Neuro Oncology: Novel Advances in Glioma Therapy

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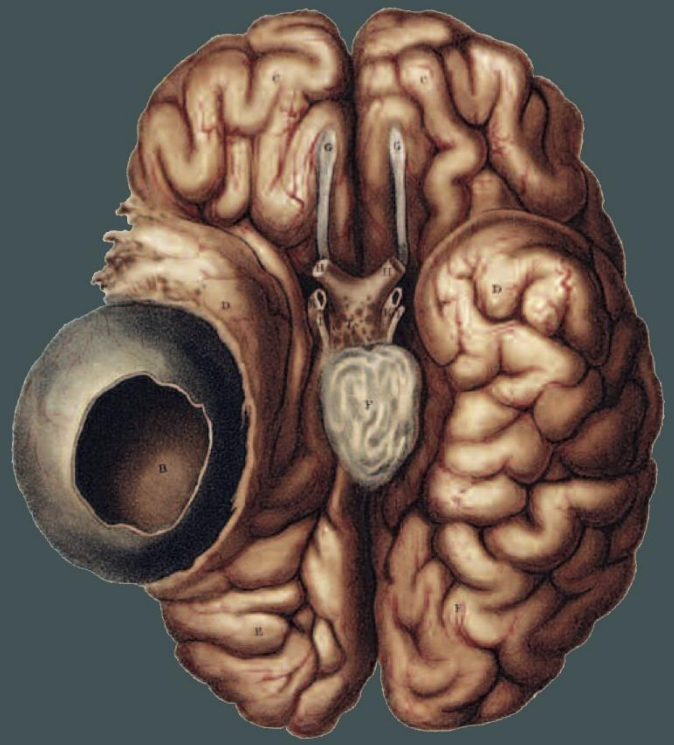
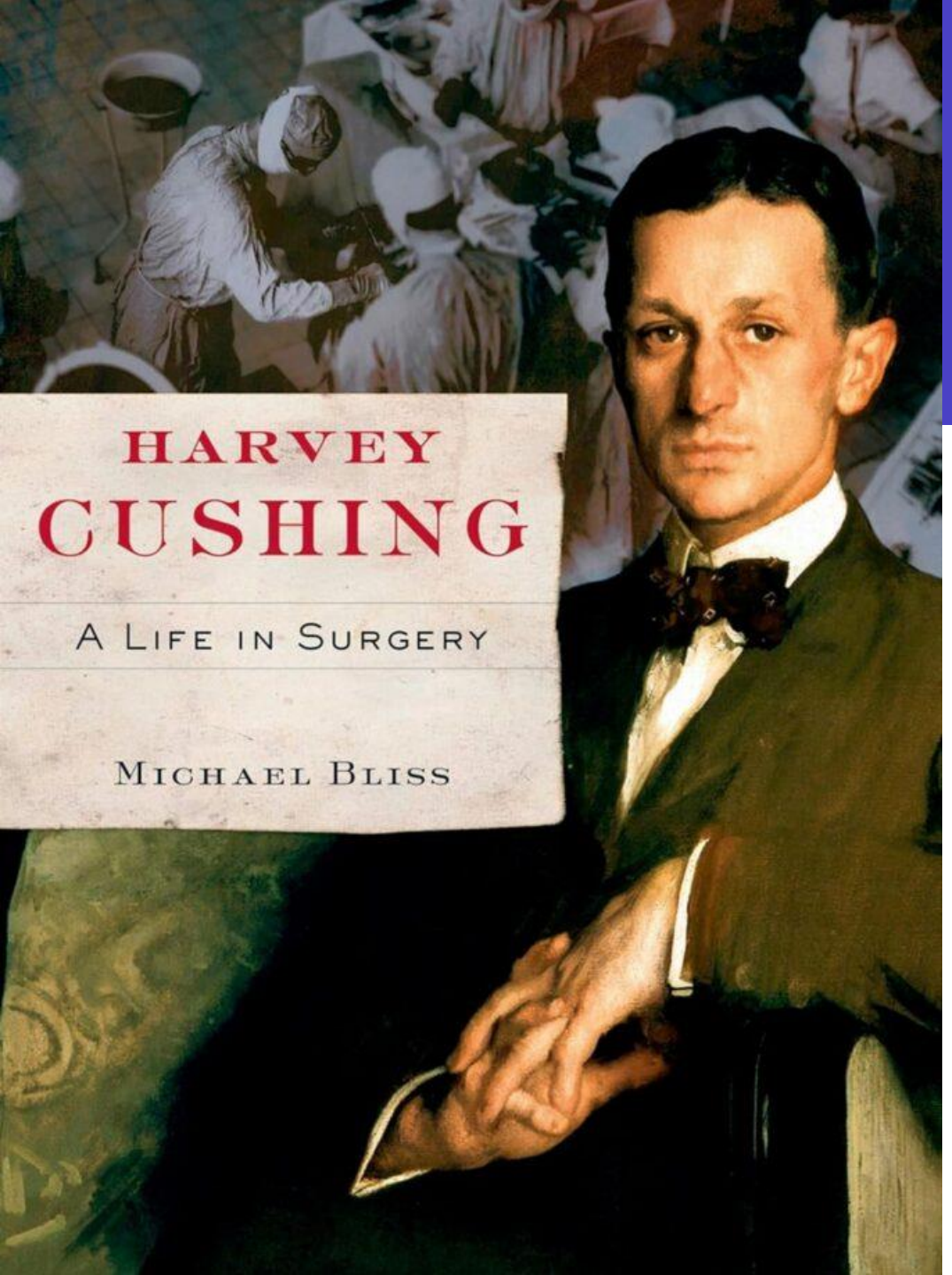


A HISTORY OF
NEURO-ONCOLOGY

ROLANDO F. DEL MAESTRO

Whoever wishes to foresee the future must consult the past…..

