

How Melanoma and Lung Cancer Oncology is Changing the Primary Brain Tumor Landscape

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Mission

To accelerate:

- Biological understanding of neurological disorders and cancer
- Drug discovery for various diseases
- Clinical development of drugs, devices in neurological diseases and cancers

Why have we not made faster progress?

Barriers

- Tumor/Disease heterogeneity
- Blood-brain barrier
- Immunosuppressive microenvironment
- Steroid use
- Radiation/Chemotherapy
- Tumors are different genetically
- Limits drug access
- Immune system inhibited
- Immune system inhibited
- Immune system inhibited/
Promotes aggressive recurrence

Better Drugs are Needed!

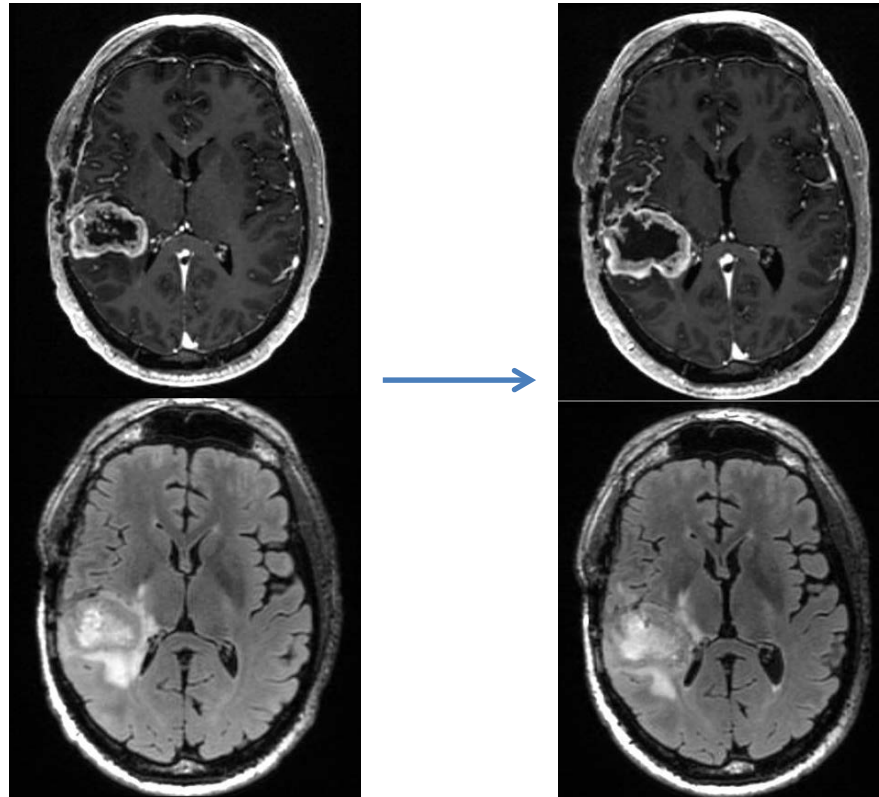
Precision medicine Adapt as the Tumors Evolve:

