Management of brain tumors: Focus on Radiation, chemotherapy, and targeted therapies

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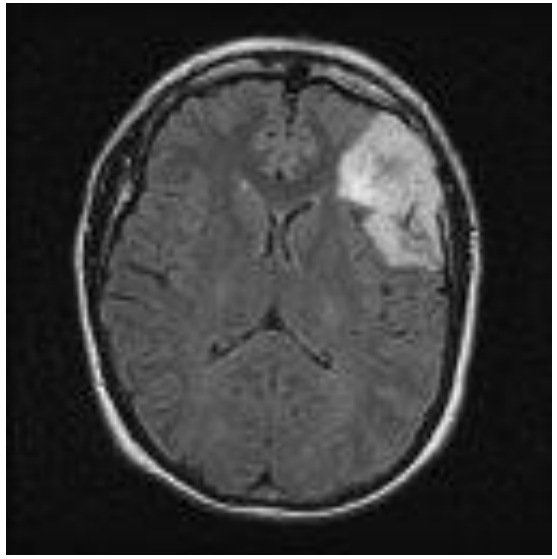
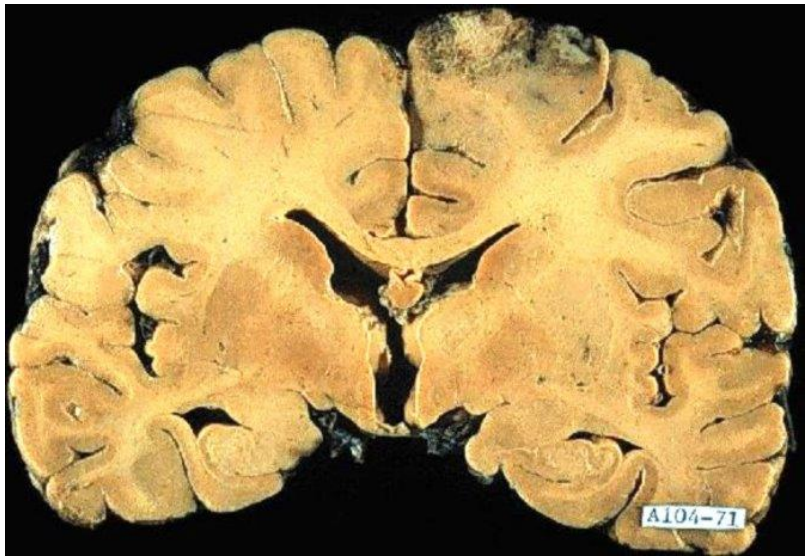


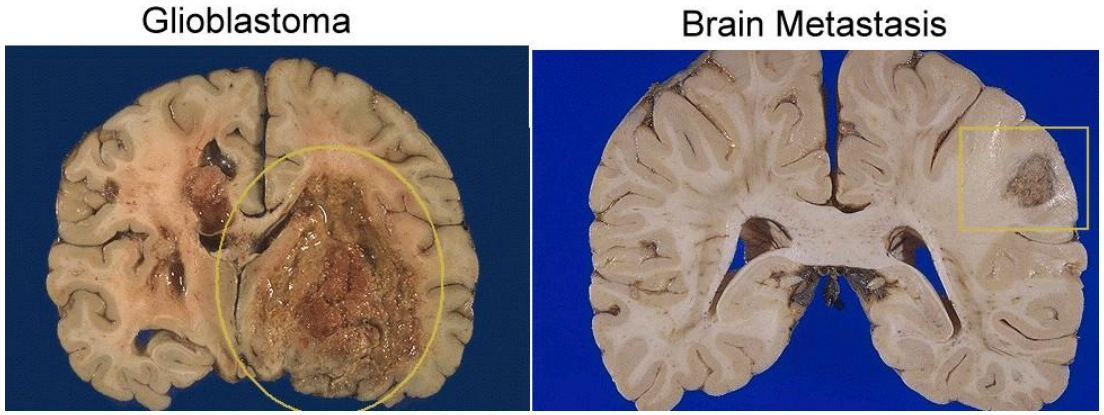


Introduction

- Brain tumors can be caused by a variety of things:
  - DNA damage
    - Radiation
    - Genetics
      - NF1 (acoustic neuromas/schwannoma)
      - Li Fraumeni syndrome
      - Tuberous sclerosis (SEGA)
      - Multiple endocrine neoplasia type 1 (pituitary macroadenomas)
    - Infection
      - HIV
  - Most tumors have an unknown cause (insidious)

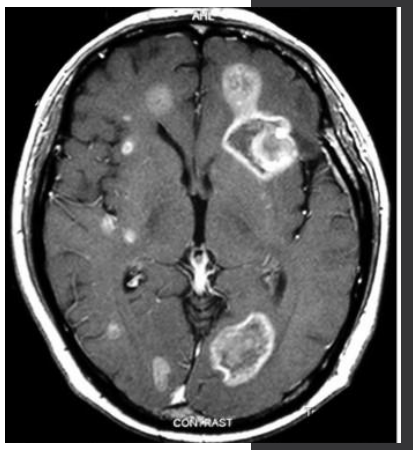
Types of Brain Tumors

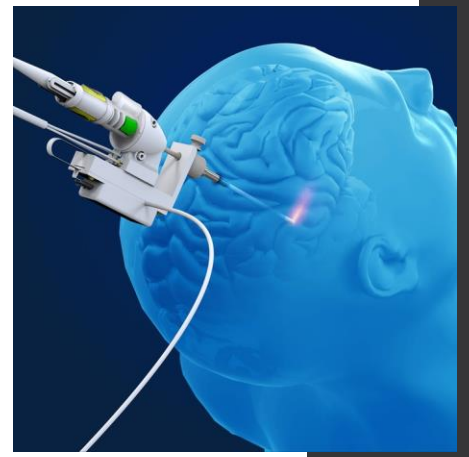
- Most commonly found are brain metastasis
  - Secondary tumors from other systemic cancer
  - Lung>Breast>melanoma
- Primary brain tumors
  - Meningioma>Glioblastoma>Pituitary>other
  - CBTRUS report



