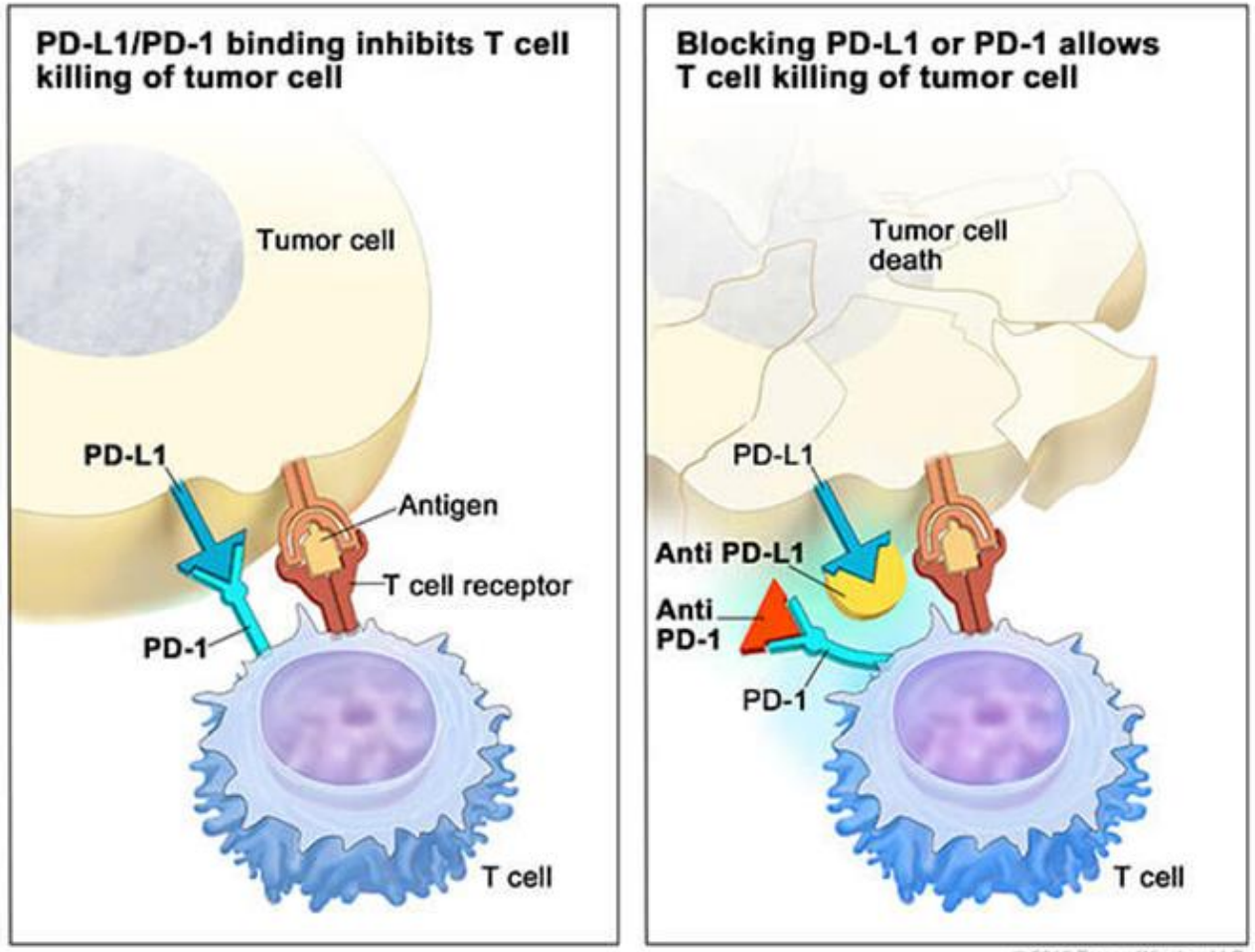
- **Oncolytic virotherapy** employs viruses with a preserved potential for an active viral life cycle.
- The chief paradigm is tumor-selective conditional viral replication, resulting in lytic tumor cell destruction and release of thousands of viral progeny.
- Newly released viruses go on to infect neighboring tumor cells, theoretically causing and maintaining a wave of virus attack throughout the tumor.



(Wollmann, Ozduman, & van den Pol, 2012)

Immune checkpoint inhibitors (ICIs):

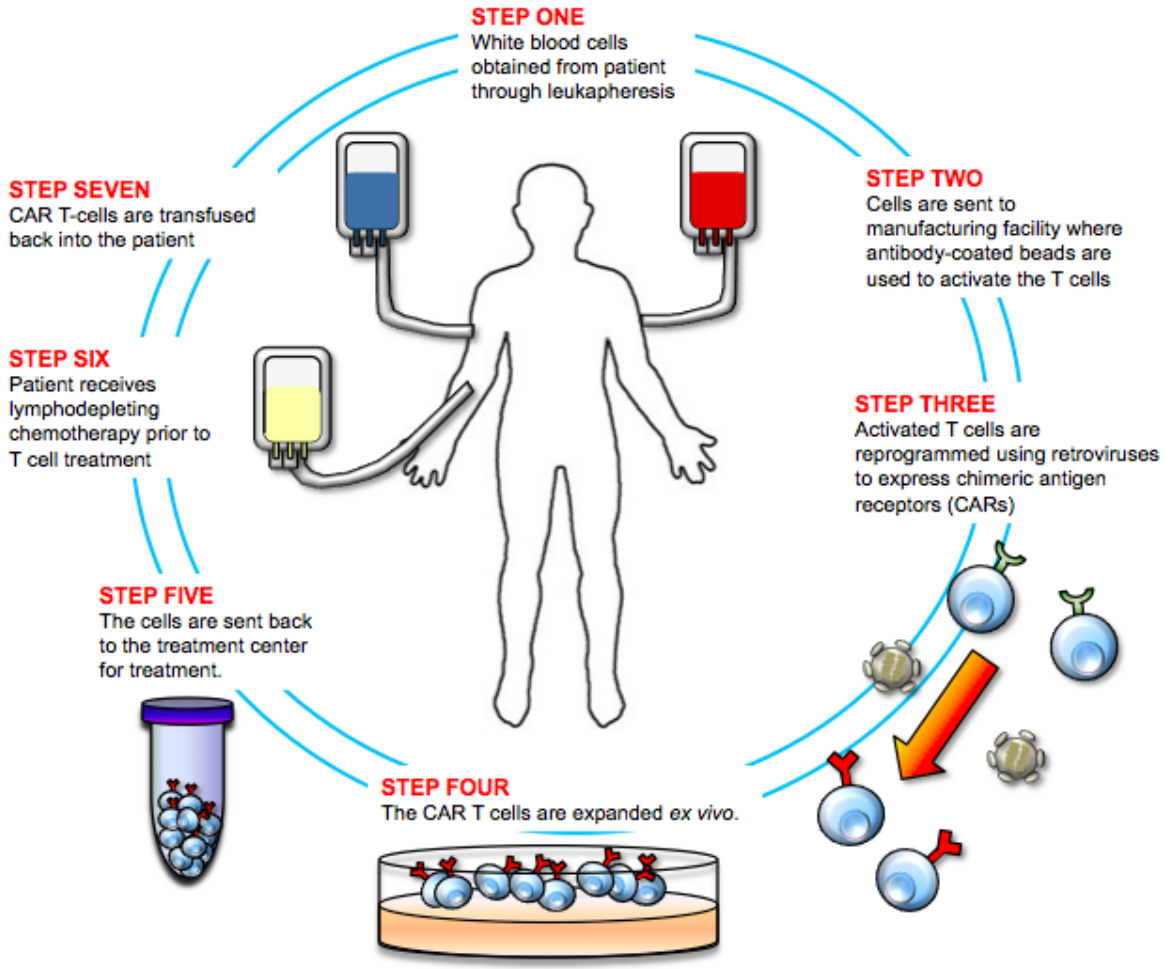
- Immune checkpoints are molecules on certain immune cells that need to be activated or inactivated to start an immune response.
- Some tumors utilize ICIs to evade immune attack
- Programmed cell death protein-1 (PD-1) dampens anti-tumor immune responses (Kamath & Kumthekar, 2018; Simonelli et al., 2018)