"Those who don't study history are doomed to repeat it. Yet those who *do* study history are doomed to stand by helplessly while everyone else repeats it."



HARVEY CUSHING'S LOST CASES OF THE "RADIUM BOMB"

- **Interstitial Brachytherapy for Glioma**
- **Cushing and Frasier explored the effects of Radium and X Rays on Gliomas and AVM's**
- **Harvey Cushing performed over 2000 Neurosurgical operations and around 832 operations were for brain tumors**

Surround yourself with good friends – think outside the box:

JASON BOURNE

JACK REACHER

JOHN WICK

JACK RYAN

ETHAN HUNT (The Impossible Mission Force)

TONY STARK (The Avengers)

THE EQUALIZER (Robert McCall)

Quotes of the Mission: Impossible Franchise

Ethan Hunt, Mission: Impossible - Dead Reckoning Part One

"A Nuclear Bomb is Something You Bother Me with Immediately"

William Brandt, Mission: Impossible - Rogue Nation

"I Can Neither Confirm Nor Deny Details Of Any Operation..."

Ethan Hunt, Mission: Impossible - Rogue Nation

"Not 'In' the Plane, 'On' the Plane"

The Warrior…

- **Fate whispers to the warrior – you will not withstand the storm – the warrior whispers back – I am the storm**

Overview

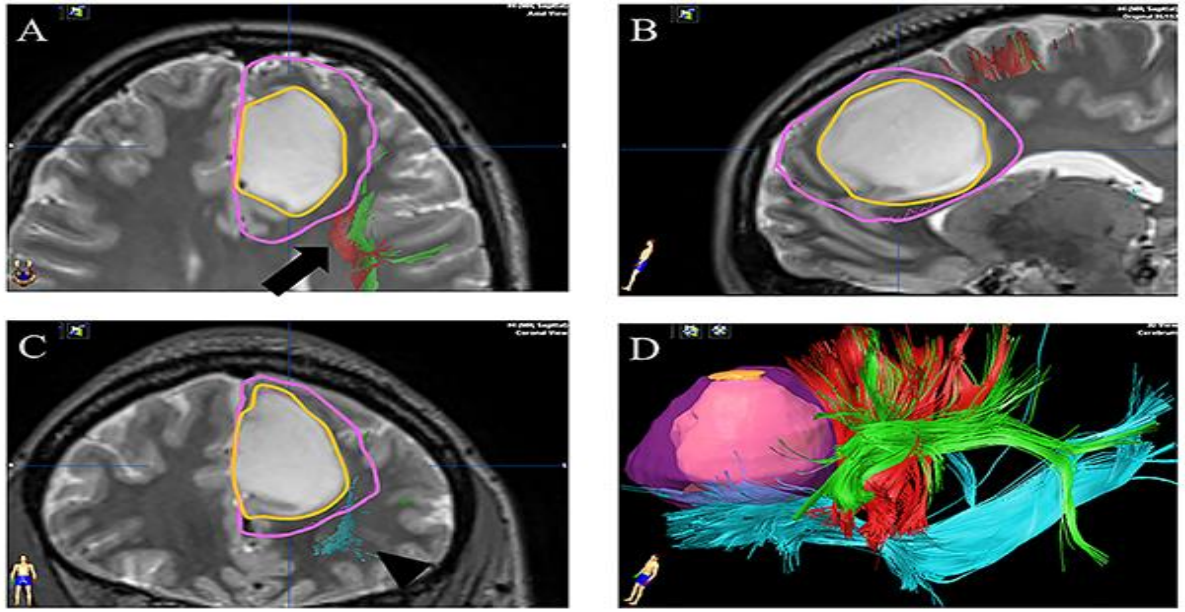
- **INTRODUCTION**
- **MOLECULAR PATHOLOGY**
- **CLINICAL TRIALS**
- **TREATMENT PARADIGMS**

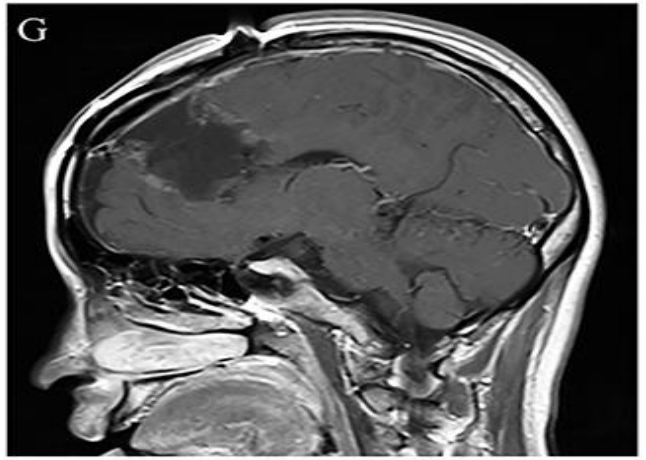
Surgical Option:

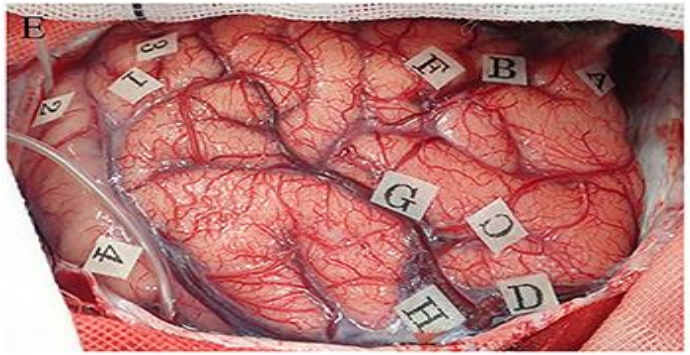
Surgical Planning:

- **Maximal Safe Surgical Resection**
- **Supra – Maximal Resection**
- **Fluorescence Guided Surgery / 5 ALA**
- **Connectomics / Fiber Tracking**
- **Intra – Operative MRI**
- **Awake Craniotomy**