Brain metastasis

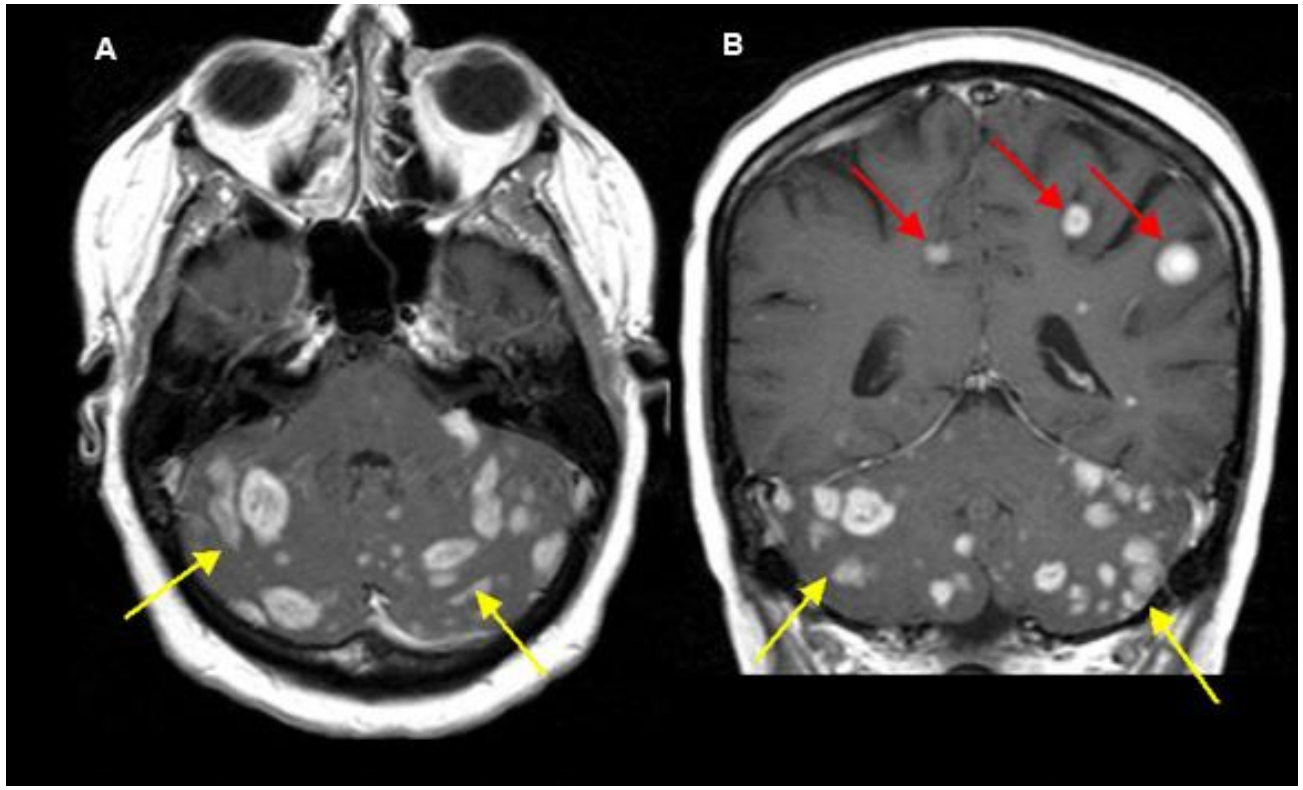
- Treatment depends on primary cancer and its extent
  - Some therapies cross BBB—allows for treatment of both systemic disease and brain mets
    - Osimirtinib (Tagrisso)
    - fam-trastuzumab-duruxtecan-nxki (Enhertu)
- Treatment also hinges on patients fitness/ability to tolerate treatment, as well as goals of care
- Radiation is foundation for multiple brain mets
  - Can consider surgical resection of larger tumors
  - Can also use gamma tile or LITT for brain mets





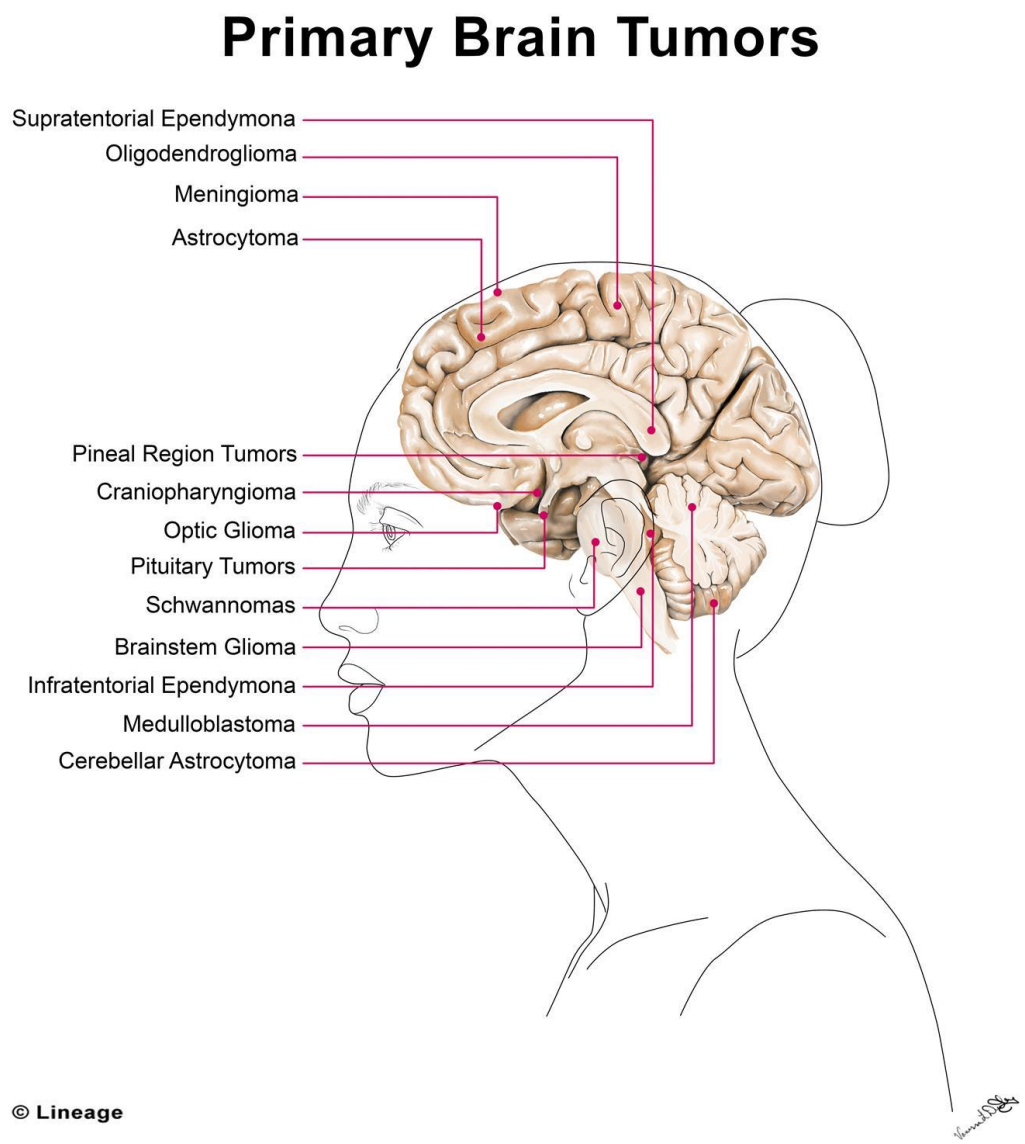
Brain metastasis

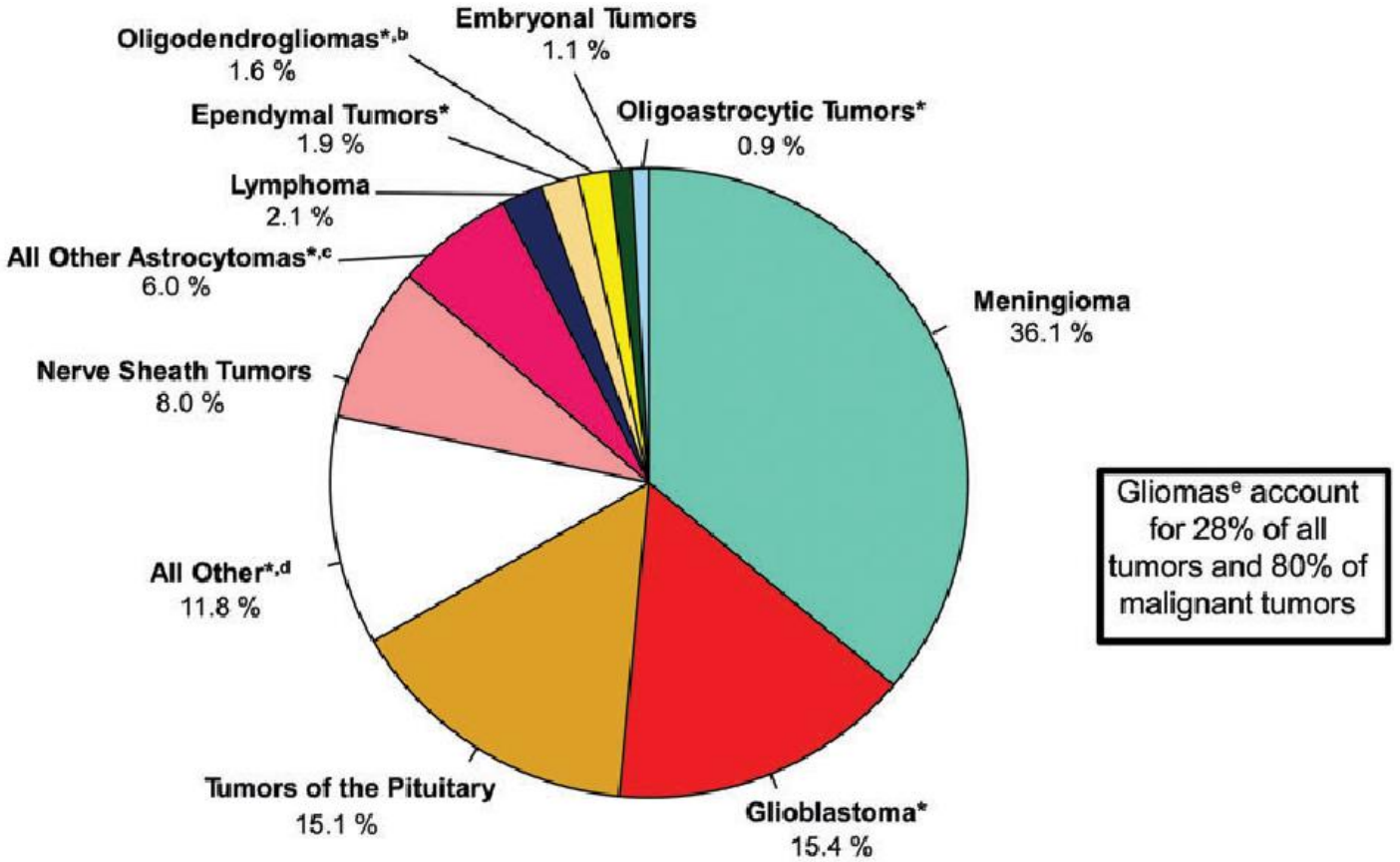
- Supportive therapy:
  - Vasogenic brain edema: steroids (dexamethasone)
  - Pain: narcotic or non-narcotic analgesia
  - Nausea: antiemetics
  - Seizures: antiepileptics
    - Can be used prophylactically in setting of surgery
    - No indication for prophylactic use in other settings
      - Risks>benefit