Chimeric antigen receptor (CAR) T cells

- CAR T cells were designed over four decades ago to overcome an ineffective immune system by genetically modifying T lymphocytes to recognize and eliminate cancer cells (Gross, Waks, & Eshhar, 1989).
- In this adoptive cell therapy, cells are harvested from patients, modified to target specific proteins expressed by the tumor, and re-introduced into the patient with the goal of destroying tumor cells.
- Shown great promise in blood-borne cancers such as relapsed or refractory B-cell lymphomas by targeting CD19 (Maude et al., 2018; Park et al., 2018).
- Currently FDA-approved for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and acute lymphoblastic lymphoma (ALL).
    - Detected in CSF

Generation of CAR T cells



(King, 2017)

Limitations of CAR T therapy for Glioma

- Tumor heterogeneity:
  - CAR T cells are particularly successful at targeting and destroying B-cell malignancies because these T cells are engineered to bind to a single molecule that is uniformly expressed on the surface of all B-cell derived tumors, CD19.
  - GBM tumors are notorious for having intra-tumor, and inter-tumor heterogeneity of cellular, genetic and molecular signatures (Brown, Stylli, Kaye, & Mantamadiotis, 2019; Neftel et al., 2019; Verhaak et al., 2010).

GBM “Harsh” Microenvironment

- GBM tumors actively contribute to immune suppression through a host of well-orchestrated strategies to create a T-cell suppressive tumor microenvironment.
    - Microenvironment suppress their activity and proliferation by expressing inhibitory cell-surface molecules (such as PD-L1, CD95) (Ricklefs et al., 2018) or by releasing immunosuppressive tumor-derived soluble factors and cytokines (such as prostaglandin E2, IL6, IL10 and TGFβ) (Hao et al., 2002).

- Microenvironment preferentially promotes trafficking of suppressive cell populations, such as regulatory T cells (Tregs), tumor-associated macrophages, microglia and myeloid-derived suppressor cells (Choi, Maus, June, & Sampson, 2019; Dubinski et al., 2016; Hussain et al., 2006) and creates other physical and metabolic blockades (Mirzaei, Sarkar, & Yong, 2017; Newick, O'Brien, Moon, & Albelda, 2017).

What if the therapy works TOO well…

- **Cytokine release syndrome (CRS),** or the systemic elevation in several cytokines including IL-6 and IFN-γ, is a common toxicity associated with CD19-CAR T cells that is indicative of immunotherapeutic potency (Lee et al., 2014).

- Neurotoxicity (encephalopathy, delirium, seizures, edema) is also a common treatment-related toxicity of CD19-CAR therapy, resulting from increased inflammatory cytokine levels and endothelial dysfunction of the blood-brain barrier (Gust and Turtle, 2017; Santomasso and Brenjens 2018; Gauthier and Turtle, 2018)

- Avoiding any severe brain inflammation and severe CRS is of utmost importance in GBMs, as increased intracranial pressure in patients already with increased mass effect from tumor can lead to deadly outcomes.

- CAR T cell trials in GBM have thus far reported less severe CRS and neurotoxicity-like adverse events as compared to CAR T cells targeting hematological cancers.

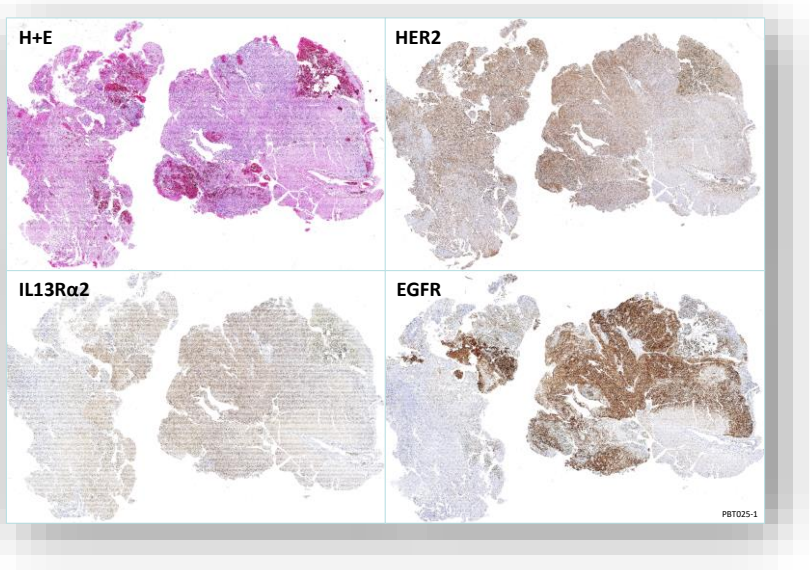
- To give Dex or not??