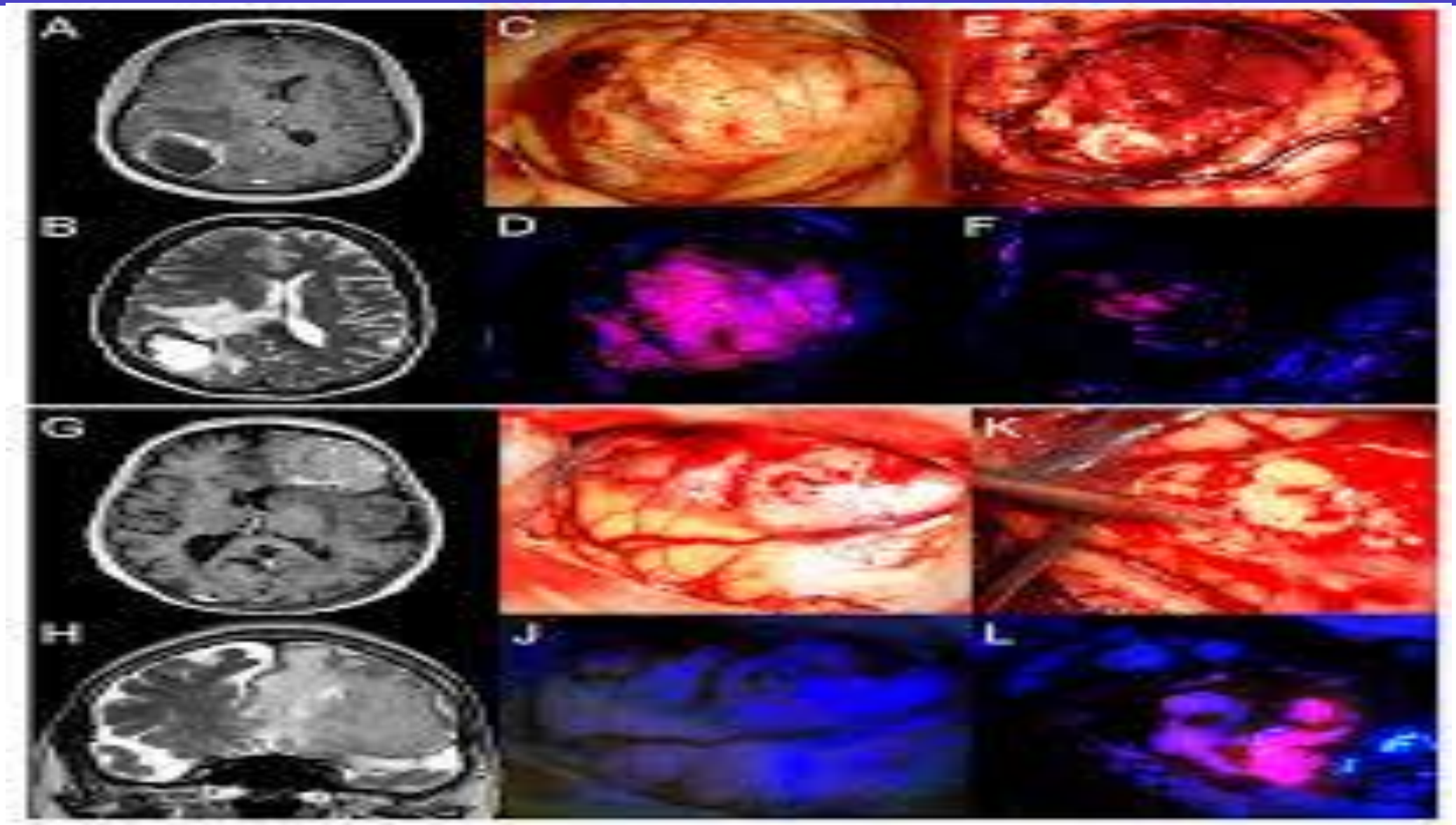
Supra – Maximal Resection:



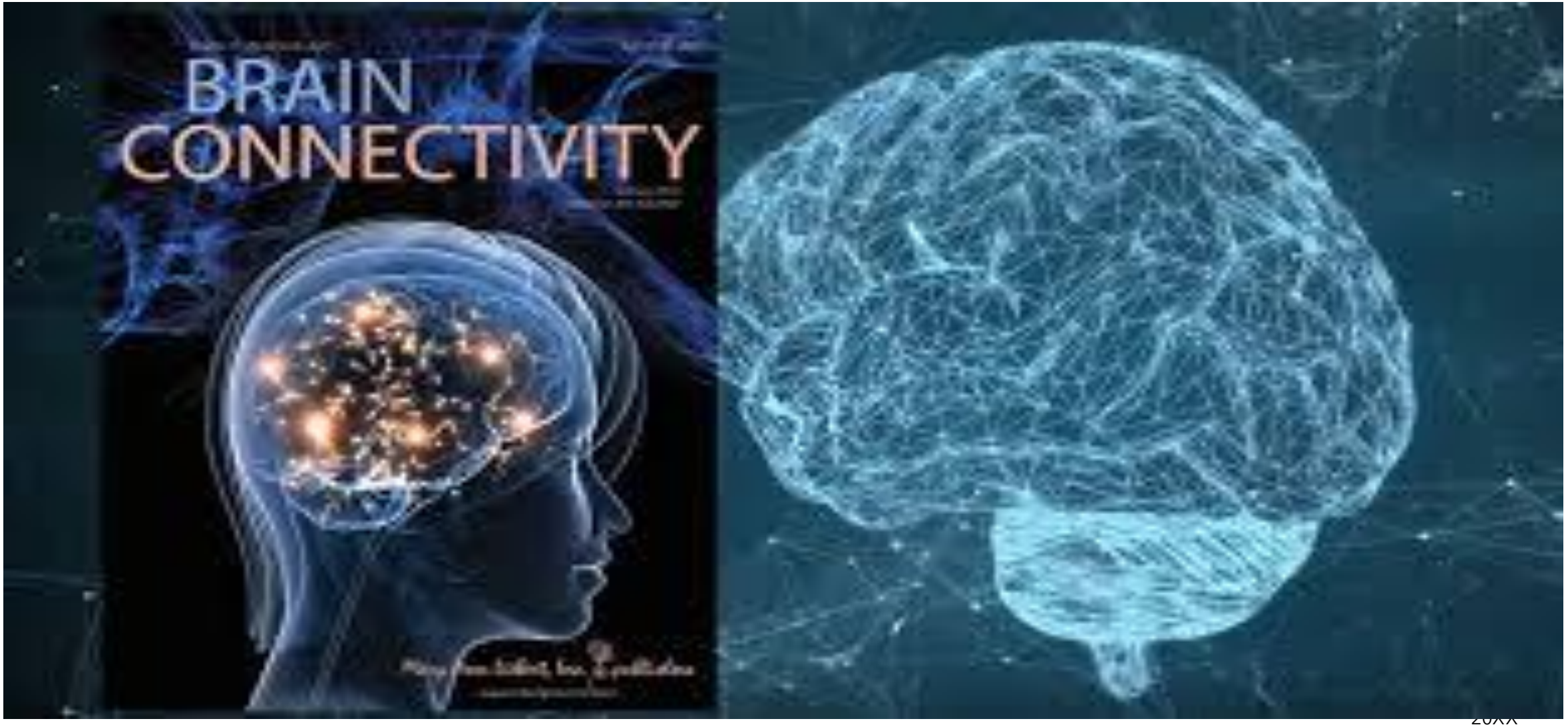




Fluorescence Guided Surgery:

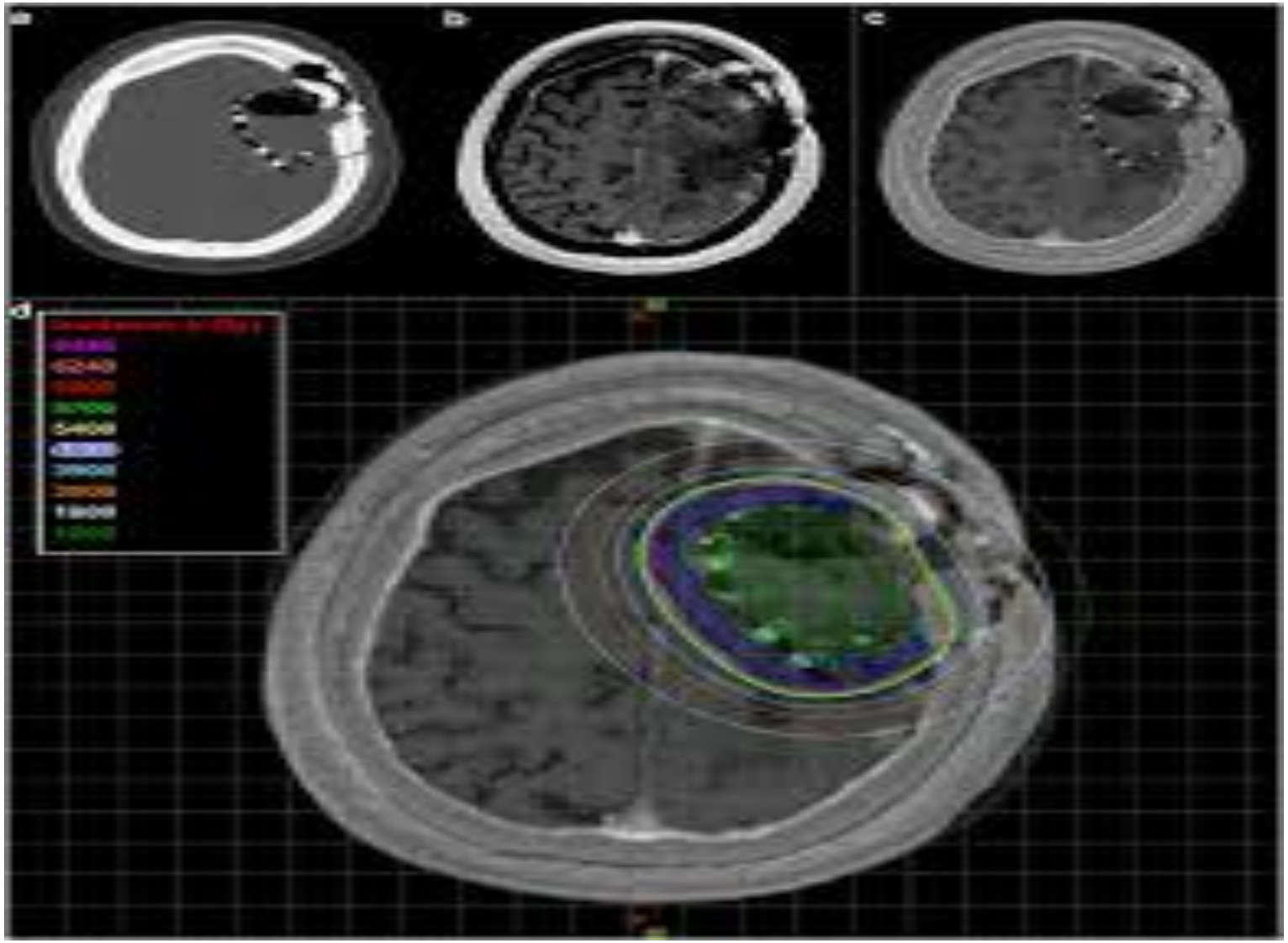


The Brain Connectome:



The Human Connectome Project:

Intra – Cavitary Brachytherapy:



New GBM: “Gestalt Trial” GTM 103

- **Cesium 131 Radioactive Seeds embedded in an absorbable collagen matrix**
- **Brachytherapy in the surgical cavity of GBM followed by reduced dose IMRT + TMZ**

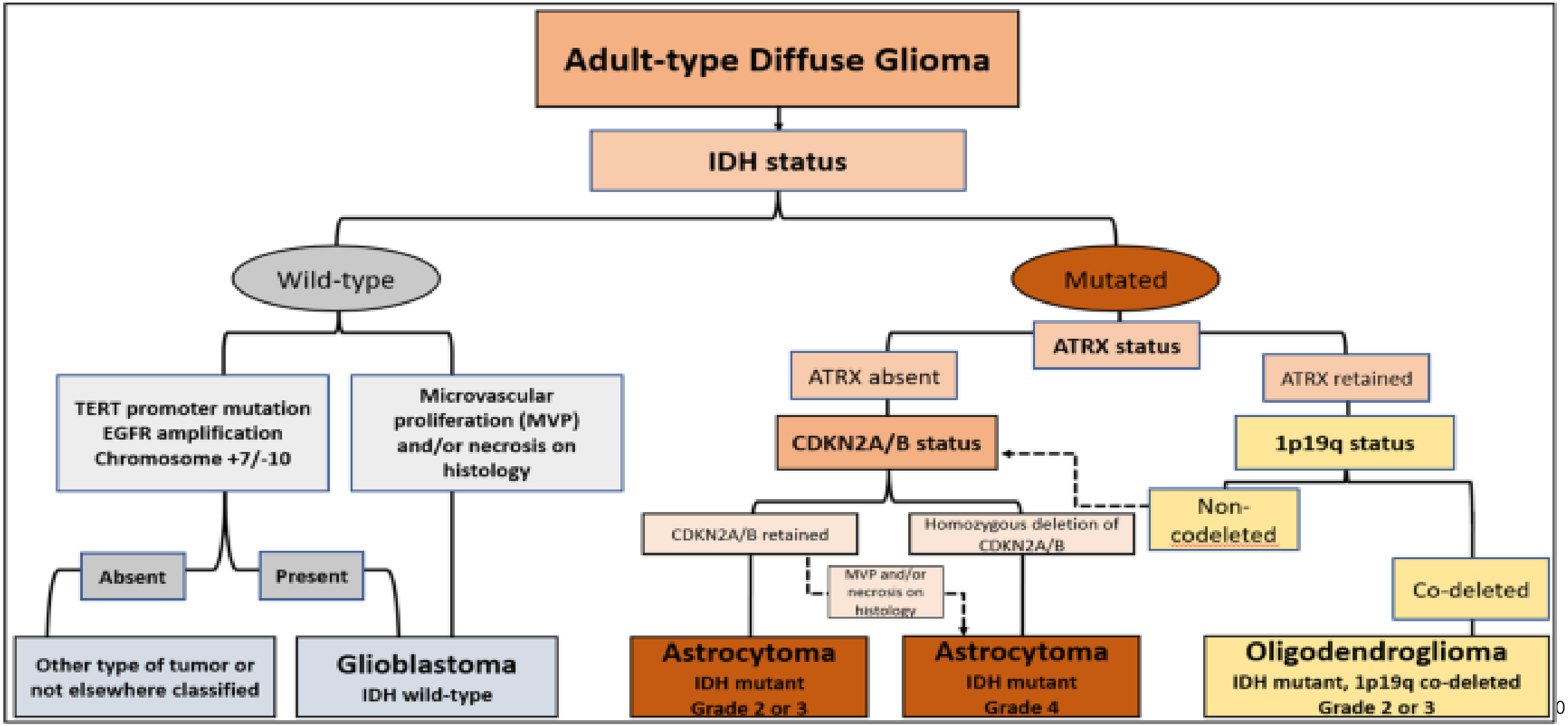
CNS Metastasis: GTM 102

- **“ROADS TRIAL”**
- **Resectable CNS Metastasis**
- **50 / 50 Randomization between Resection + Cesium 131 Brachytherapy VS Resection + SRS**

Ethan Hunt, Mission: Impossible - Dead Reckoning Part One

"We Live And Die In The Shadows..."

Glioma Molecular Pathology:



Radiotherapy:

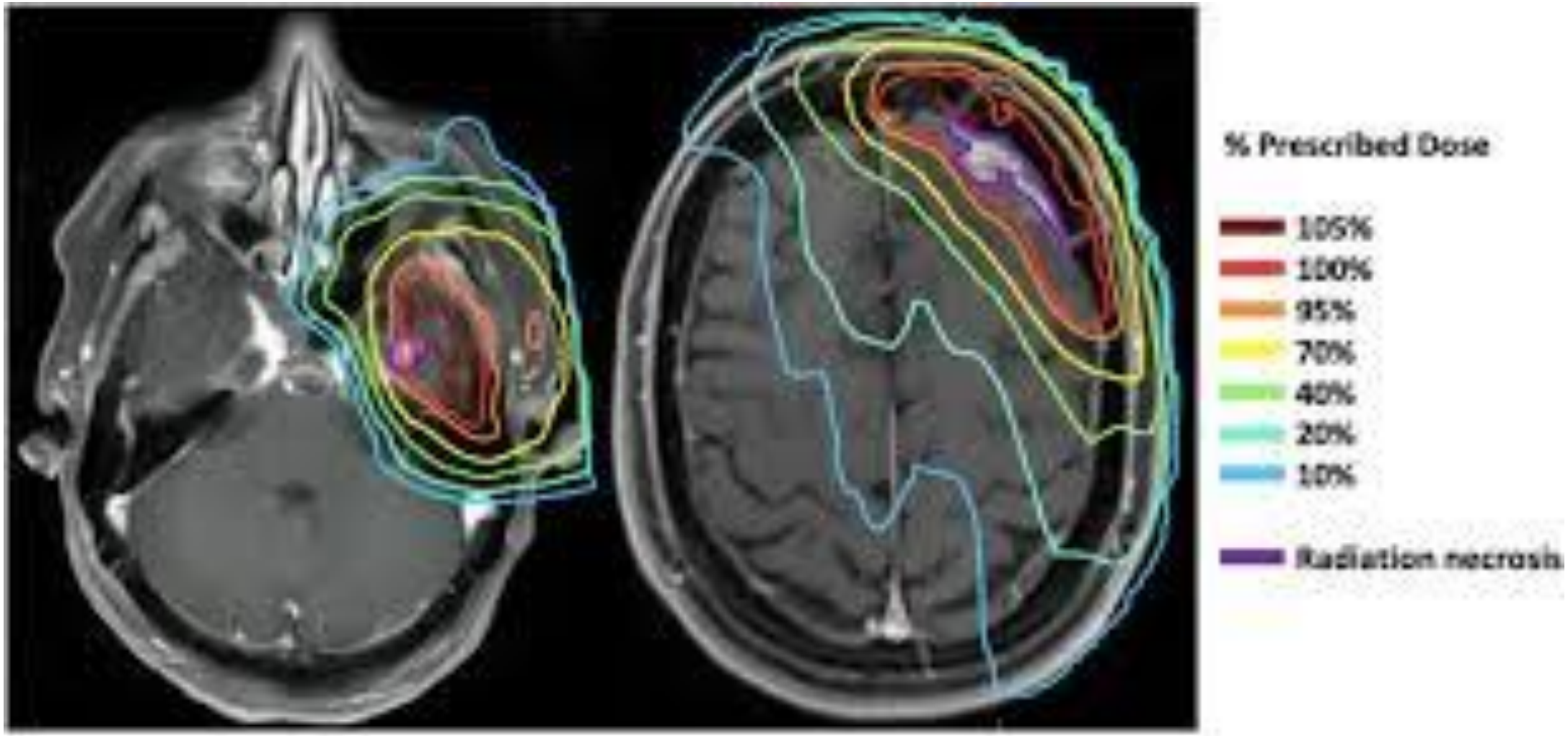
Photon Based RT

- **IMRT**
- **SRS / SRT**
- **Intracavitary Brachytherapy**

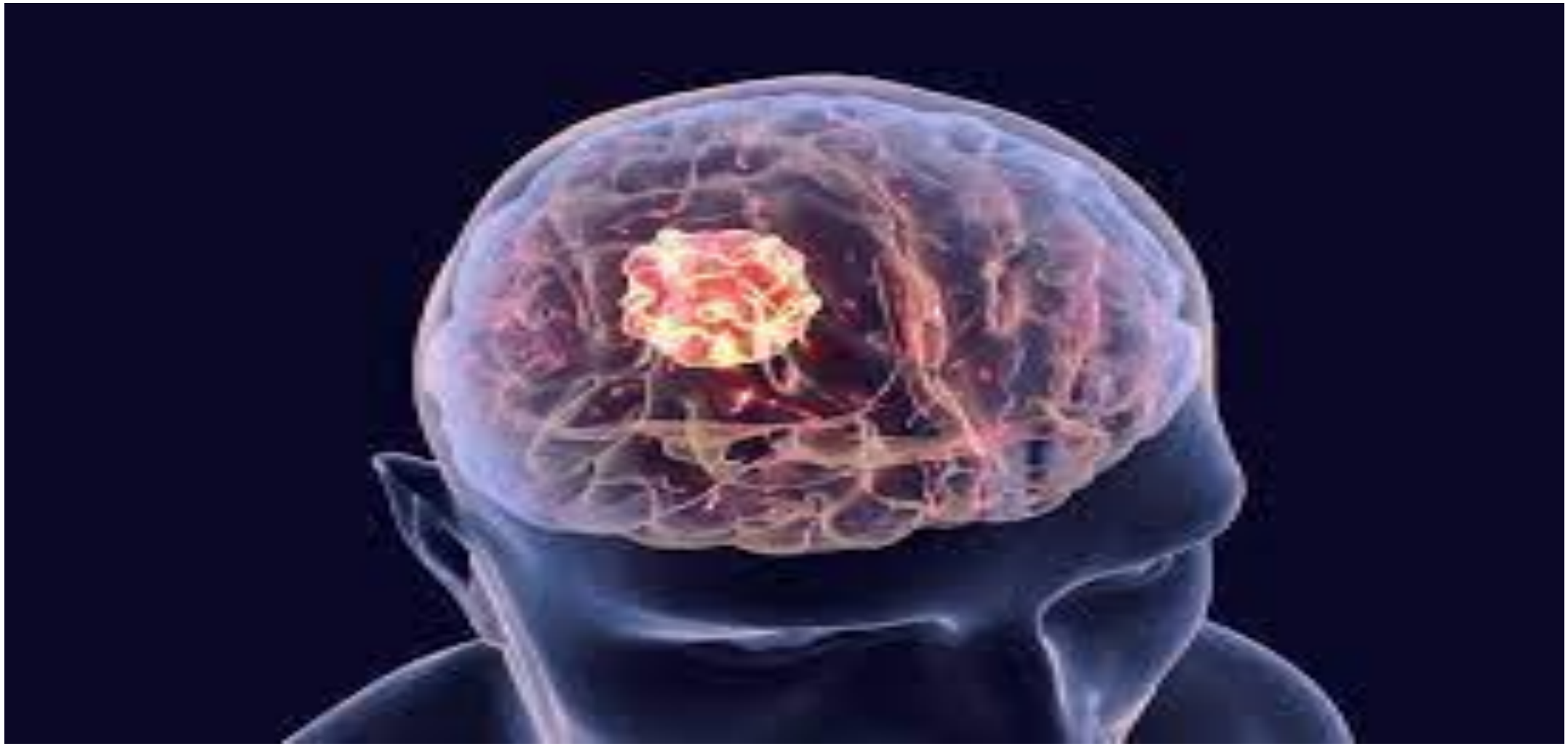
Proton Based RT

- **IMPT**

Proton vs Photon RT:



Laser Interstitial Thermal Therapy:



Laser Interstitial Thermal Therapy:

Barriers in Glioma Management: Is a Cure Imminent?