Primary brain tumors

- Glioma
  - Astrocytoma, Oligodendroglioma, ganglioglioma, DIPG, Ependymoma
- Glioblastoma
- Primary CNS Lymphoma
- Pineal region tumors
  - Pineal cell tumors, germ cell tumors
- Pituitary tumors
- Meningioma
- Acoustic neuroma
- Others





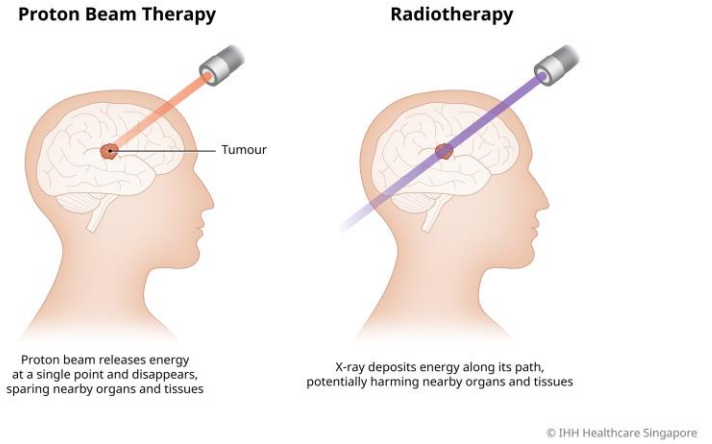
** All or some of this histology is included in the CBTRUS definition of gliomas, including ICD-O-3 histology codes 9380-9384, 9391-9460, 9480 (Table 2a).*
a. Percentages may not add up to 100% due to rounding. b. Includes oligodendroglioma and anaplastic oligodendroglioma (Table 2a). c. Includes pilocytic astrocytoma, diffuse astrocytoma, anaplasti astrocytoma, and unique astrocytoma variants (Table 2a). d. Includes glioma malignant, NOS, choroid plexus tumors, other neuroepithelial tumors, neuronal and mixed neuronal-glial tumors, tumors o the pineal region, other tumors of cranial and spinal nerves, mesenchymal tumors, primary melanocytic lesions, other neoplasms related to the meninges, other hematopoietic neoplasms, hemangion neoplasm, unspecified, and all other (Table 2a). e. ICD-O-3 histology codes: 9380- 9384, 9391-9460,9480 .

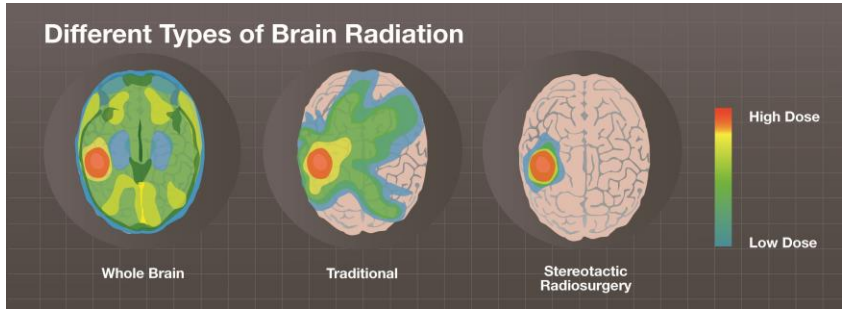
CBTRUS Report, 2007-2011

https://www.semanticscholar.org/paper/CBTRUS-statistical-report%3A-primary-brain-and-system-Ostrom-Gittleman/72d612233a341ef8126b71957b4697f0bb1ache

Introduction to Radiation Therapy

- Several modalities
  - Photon
    - Traditional radiation
    - IMRT and 3D conformal radiotherapy—computer planning to allow for more focused dose of radiation to the target area, sparing surrounding areas. IMRT is intensity modulated, allowing for different doses to different areas
  - Proton
    - Limits exit dose of radiation
    - Limits exposure to sensitive areas (optic nerve, brainstem, growth plates)
  - Radiosurgery
    - Gamma Knife, LINAC





Indications for Radiation Therapy

Radiation used either alone or in combination with chemotherapy

- More aggressive tumors like glioblastoma or HGG use concurrent chemo with radiation
- Lower grade tumors use radiation alone followed by chemotherapy
- Tumors that are non-chemo sensitive use radiation alone

Craniospinal radiation therapy

- Useful for leptomeningeal disease, tumors in spinal fluid space such as pineal tumors, ependymoma, medulloblastoma