CRS Treatments

- One strategy is to desensitize CAR T cells to steroids is to genetically disrupt the glucocorticoid receptor (Menger et al., 2015), while others use anti-IL6 antibody (O'Rourke et al., 2017) or Bevacizumab (Migliorini et al., 2018) to reduce local inflammation.

- A balance is needed in treating CAR T patients with symptomatic brain edema while prioritizing for CAR T cell therapeutic activity, and at City of Hope we do this by limiting dexamethasone to 6 mg in a 24-hour period in our patients.

Clinical Studies of CAR-T Cells for Glioblastoma



City of Hope

IL13Rα2+
NCT00730613 (2002-2008)
NCT01082926 (2011-2013)

NCT02208362 (2015-ongoing)
41BBζ -CAR Tmem

HER2+
NCT03389230 (2018-ongoing)
41BBζ -CAR Tmem

Baylor

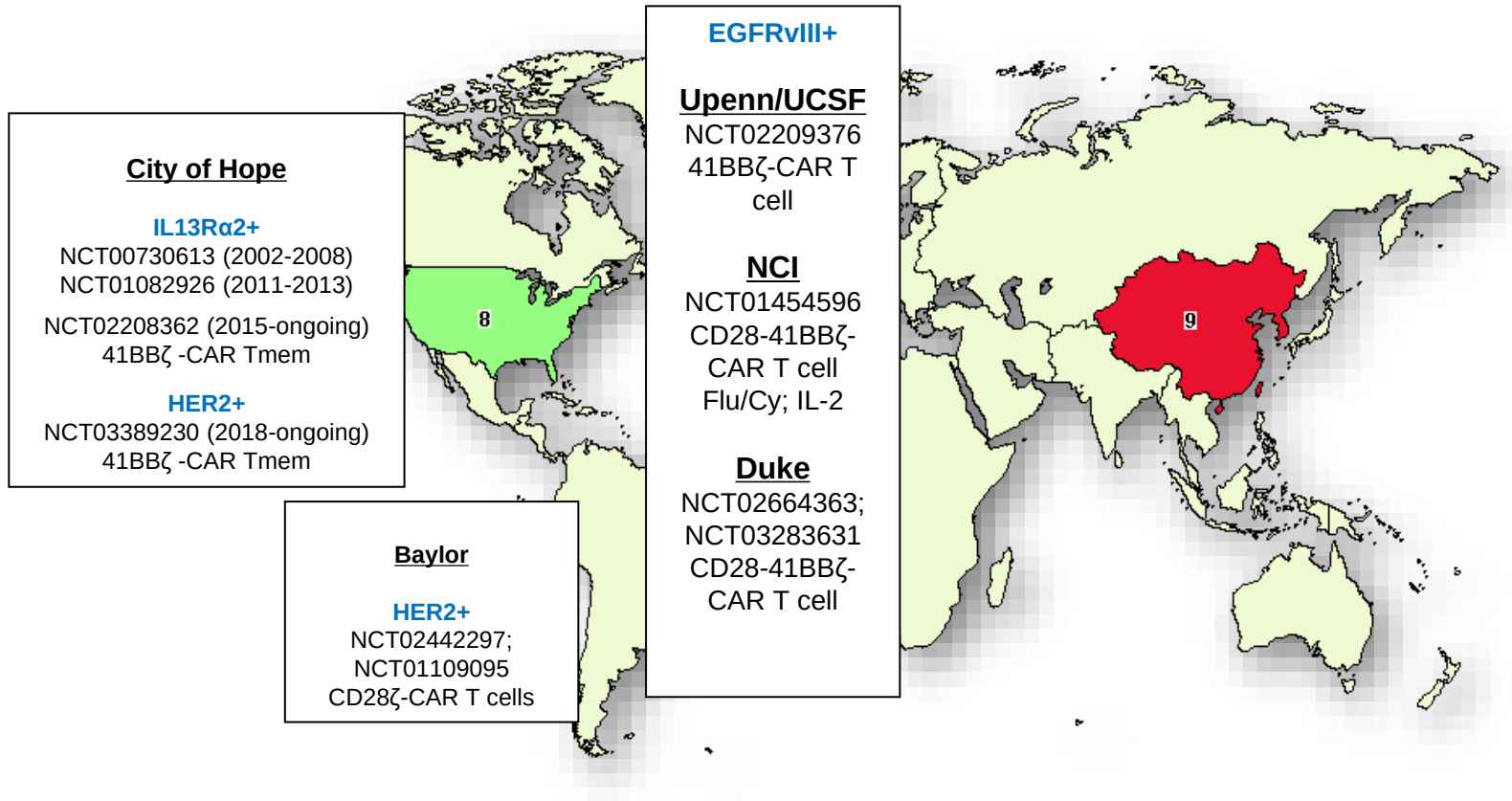
HER2+
NCT02442297;
NCT01109095
CD28ζ-CAR T cells