- Defining Biologically Active Tumor Regions (? role of Amino Acid PET Imaging as F DOPA – PET, FET – PET, Methionine PET Imaging)
- We should look at Gliomas "inside – out instead of outside – in"?
- Do we focus on the TME (Tumor Micro – Environment)?
- Do Immunotherapies / Glioma Vaccines have a role?
- Angiogenesis?
- Multi – Targeting Agents?
- Individualizing Therapies? (Ex Vivo Assays and Drug Sensitivity – Kiyatec? – Chemo ID Assay and other assays)

Alan Hunley, Mission: Impossible - Rogue Nation

"We Need Reliable Intelligence, And We Need It Now..."

Challenges in "Sustained Glioma Suppression":

- Tumor Heterogeneity
- Driver Mutations
- Intra-tumoral Genomic Heterogeneity
- Inter-tumoral Genomic Heterogeneity
- Temporal Genomic Heterogeneity
- Immunologically Cold Tumors
- Drug Target Engagement – "Weaponizable Targets"
- Blood Brain Barrier Challenge

High Intensity Focused Ultrasound:

Next Generation Clinical Trials:

NRG TRIALS

ALLIANCE TRIALS

BRACHYTHERAPY TRIALS

CONVECTION ENHANCED DELIVERY TRIALS (CED TRIALS)

PHARMA SPONSORED TRIALS

IMMUNOTHERAPY TRIALS

CAR T CELL THERAPY TRIALS

VACCINE TRIALS

ONCOLYTIC VIRUS TRIALS

NRG BN 005:

- A Phase II Randomized Trial of Proton vs. Photon Therapy (IMRT) for Cognitive Preservation in Patients with IDH Mutant, Low to Intermediate Grade Gliomas
- Open to accrual

NRG BN 007:

- A Randomized Phase II/III Open-Label Study of Ipilimumab and Nivolumab Versus Temozolomide In Patients With Newly Diagnosed MGMT (Tumor O-6-Methylguanine DNA Methyltransferase) Unmethylated Glioblastoma

NRG BN 010:

- A Safety Run-In and Phase II Study Evaluating the Efficacy, Safety, and Impact on the Tumor Microenvironment of the Combination of Tocilizumab, Atezolizumab, and Fractionated Stereotactic Radiotherapy in Recurrent Glioblastoma
- Open to accrual

NRG BN 011:

- A Phase III Trial of Lomustine-Temozolomide Combination Therapy Versus Standard Temozolomide in Patients with Methylated MGMT Promoter Glioblastoma
- Open to accrual

NRG BN 012:

- A Randomized Phase III Trial Of Pre-Operative Compared To Post-Operative Stereotactic Radiosurgery In Patients With Resectable Brain Metastases
- ? Reduction in the risk of Leptomeningeal Metastasis with Pre-Op SRS followed by resection

IDH 1 / IDH 2 Mutated Glioma:

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

Mellinghoff IK et al. DOI: 10.1056/NEJMoa2304194

CLINICAL PROBLEM

Gliomas, the most common malignant primary brain tumor type in adults, are categorized by histologic and molecular features and by tumor grade. Almost all grade 2 gliomas have mutations in the genes encoding the metabolic enzymes isocitrate dehydrogenase 1 (IDH1) or 2 (IDH2).

CLINICAL TRIAL

Design: This phase 3, double-blind, randomized, placebo-controlled trial tested the clinical effects of vorasidenib — an oral brain-penetrant inhibitor of mutant IDH1 and IDH2 enzymes — in patients with residual or recurrent grade 2 IDH-mutant glioma who had undergone surgery as their only previous treatment.

Intervention: 331 patients were assigned to receive oral vorasidenib (40 mg once daily) or matched placebo in 28-day cycles. The primary end point was imaging-based progression-free survival.

RESULTS

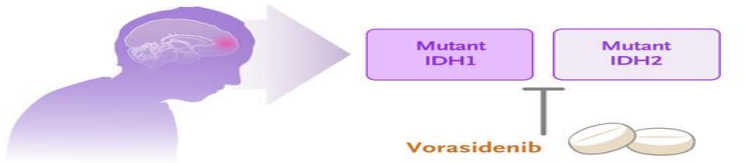
Efficacy: Progression-free survival was significantly longer with vorasidenib than with placebo.

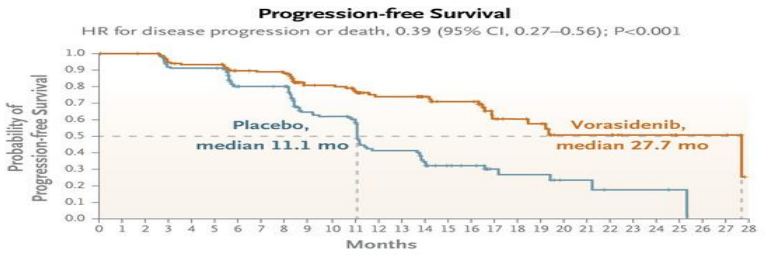
Safety: Although most adverse events with vorasidenib were mild, events of grade ≥3 were more frequent with vorasidenib than with placebo; the most common was an increase in alanine aminotransferase level. Serious adverse events that were determined by the investigators to be related to the trial drug or placebo occurred in 1.8% of vorasidenib recipients and in no placebo recipients.