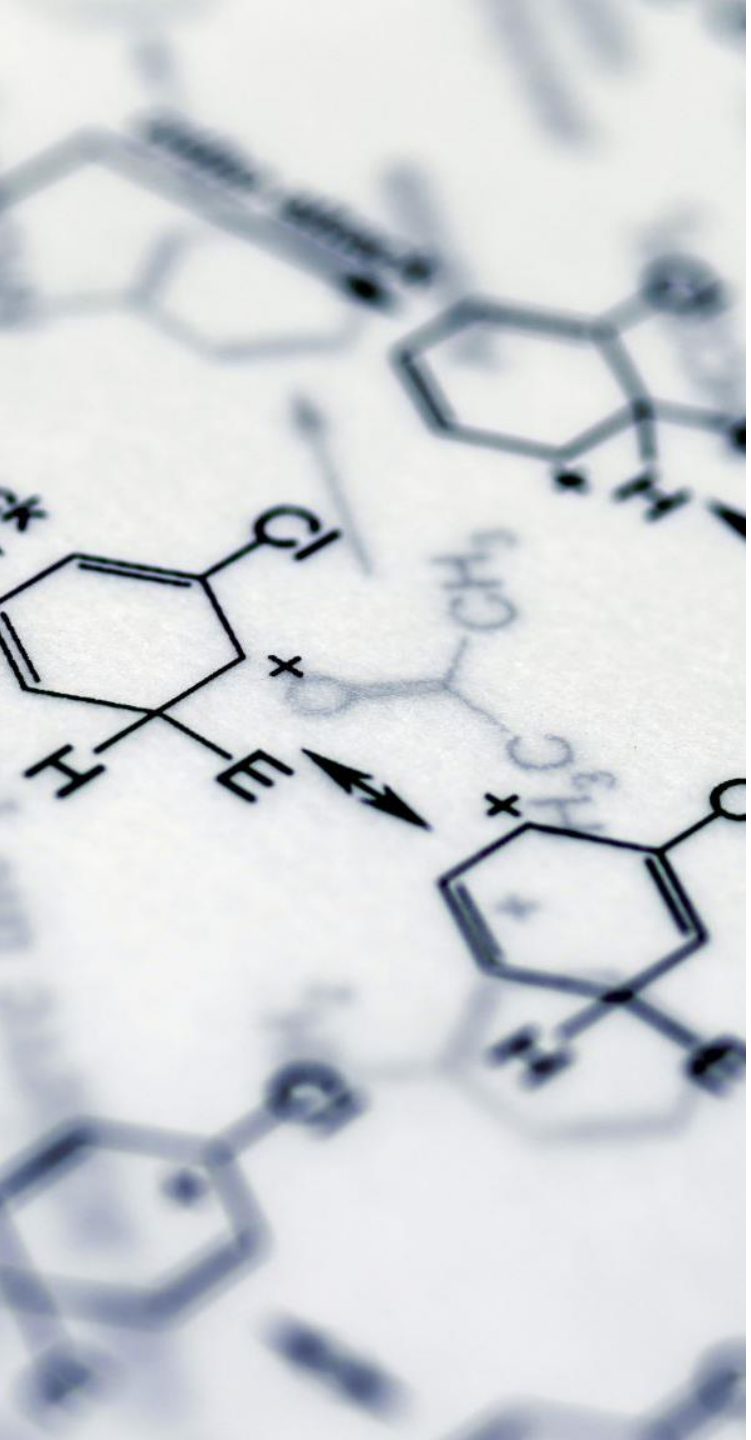
Side Effects of Radiation Therapy

Immediate side effects:

- fatigue
- hair loss
- Skin burns

Long term side effects:

- cognitive decline
- Bone marrow suppression
- Development of radiation induced neoplasm (meningioma)
- Vascular abnormalities



Introduction to Chemotherapy

- Different drugs used for different tumors
- Different mechanisms behind each one
  - Alkylating agents: cyclophosphamide, temozolomide, carmustine, cisplatin, carboplatin
  - Antimetabolites: MTX, Cytrabine, 5-Fu
  - Antitumor antibiotics: anthracyclines, dactinomycin
  - Plant alkaloids: vinca alkaloids, etoposide
  - Topoisomerase I inhibitors: topotecan, irinotecan

Timing of chemotherapy

Neoadjuvant	Adjuvant	Primary
• Germinoma ??	• Medulloblastoma • Gliomas • Metasteses	• PCNSL • Germinoma

Goals of chemotherapy

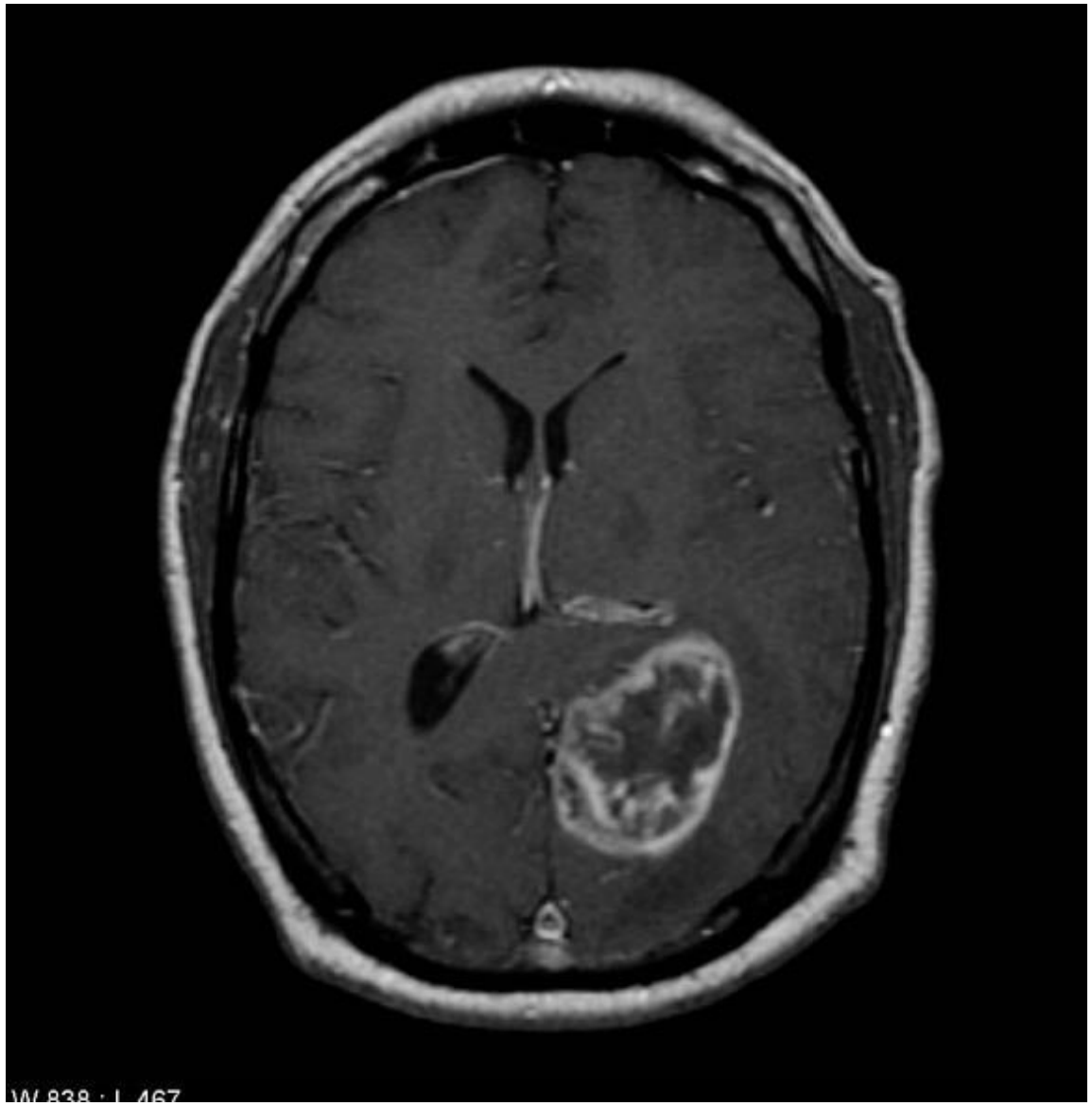
- Neoadjuvant: shrink tumor prior to surgery, enable a GTR
- Adjuvant: prolong time to recurrence, maintain good quality of life
  - Typically have a defined number of cycles
  - Occurs after surgery +/- radiation
- Primary: only used for very chemosensitive tumors, goal is a cure
- Recurrence
  - Number of cycles are limited by side effects
  - Goal is to improve symptoms, qualify of life, and to slow progression of disease

Challenges of chemotherapy

Tumors are biologically aggressive	Drug delivery	Toxicity to normal brain
• Most tumors unresponsive to chemotherapy • Need radiation to make tumor sensitive to radiation, but in some cases still not sensitive to chemo	• Blood Brain Barrier (BBB) keeps most chemotherapy out of the CNS • Most chemo by design is too large to pass through BBB to prevent neurologic side effects	• Limited in how much chemotherapy we can deliver before neurologic side effects occur (i.e MTX induced leukoencephalopathy)

Strategies to overcome the BBB

 Interstitial chemotherapy	Gliadel (wafers with carmustine) approved for use in primary brain tumors Causes significant cerebral edema and are commonly removed
 Intrathecal chemotherapy—delivery to the spinal fluid space	Not effective for parenchymal tumors such as metastasis or gliomas, but is effective for LMD
 Intra-arterial chemotherapy	Chemotherapy delivered to tumor using small catheters Still in clinical trials
 Convection-enhanced delivery	Catheters placed into tumor and drug delivered slowly and continuously Still in clinical trials