EGFRvIII+

Upenn/UCSF
NCT02209376
41BBζ-CAR T cell

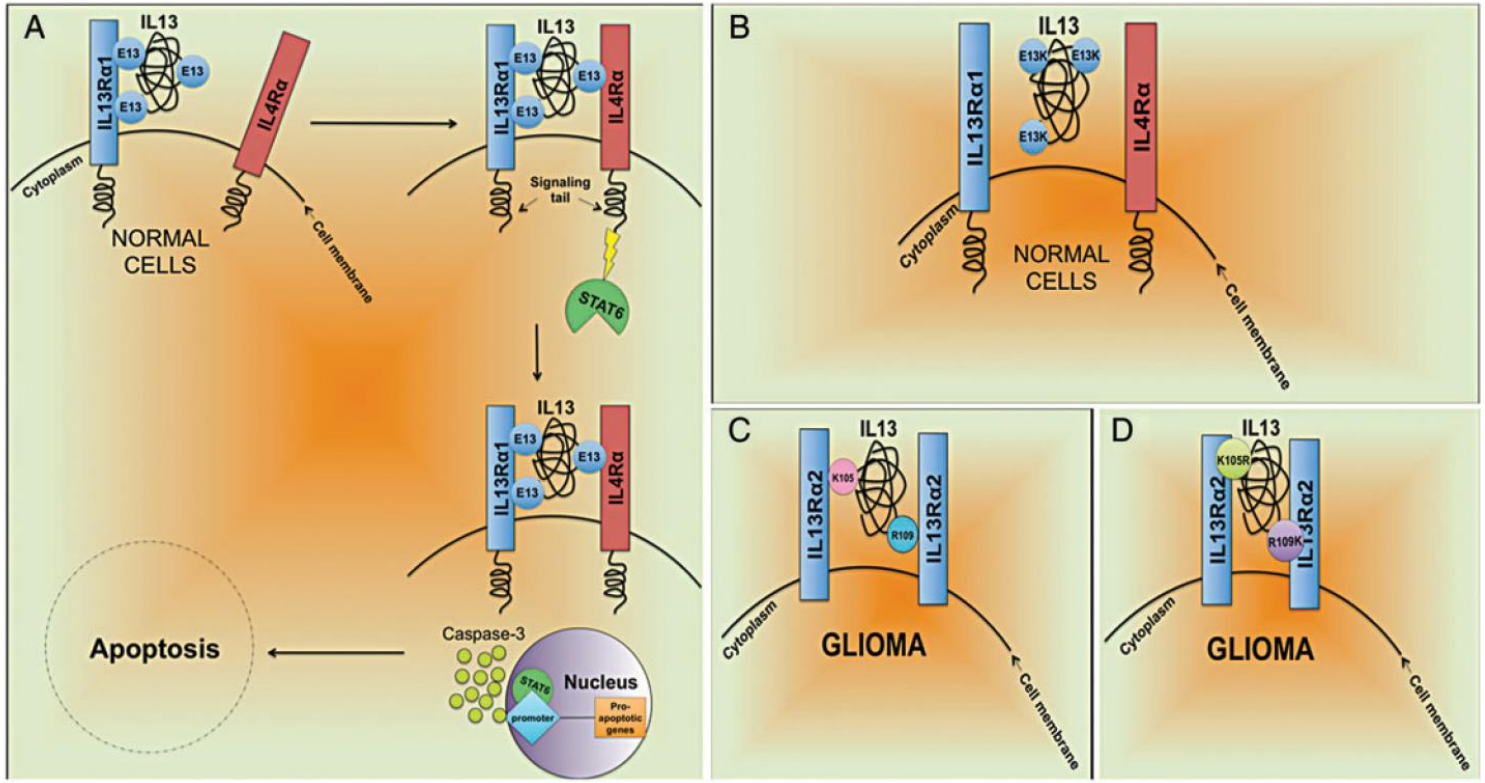
NCI
NCT01454596
CD28-41BBζ-CAR T cell
Flu/Cy; IL-2