Case 1: 42 yo RHM uMGMT GBM

2nd Profiling:
EGFR mut gone

OS 34 months

Affinitor
→
Tarceva



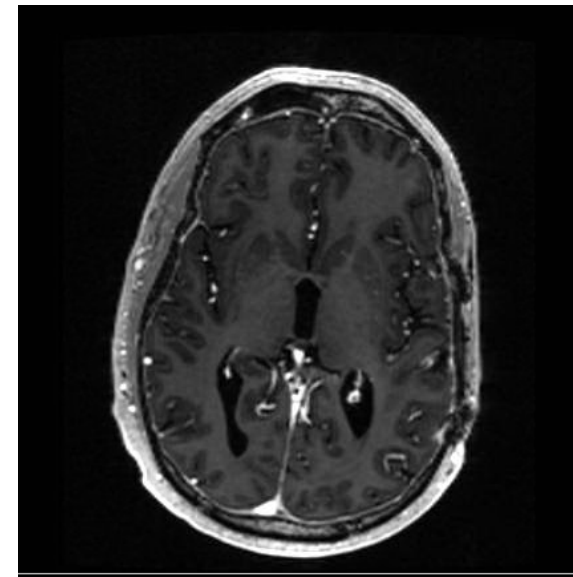
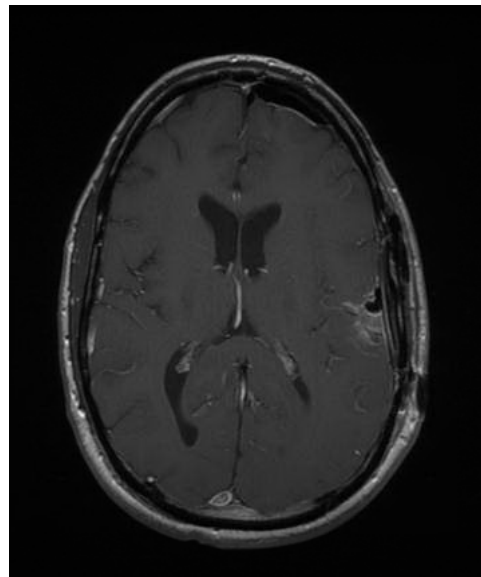
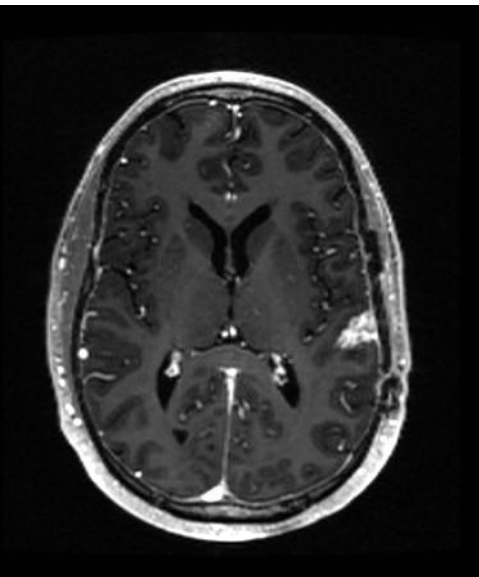
Precision medicine Adapt as the Tumors Evolve:

Case 2: 44 yo RHM uMGMT GBM

Progressed on
XRT +Temodar
PFS 6.9 months

Profiling:
TOPO1+, BRAF
V600E

**OS > 21.3
months**

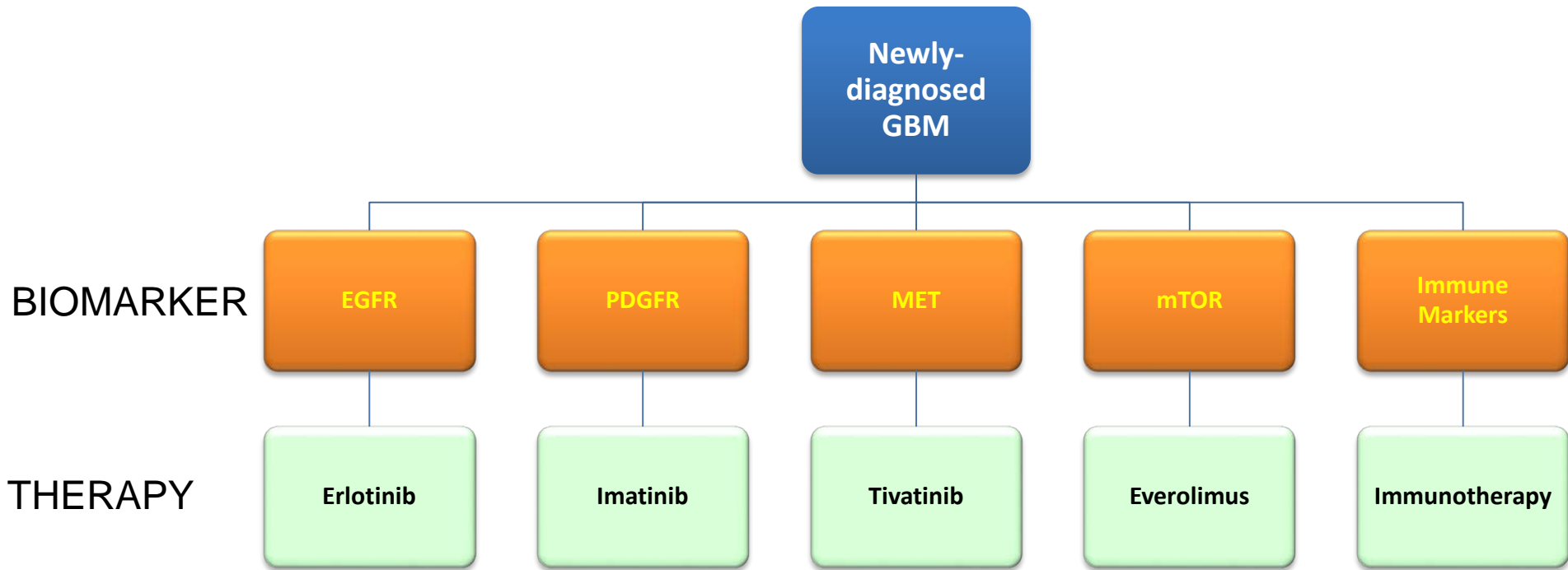


Surgery

Treatment with
Irinotecan +
zelboraf

Precision Medicine Pathway:

NextGen GBM Signature Biomarker-Driven Trials



Treat patients individually based on their own unique characteristics

Background:

Why have we not made faster progress?

Barriers

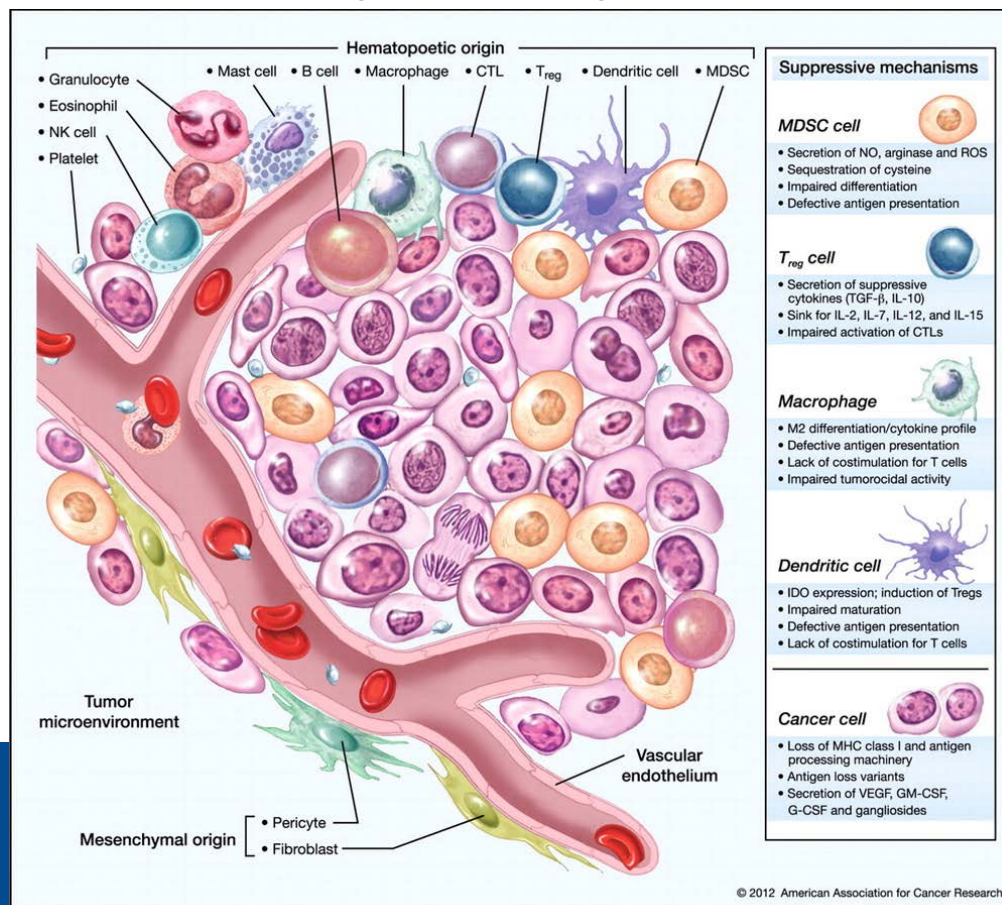
- Tumor/Disease heterogeneity
- Blood-brain barrier
- **Immunosuppressive microenvironment**
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Progress in Immuno-Oncology