Glioblastoma

- Current standard of care is Stupp protocol
  - Radiation + concomitant temozolomide
    - 30Fx RT (60Gy total dose)
    - TMZ 75mg/m2/day
    - TMZ is a radiation sensitizer at this dose and allows the radiation to become more effective
  - 6 cycles adjuvant TMZ
    - TMZ dosed 150-200mg/m2 days 1-5 of the 28 day cycle
- Compared to radiation alone, RT + TMZ showed significant survival benefit

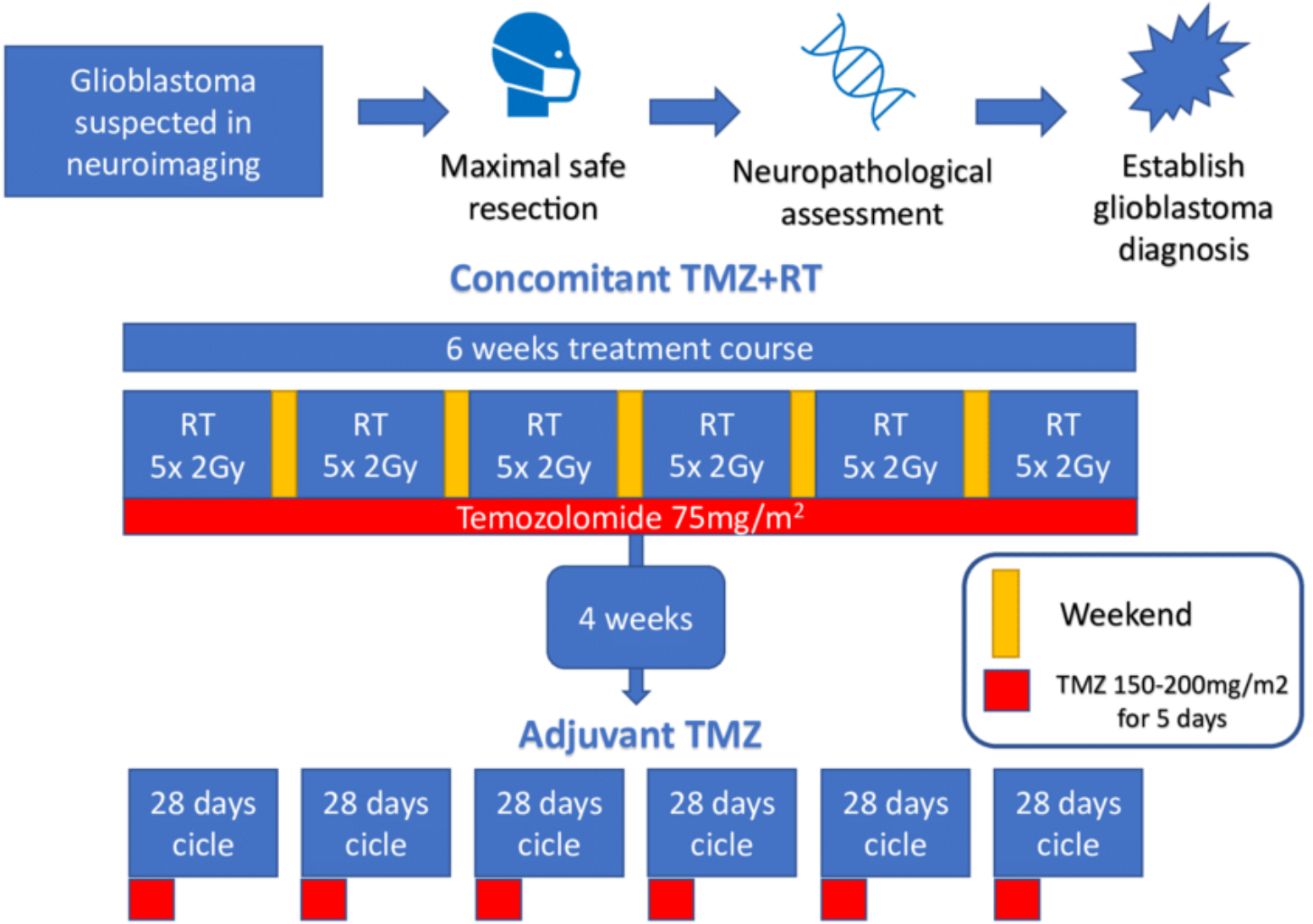
ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Authors: Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., +12, for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group* Author Info & Affiliations

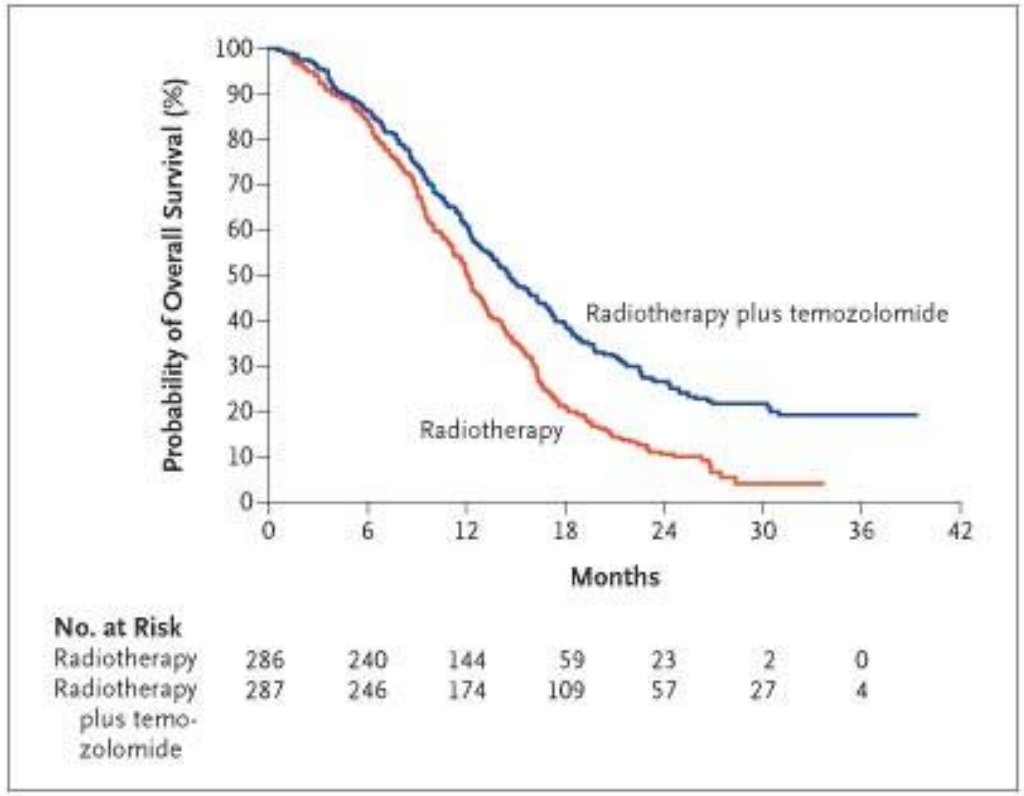
Published March 10, 2005 | N Engl J Med 2005;352:987-996 | DOI: 10.1056/NEJMoa043330 | VOL. 352 NO. 10