Duke
NCT02664363;
NCT03283631
CD28-41BBζ-CAR T cell



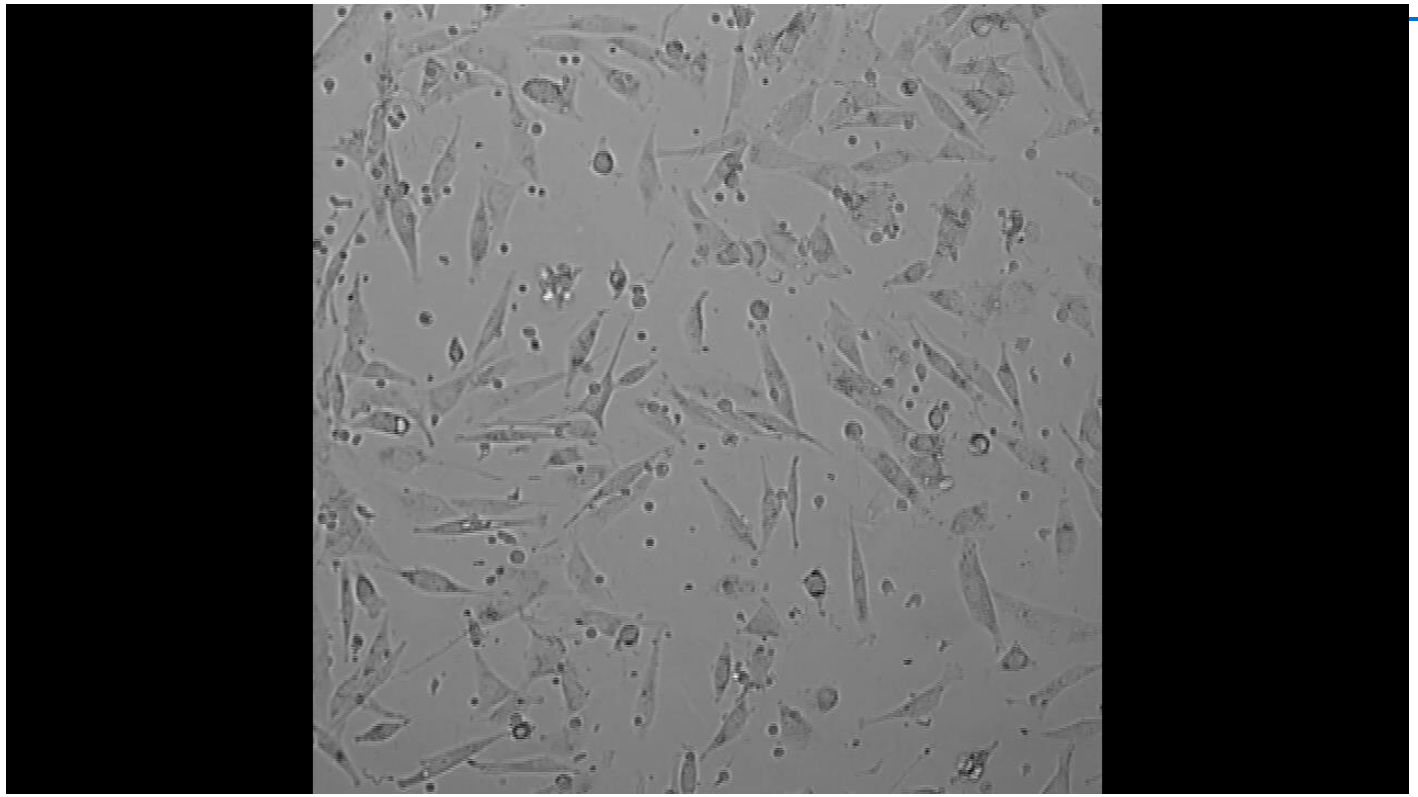
Clinicaltrials.gov

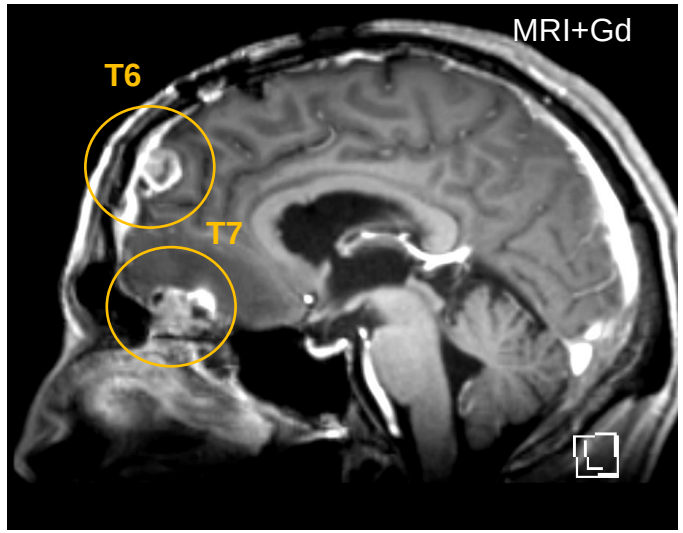
Interleukin 13 Receptor α2 (IL-13Rα2)

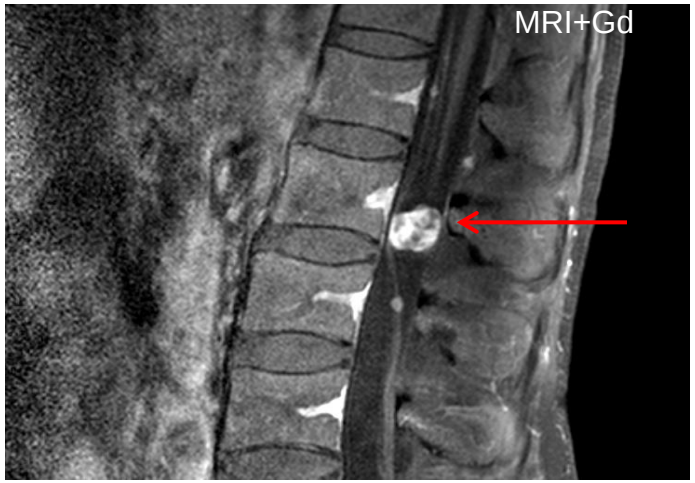


- IL-13Rα2 not only blocks the normal apoptotic pathway, but also induces upregulation of STAT3, promotes invasion and metastasis via extracellular signal-regulated kinase/activator protein 1, and promotes tumor immune escape via upregulation of transforming growth factor β (Thaci et al., 2014)
- Expressed in up to 75% GBMs with high variability (Jarboe, Johnson, Choi, Lonser, & Park, 2007; Joshi, Plautz, & Puri, 2000; Liu et al., 2000; Saikali et al., 2007)

CAR-T Cells Therapy for Glioblastoma: Laboratory to Clinic



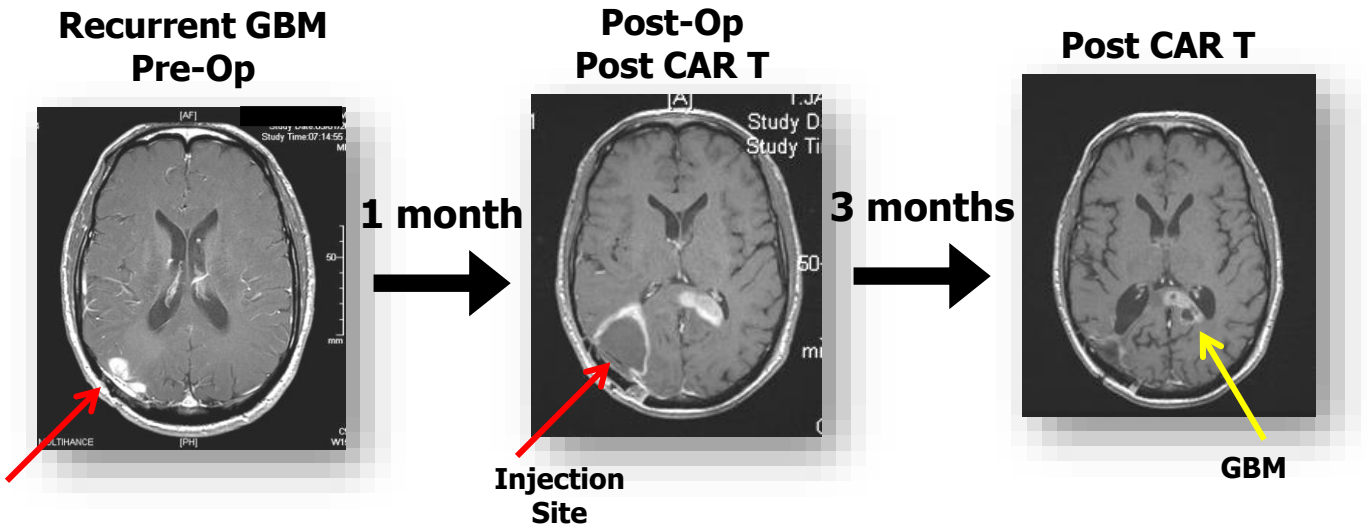


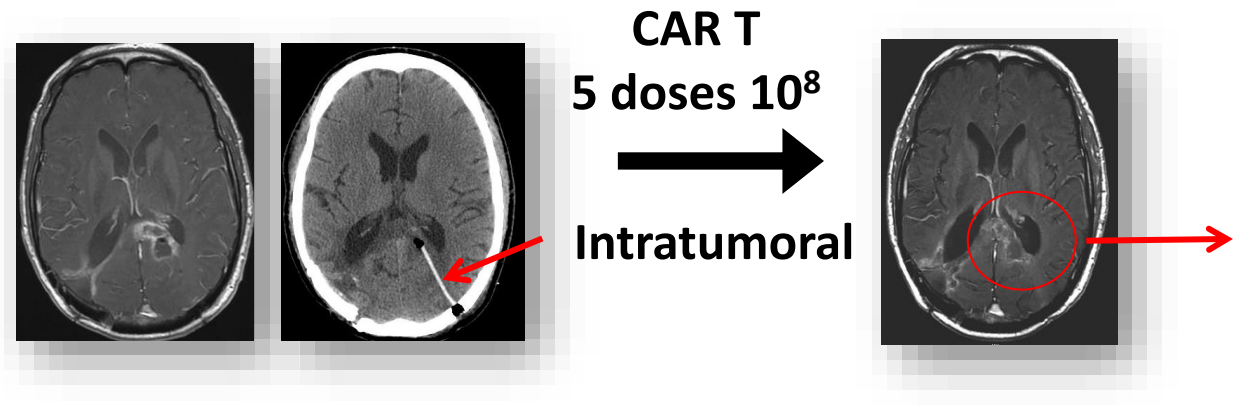


Primary patient-derived gliomas incubated with autologous T cells (captured over 8-12 hrs)