- Antibodies
 - VEGF
 - EGFR
 - PDGFR
- Vaccines
 - Peptide/Protein/Tumor cell lysates
 - Viral
 - Dendritic Cell
 - Oncolytics
- Small molecule agonists and inhibitors
 - IDO
 - TGF-beta
- Cytokines
 - IL-2
- Immune checkpoint modulation
 - CTLA-4
 - PD-1, PD-L1
 - TNFSRF
- Cellular therapy
 - CARs, TCRs

Brain Cancers

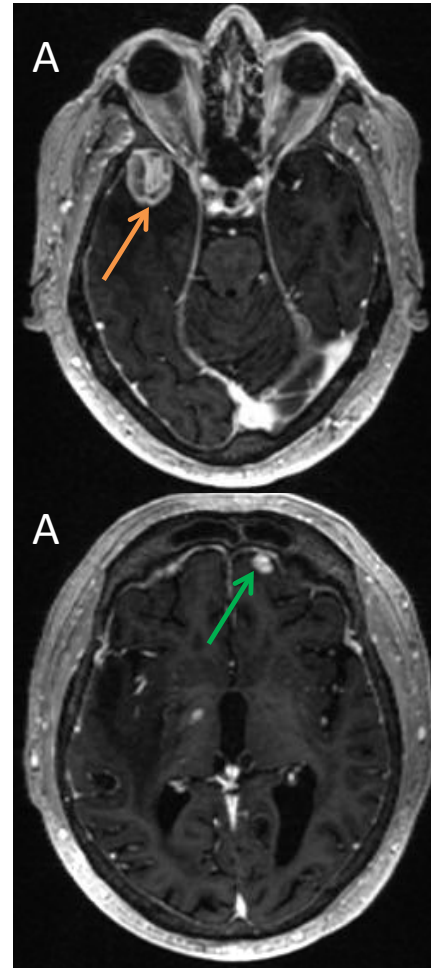
- We have tried them all
- Need complete removal
- Steroids limiting
- Toxicity limiting with newer agents



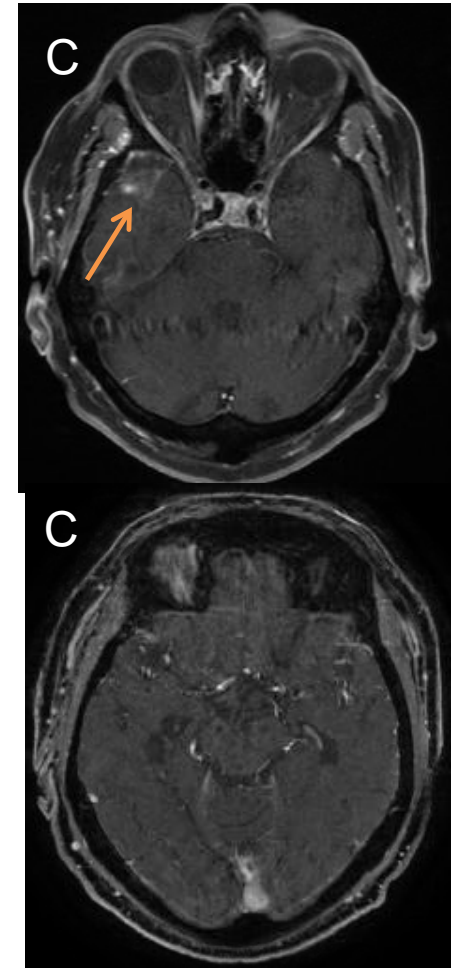
Immunotherapy Responses in Brain Cancer: PCNSL

- 70 yo fireman with PCNSL that relapsed following kitchen sink including chemotherapy, transplant and radiation.
- Started Nivolumab