Stupp protocol schema

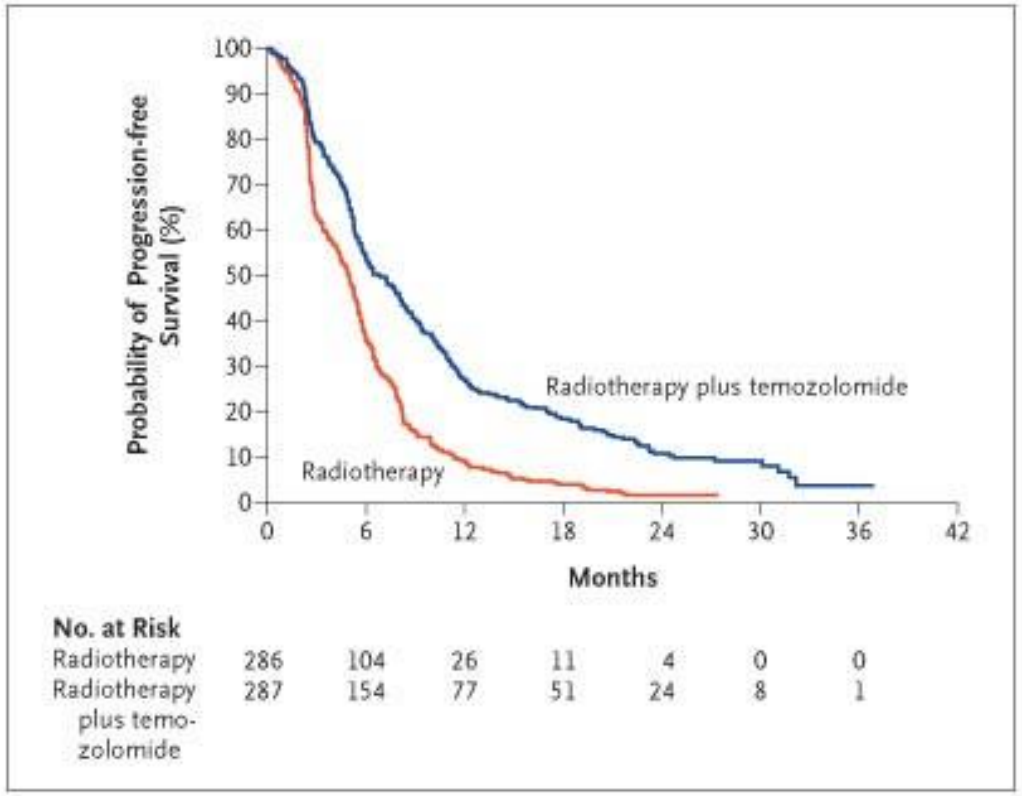


https://www.researchgate.net/figure/EORTC-NCIC-protocol-Stupp-protocol_fig1_350182554

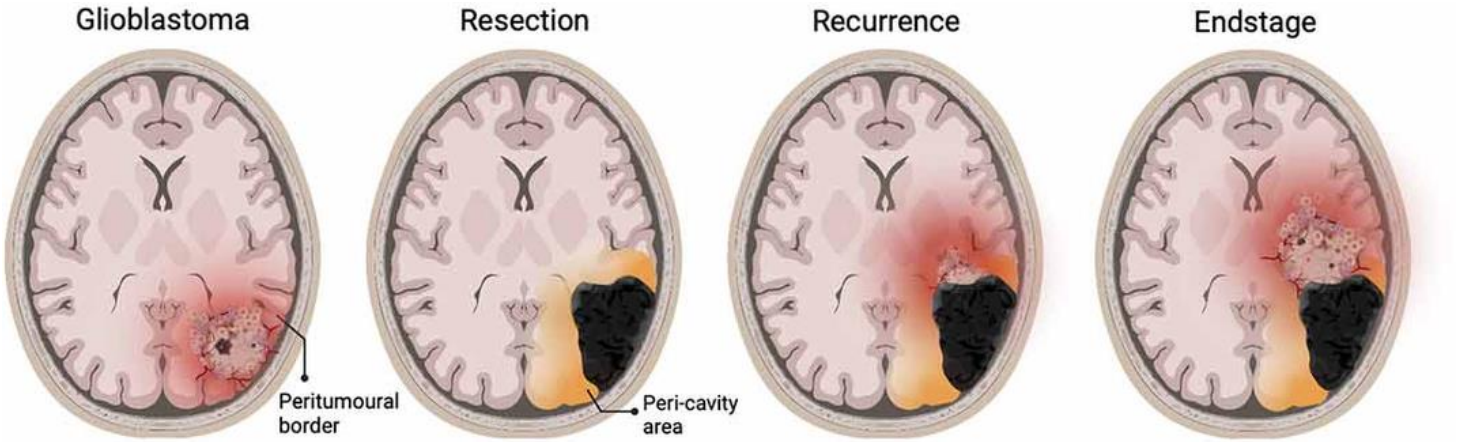
Stupp regimen



Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

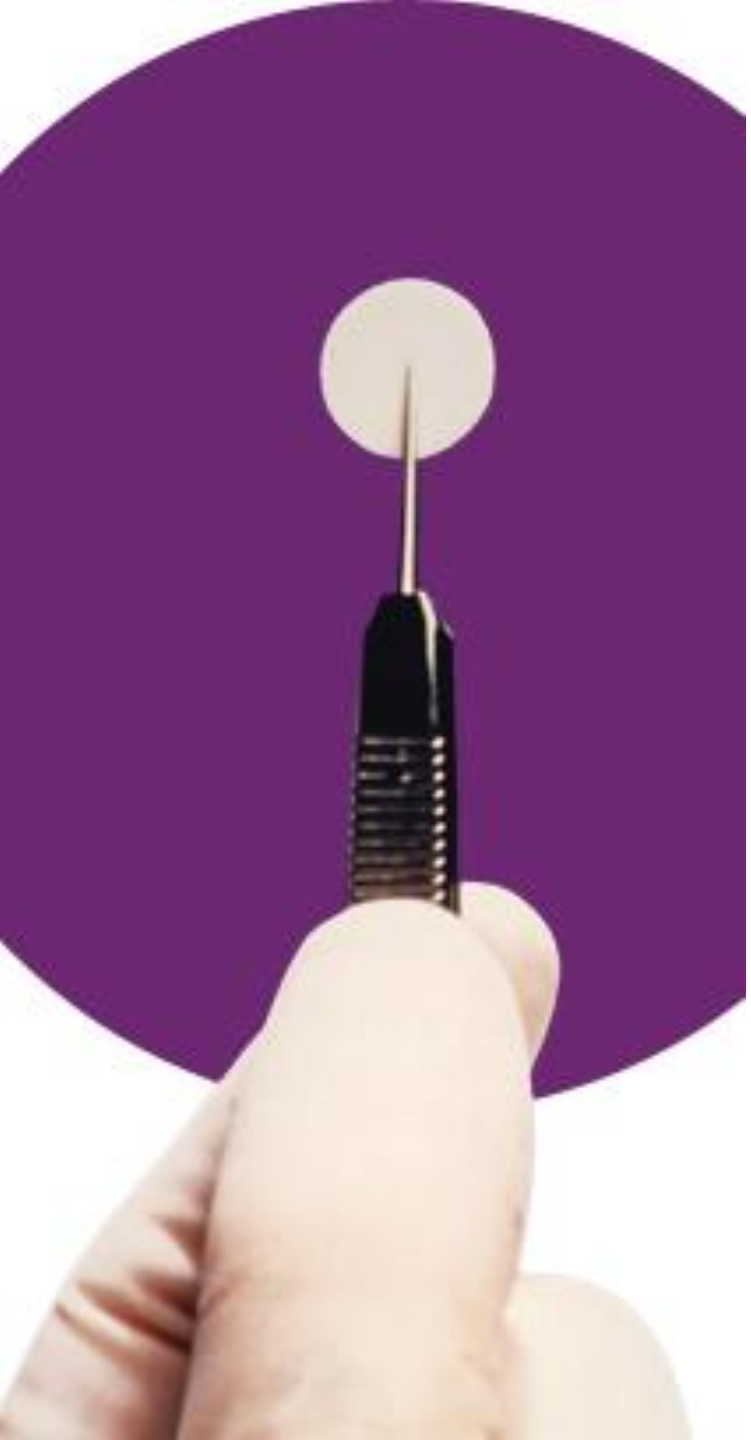


Kaplan–Meier Estimates of Progression-free Survival According to Treatment Group.