Clinical Evaluation of First-Generation Autologous IL13-zetakine T cells Locally injected for the Treatment of GBM

Patient Safety and Tolerability					
Patient	T cell Doses	Max Tolerated Dose	Cumulative Cell Dose	Serious Adverse Events (SAE) (therapy related probable)	Survival post-recurrence (months)
UPN028	11 of 12 (dose 7)	10^8	$9.6x10^8$	none	10.3
UPN031	12 of 12	10^8	$10.6x10^8$	Transient neurologic worsening (grade 3)	8.6
UPN033	12 of 12	10^8	$10.6x10^8$	none	13.9



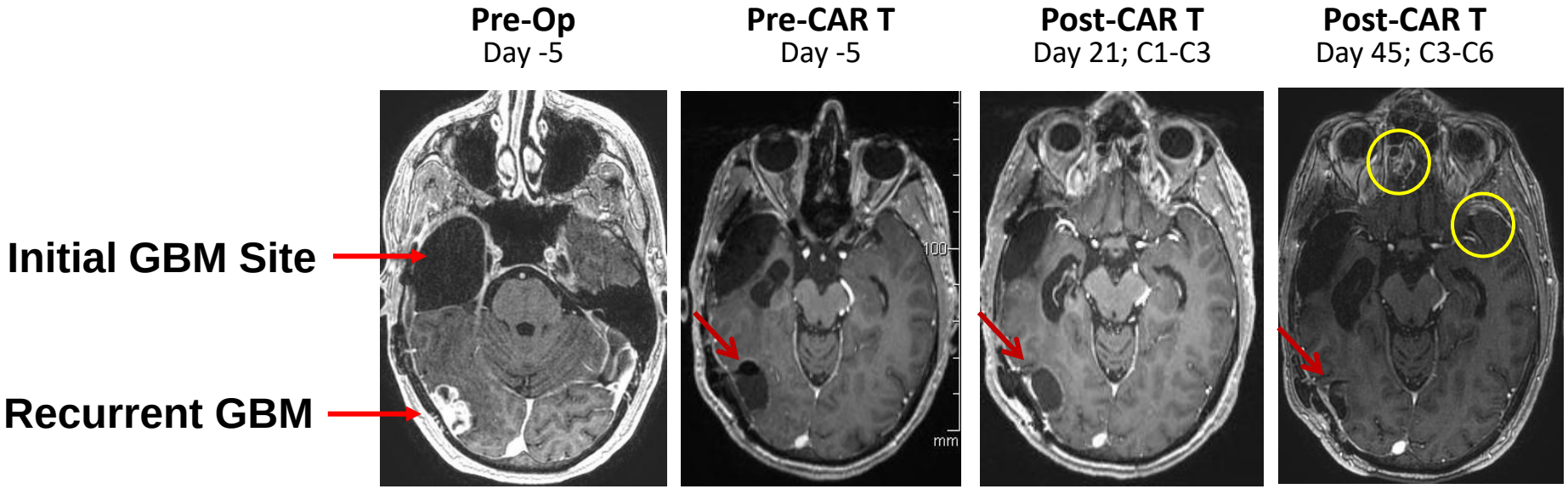


(Brown et al., 2015)

Case Study: IL13Rα2-targeted CAR T cells

- 50 y/o male
- Recurrent multifocal GBM (5 intracranial tumors)
- IL13Rα2+ (H score 100)
- Poor prognostic features (MGMT unmethylated, 60% Ki67)
- Prior therapy: surgery, radiation, temozolomide, tumor treating fields; FGFR kinase inhibitor

6 infusions into tumor resection cavity (ICT)