Nov 2015



Feb 2016



Immunotherapy Responses in Brain Cancer: bMMRD Glioblastoma

Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency

Eric Bouffet, Valérie Larouche, Brittany B. Campbell, Daniele Merico, Richard de Borja, Melyssa Aronson, Carol Durno, Joerg Krueger, Vinja Gabric, Vijay Ramaswamy, Nataliya Zhukova, Gary Mason, Roula Fanah, Samina Afzal, Michal Yalon, Gideon Rechavi, Varun Maginnairajan, Michael F. Walsh, Shlomi Constantini, Rina Dvir, Ronit Elhasid, Alyssa Reddy, Michael Osborn, Michael Sullivan, Jordan Hansford, Andrew Dodgshun, Nancy Klauber-Demore, Lindsay Peterson, Sunil Patel, Scott Lindhorst, Jeffrey Atkinson, Zane Cohen, Rachel Laframboise, Peter Dirks, Michael Taylor, David Malkin, Steffen Albrecht, Roy W.R. Dudley, Nada Jabado, Cynthia E. Hawkins, Adam Shlien, and Uri Tabori

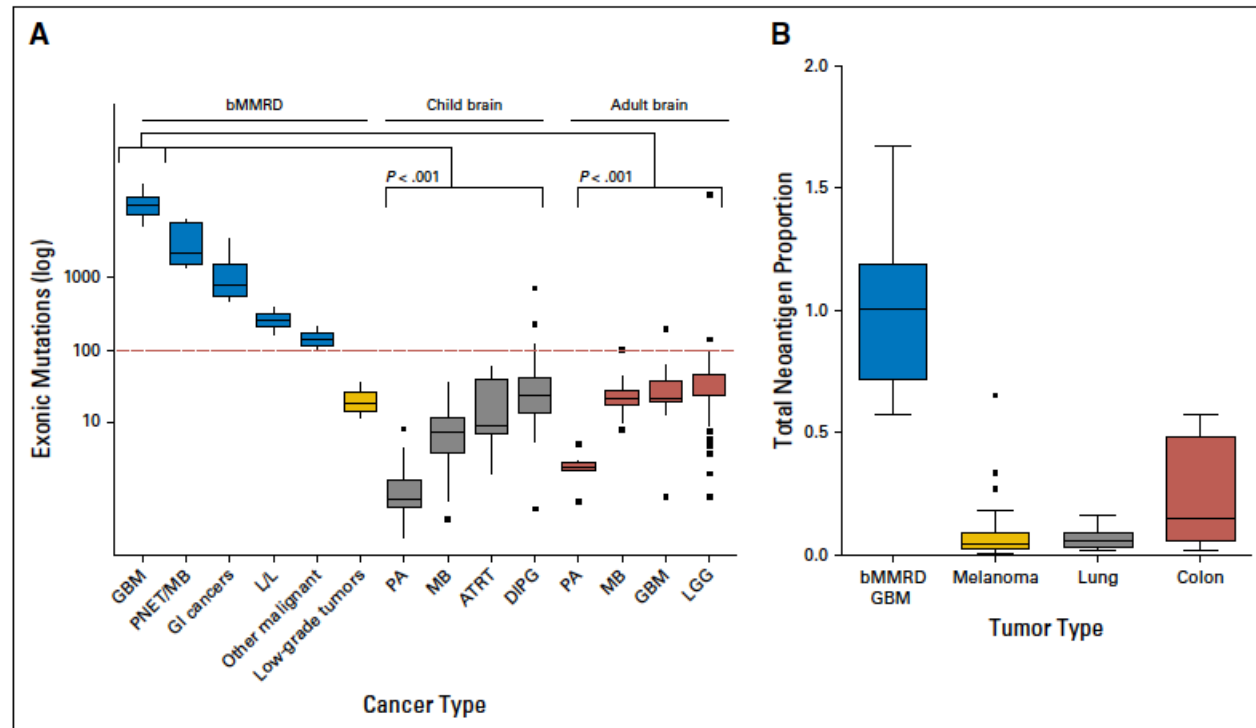


Fig 2. Tumor mutation and neoantigen analysis. (A) Boxplot comparing the number of mutations per tumor exome in several biallelic mismatch repair deficiency (bMMRD) cancer types with pediatric and adult brain tumors. (B) Ratio of the number of neoantigens found in immunoresponsive tumors from melanoma ($n = 27$), lung cancer ($n = 14$), and colon cancer ($n = 7$) data sets compared with median number of neoantigens in bMMRD glioblastoma multiforme (GBM; $n = 13$). ATRT, atypical teratoid rhabdoid tumor; DIPG, diffuse intrinsic pontine glioma; L/L, leukemia/lymphoma; LGG, low-grade glioma; MB, medulloblastoma; PA, pilocytic astrocytoma; PNET, primitive neuroectodermal tumor.