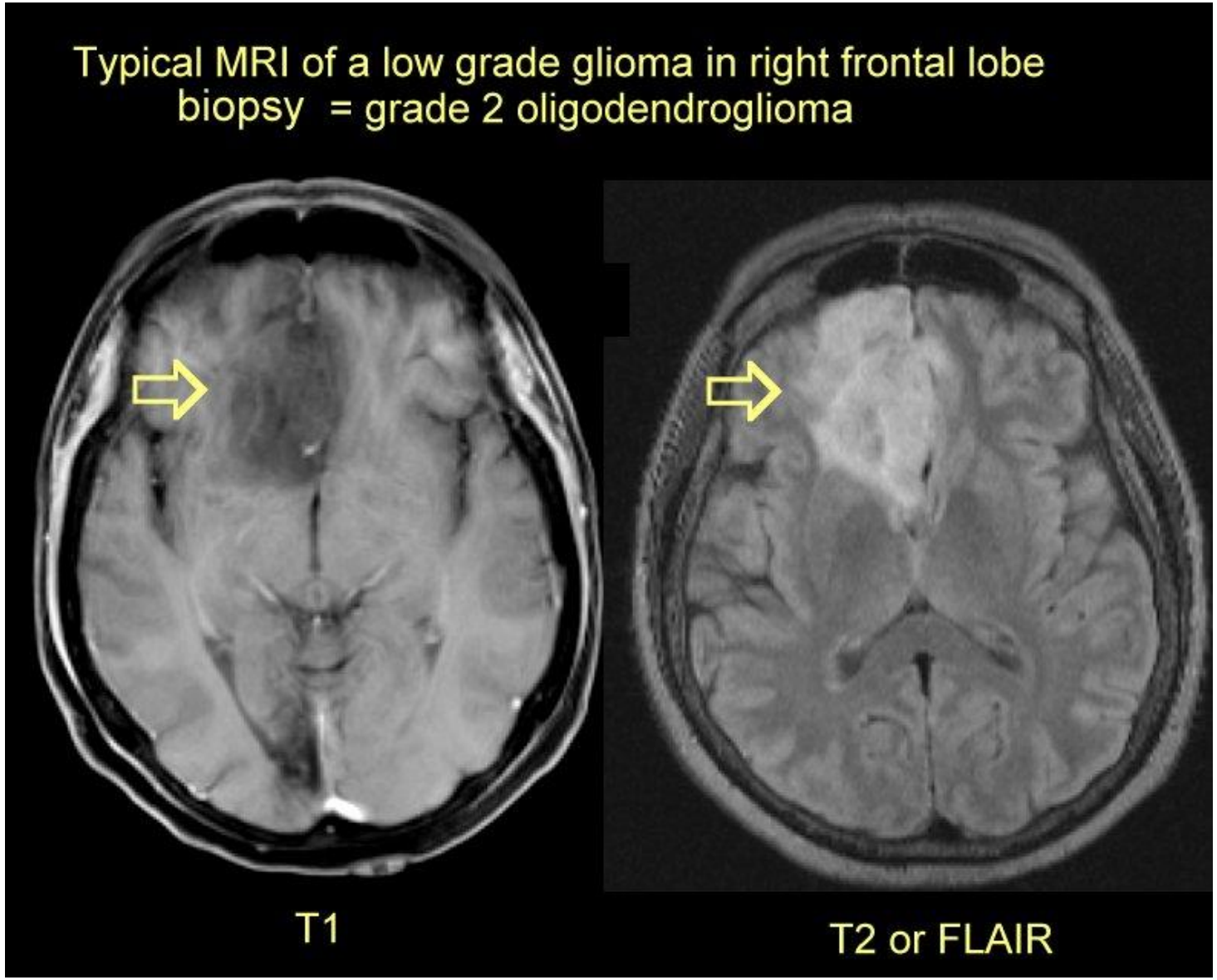
HGG progression

- Progression after first line therapy requires new treatment
  - Repeat resection?
  - Repeat radiation?
  - Temzolomide rechallenge?
- Role for clinical trials
- Other standard of care drugs



Lomustine (carmustine, BCNU)

- Used in several treatment regimens:
  - PCV—oligodendroglioma (procarbazine, lomustine, vincristine)
  - Medulloblastoma
  - Recurrent astrocytoma
- Oral formulation—Lomustine
  - Most common
  - Adminsitered once every 42 days
  - Side effects: n/v, constipation, fatigue, bone marrow suppression, pulmonary fibrosis
- Wafer delivery—Gliadel
  - Placed during surgical resection
  - Side effects: seizures, cerebral infection, vasogenic edema
- IV formulation—BCNU
  - Similar side effects and regimen to oral formulation



Low grade glioma

- Grade 2 Astrocytoma or Oligodendroglioma
  - Observation vs treatment vs targeted therapy
    - Considerations: Age, extent of resection, functional status
- Treatment:
  - Radiation alone followed by chemotherapy
  - TMZ vs PCV (procarbazine, lomustine, vincristine)
  - Targeted therapy:
    - IDH-mutant low grade glioma—vorasidenib (Voranigo)