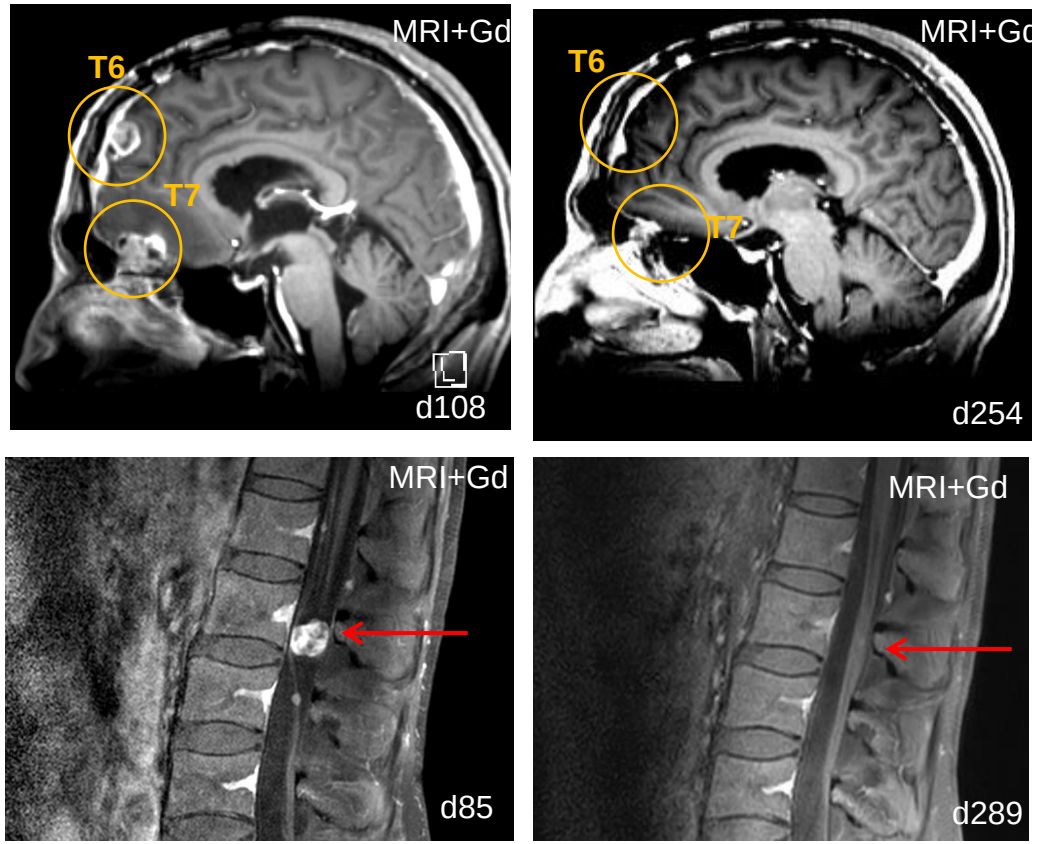


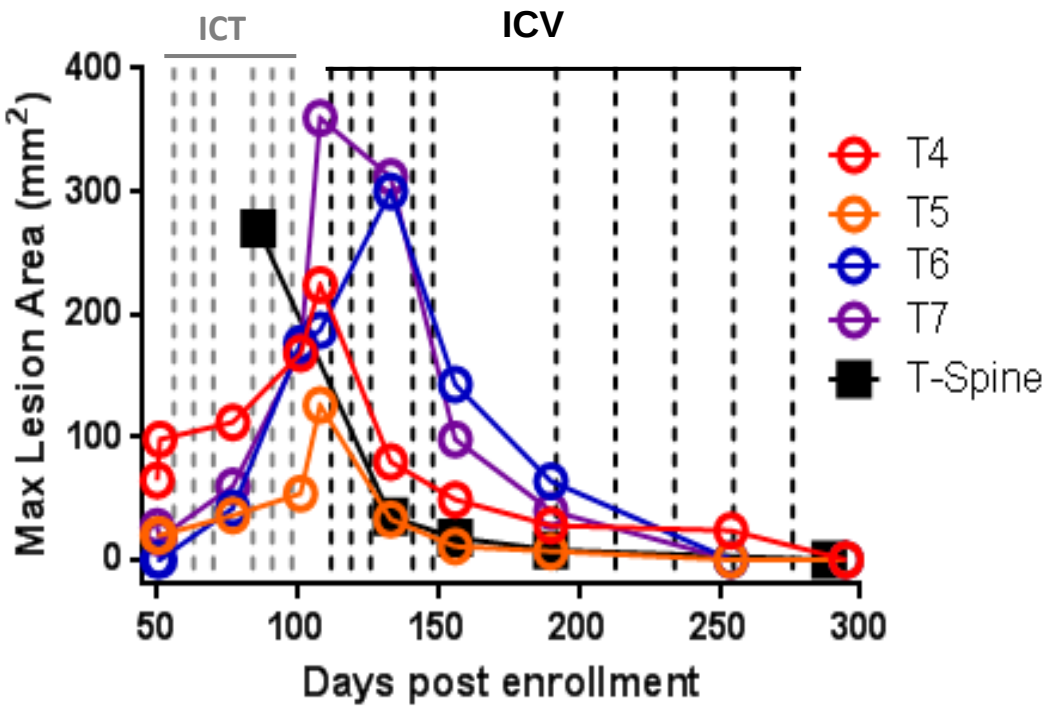
(Brown et al., 2018)

Regression of Recurrent Multifocal GBM Following Intraventricular Delivery of IL13Rα2-CAR T cells

10 intraventricular (ICV) infusions

post-ICT CAR-T → post-ICV CAR-T

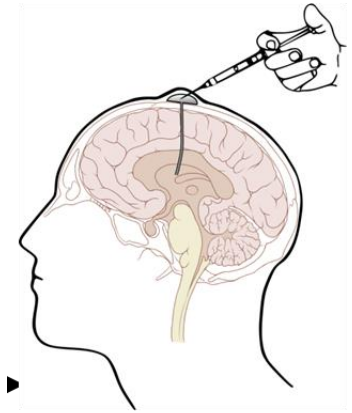




(Brown et al., 2018)

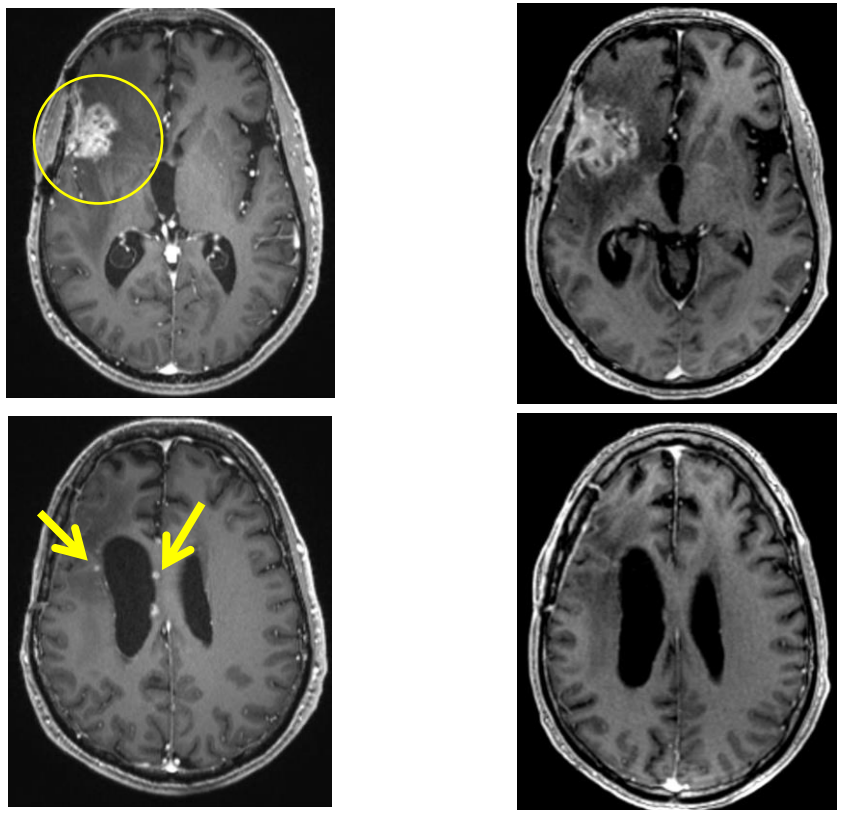
Intraventricular Delivery of IL13Rα2-CAR T cells