Immunotherapy Responses in Brain Cancer: bMMRD Glioblastoma

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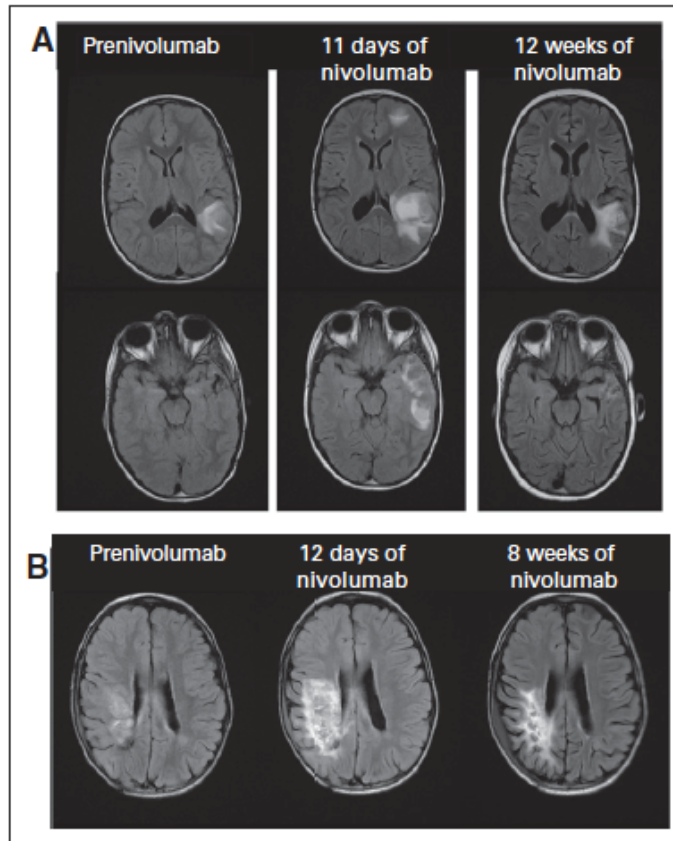


Fig 3. Initial changes and resolution of magnetic resonance imaging findings during treatment with nivolumab. (A) T2 flair sequences pretreatment, during clinical deterioration after treatment initiation, and resolution in subsequent scans for the index patient with glioblastoma multiforme (GBM). (B) Similar sequences for the patient's brother with GBM.