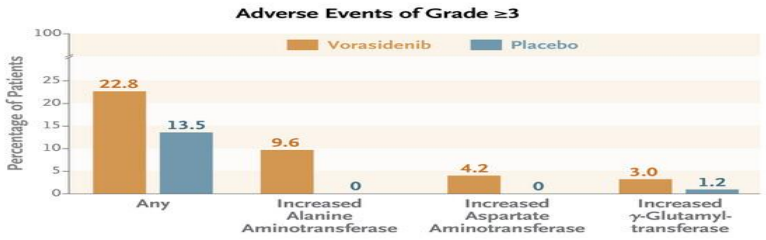
LIMITATIONS AND REMAINING QUESTIONS

- Patients with high-risk features were excluded from the trial.
- Additional end points, including health-related quality of life and neurocognition, were not reported.
- Results for the overall survival end points remain to be determined.

Links: Full Article | NEJM Quick Take | Editorial | Science behind the Study

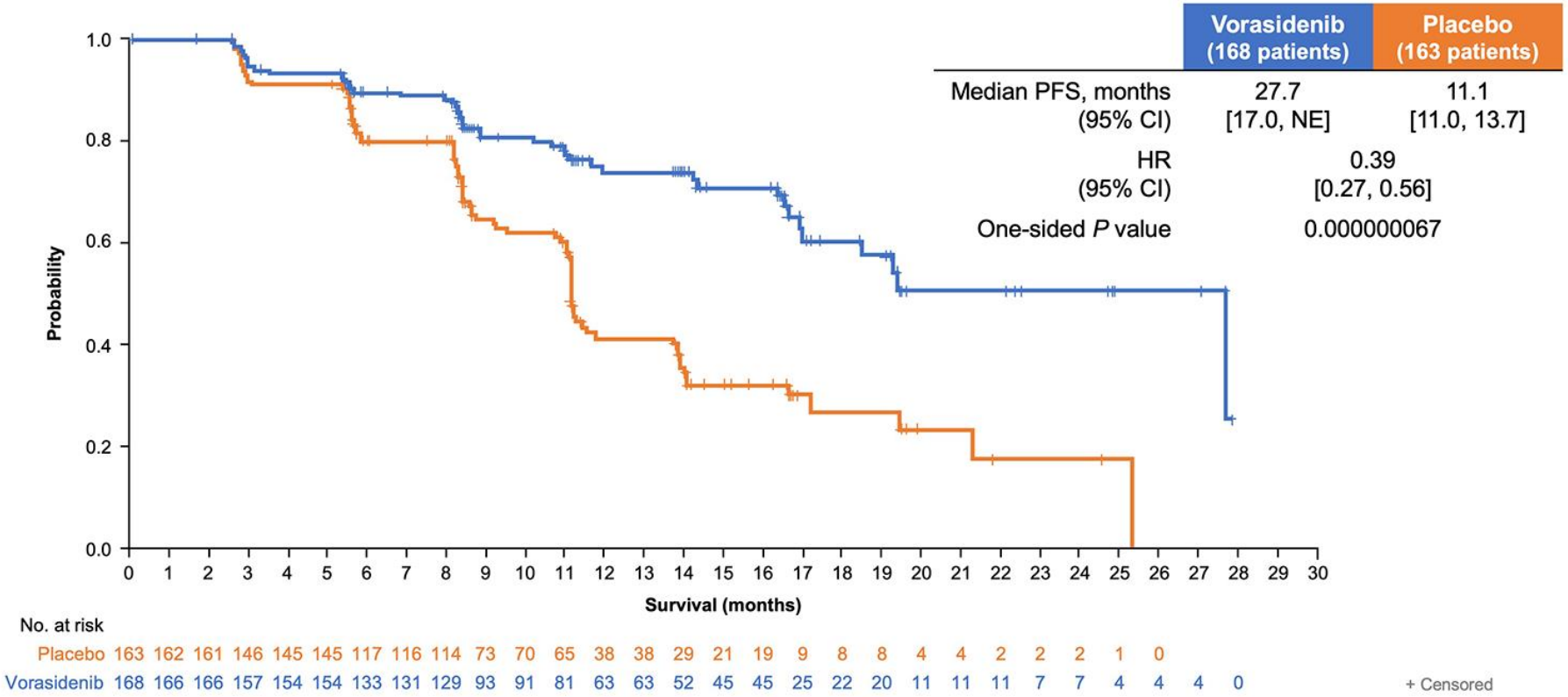






CONCLUSIONS

Among patients with grade 2 IDH-mutant glioma, progression-free survival was significantly longer with vorasidenib than with placebo.



Indigo Trial Data for IDH Mutated Glioma Tumors

"Fait Accompli" for IDH Mutated Glioma?

- The Indigo Trial included:
  - Biopsied and Resected Tumors that were progressive in follow up
  - Only included Grade 2 Tumors
  - Not all IDH Mutated Gliomas responded
  - Up regulation of other driver mutations
  - Does neutralizing IDH 1 / 2 signaling change the trajectory of other compensatory drivers
  - How do we negotiate IDH 1 / 2 mutated Grade 3-4 Gliomas and Grade 2 Gliomas that have failed RT + TMZ

Alliance A072301:

- Newly Diagnosed CNS WHO Grade 2 / 3 IDH 1/2 Mutated Glioma
- Radiation (54 GY for Grade 2 and 59.4 GY for Grade 3 Tumors)
- Followed TMZ + IDH Inhibitor (Vorasidenib) VS TMZ + Placebo

Alliance A072302:

- Recurrent IDH 1/2 Mutated Glioma with ATRX Loss
- ATR Protein Kinase Inhibitor (ATR Inhibitor): Tuvusertib
- Tuvusertib + Pembrolizumab
- Tumor Microenvironment – TILS (Tumor Infiltrating Lymphocytes)

The Future:

- **“This is not the end, not even the beginning of the end, this may be the end of the beginning”**
  - **THE KINGSMEN**

Thank you