Intraventricular

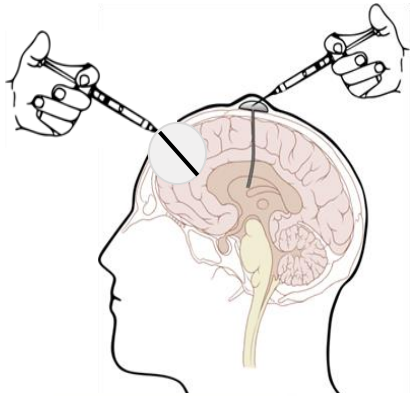


3 intraventricular (ICV) infusions

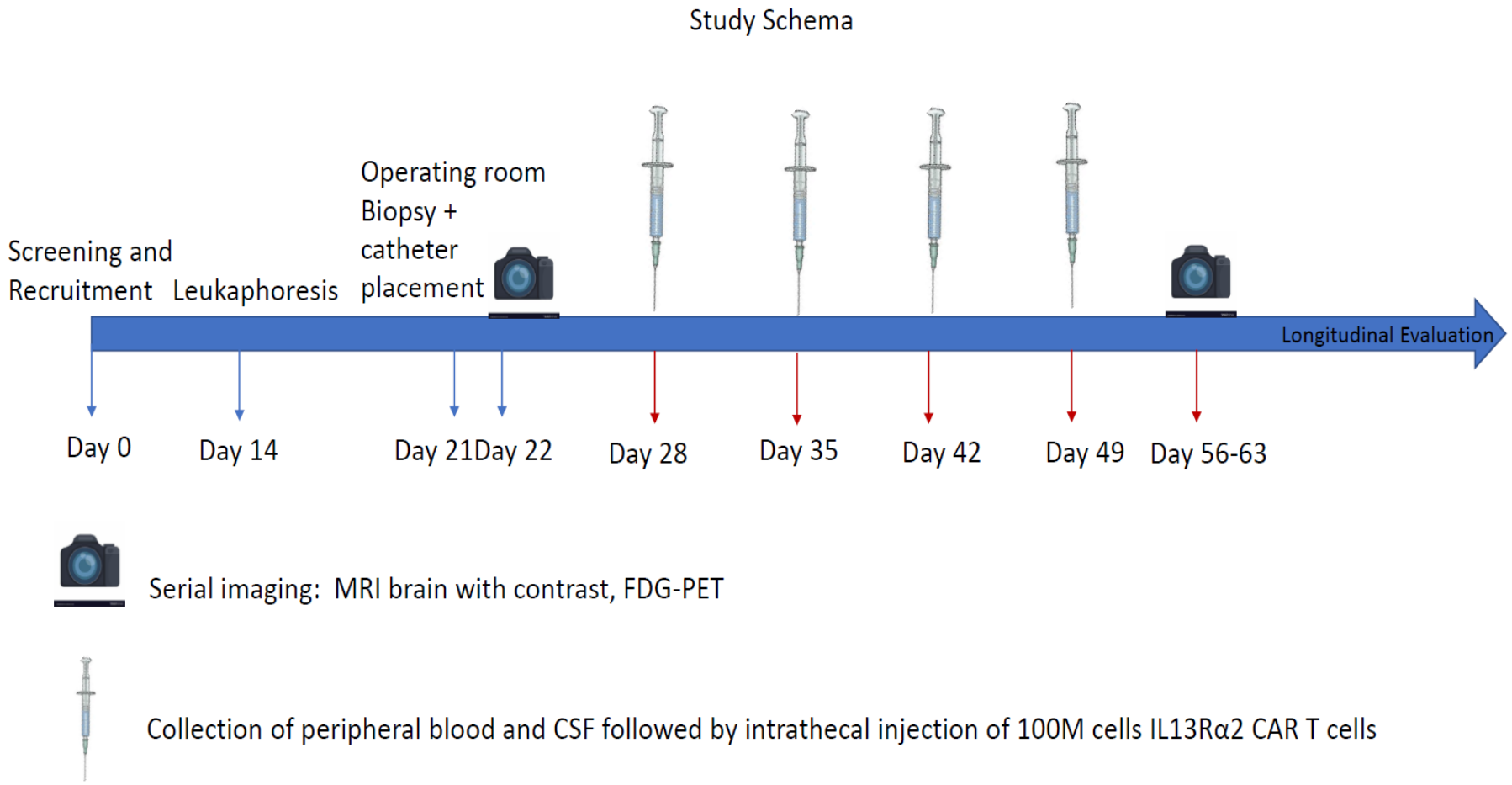
pre -CAR T (ICV) → **post -CAR T (ICV)**



Dual-Delivery



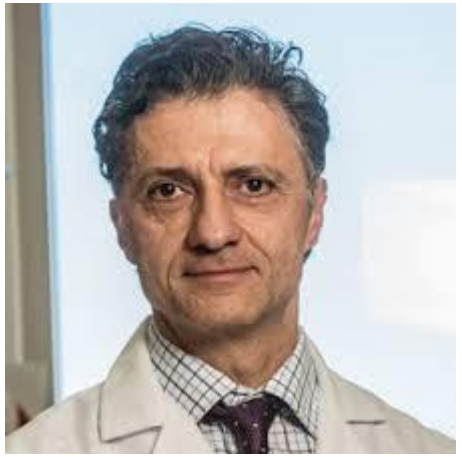
IL13Rα2-targeted CAR T immunotherapy for leptomeningeal disease clinical trial



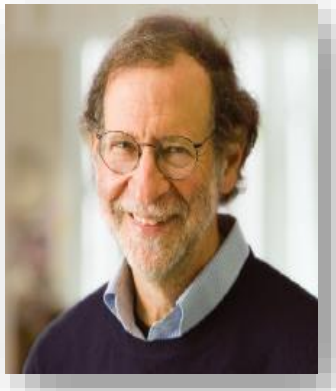
14 Current GBM clinical trials at COH

- IL13Rα2 CAR T cells with or without Nivolumab and Ipilimumab
- CAR T cells with Chlorotoxin Tumor-Targeting Domain
- IL13Rα2 CAR T cells for leptomeningeal disease
- Memory-Enriched T Cells in Treating Patients with Recurrent Grade III, IV glioma
- Genetically Modified T cells in patients with Recurrent malignant glioma

Acknowledgements



Behnam Badie, MD



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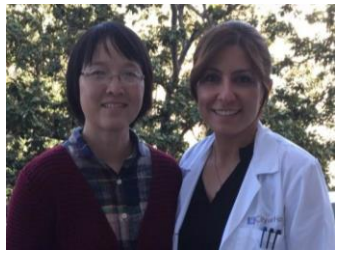

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Thank You:

Patients and their families


QUESTIONS?