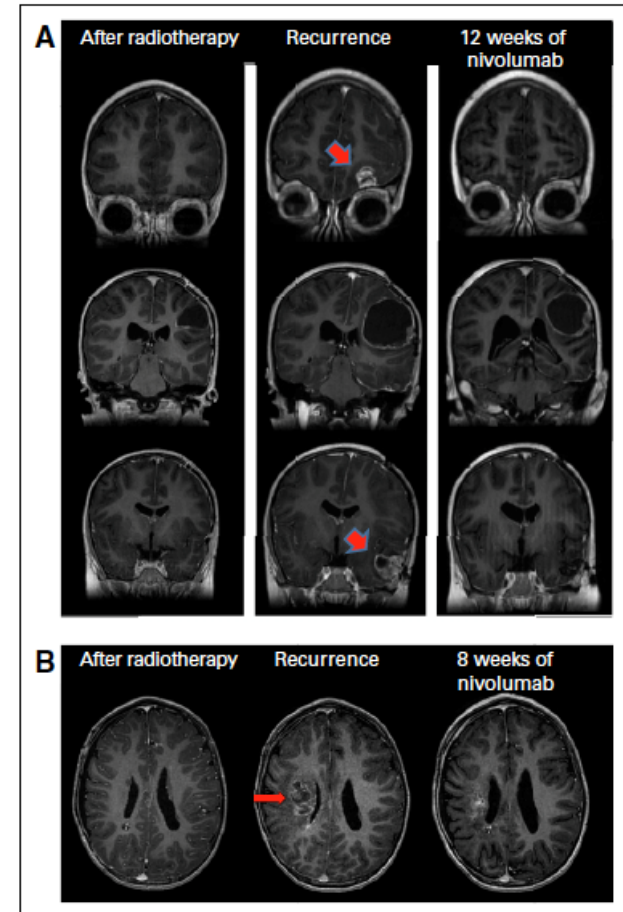
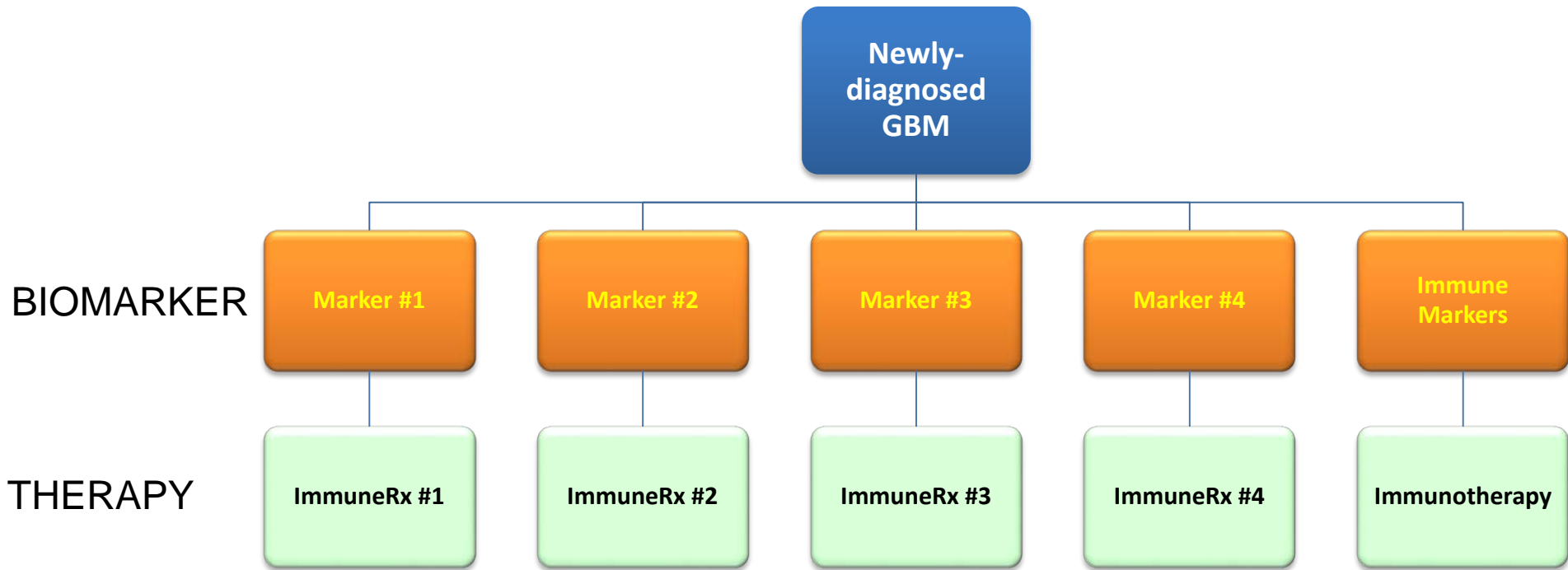


Fig 4. Tumor response by magnetic resonance imaging. (A) Gadolinium-enhanced T1 sequences of the index case showing tumor status after initial radiation therapy, at relapse, and on the recent scan during treatment. (B) Similar sequences for the patient's brother's tumor. Red arrows indicate enhancing tumor.

Precision Immunotherapy:

NextGen GBM Signature Biomarker-Driven Trials



Treat patients individually based on their own unique immune characteristics

Shift in Paradigm

Newly Diagnosed
Glioma Patients



Imaging/Labs



Surgical resection



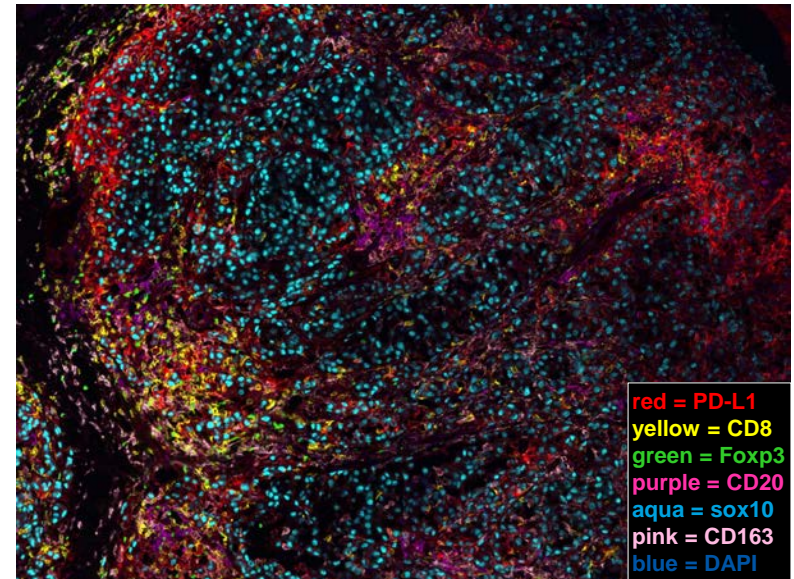
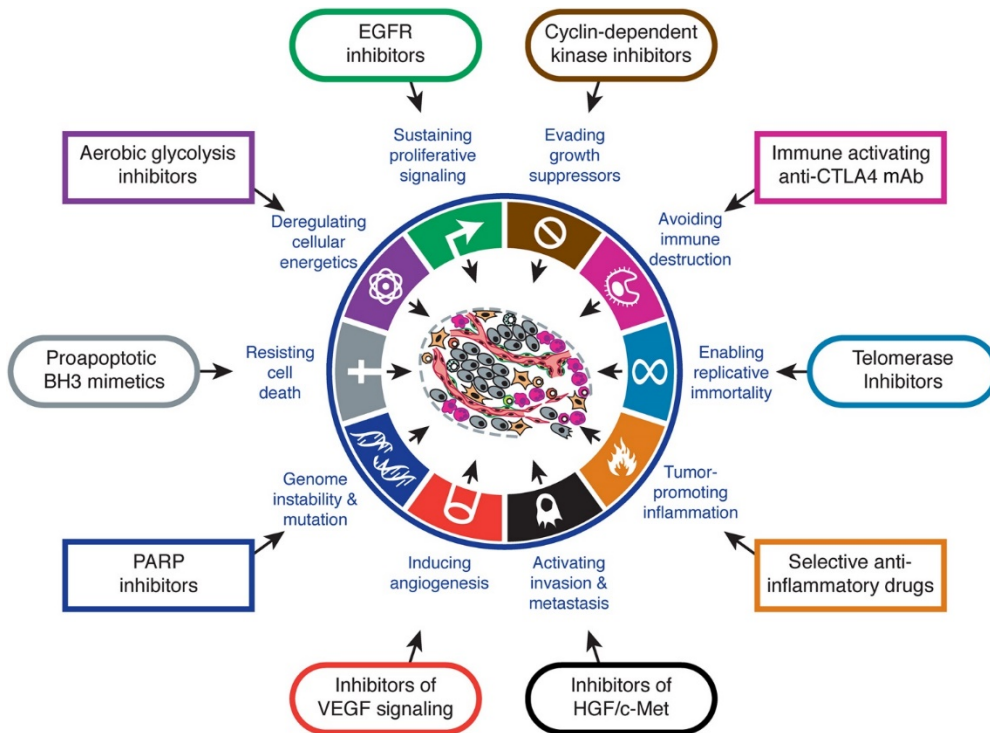
Genomic, Proteomic
Tumor Profiling



Modeling-driven Stratification:
Targeted Personalized Therapy

Precision Medicine in Action

Cancer is Complex



Advanced genomics, informatics, and Big data analytics are helping us unravel this complexity

Experimental Design: Translational Research