The NEW ENGLAND JOURNAL of MEDICINE

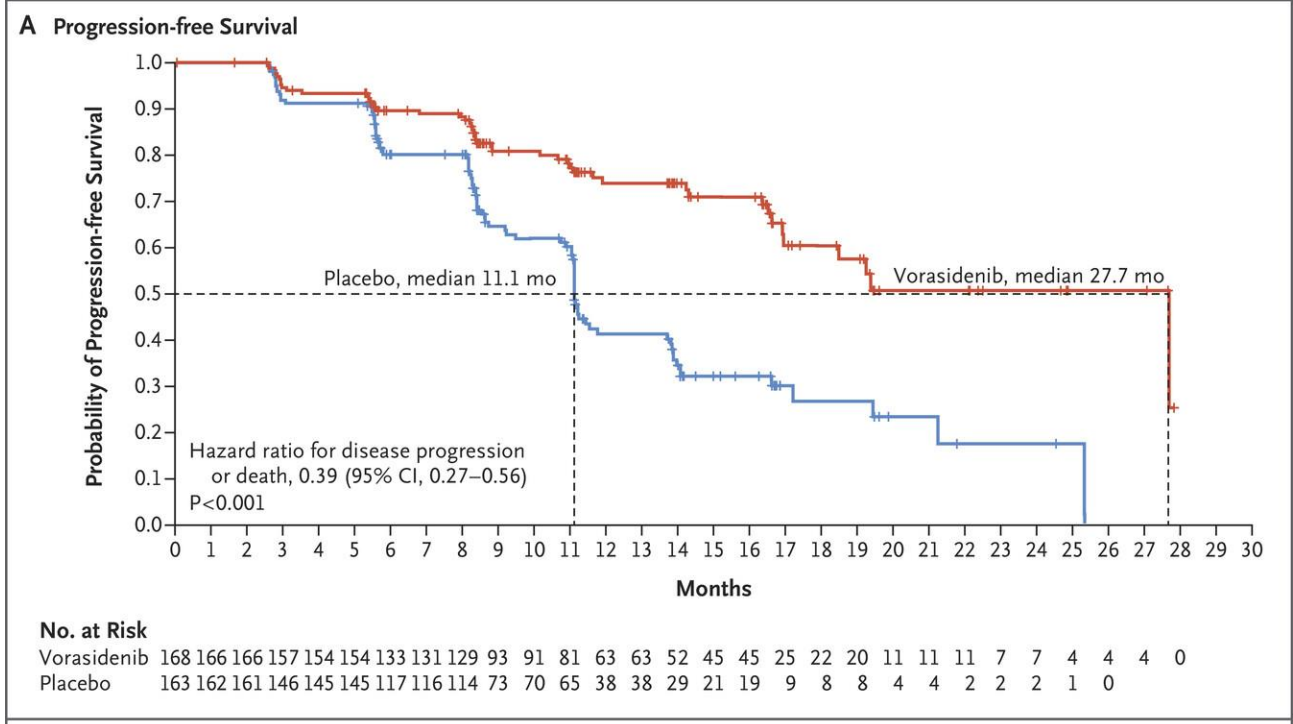
RESEARCH SUMMARY

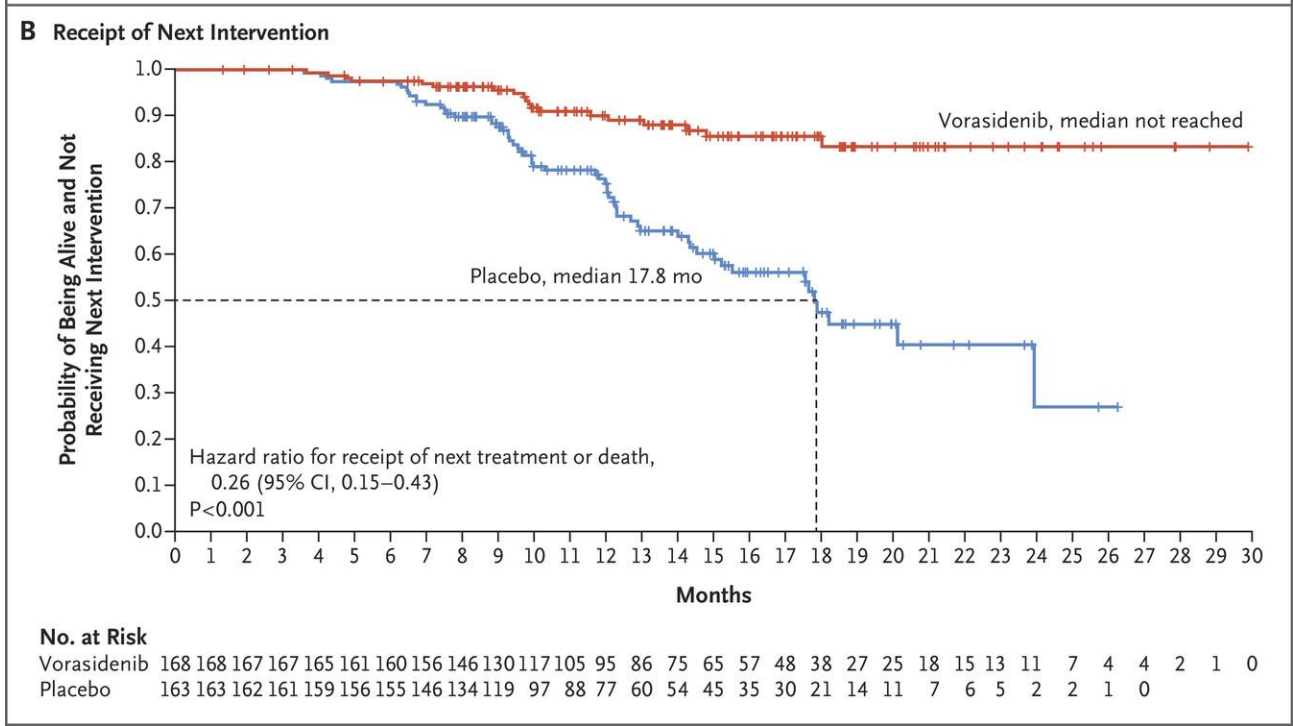
Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

Mellinghoff IK et al. DOI: 10.1056/NEJMoa2304194

Vorasidenib

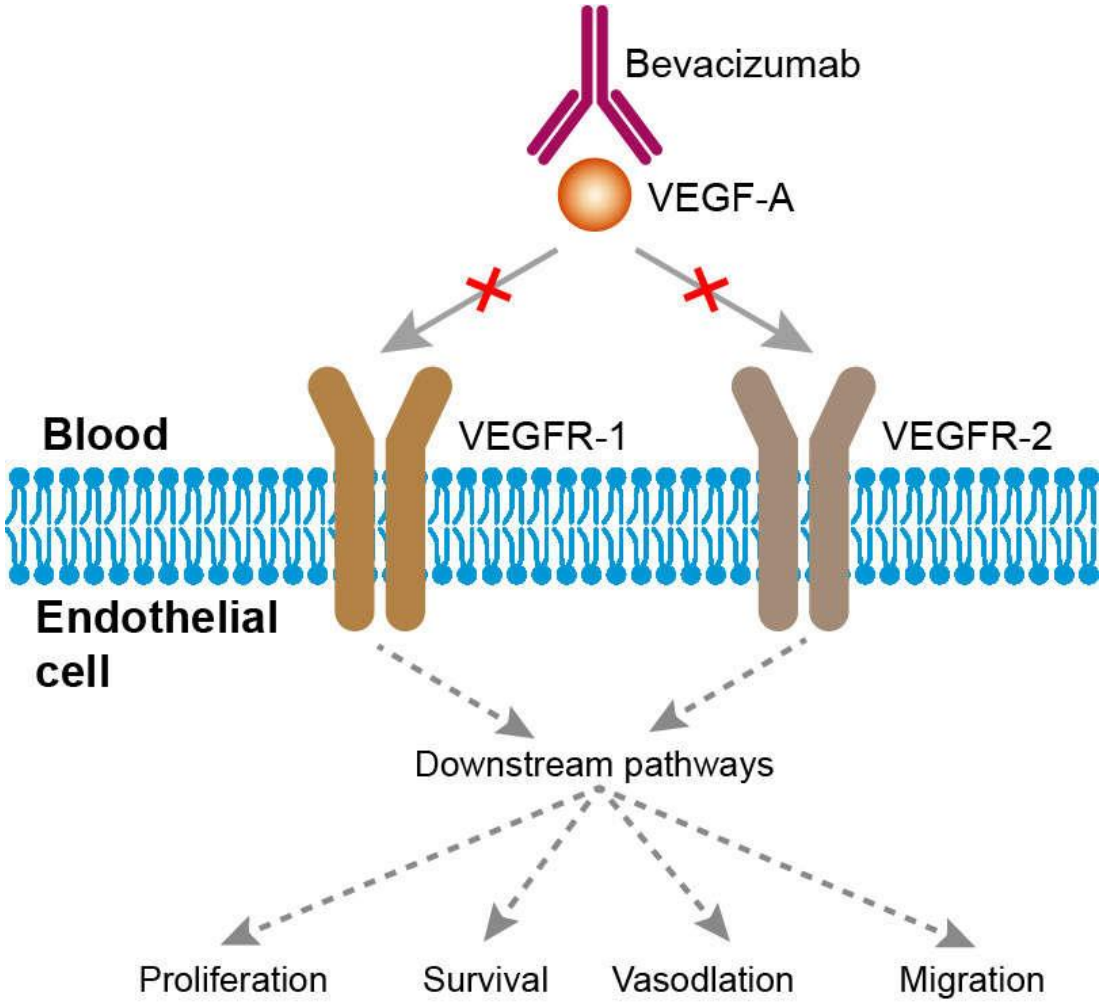
- Targets IDH-1 and IDH-2 mutation
- INDIGO study shows improved PFS and delayed time to next intervention





Bevacizumab

- VEGF inhibitor
- Targets angiogenesis
- No survival benefit however there is improvement in QoL and PFS
- Side effects:
  - Fatigue
  - Hypertension
  - Delayed wound healing
  - Venous/arterial clots, intracranial hemorrhage
  - GI perforation
  - Proteinuria
- Several studies looking at adding bevacizumab to treatment



Bevacizumab

ORIGINAL ARTICLE

Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma

Authors: Olivier L. Chinot, M.D., Wolfgang Wick, M.D., Warren Mason, M.D., Roger Henriksson, M.D., Frank Saran, M.D., Ryo Nishikawa, M.D., Antoine F. Carpentier, M.D., Ph.D., +6, and Timothy Cloughesy, M.D. Author Info & Affiliations

Published February 20, 2014 | N Engl J Med 2014;370:709-722 | DOI: 10.1056/NEJMoa1308345
VOL. 370 NO. 8 | Copyright © 2014

ORIGINAL ARTICLE

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Authors: Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Terri S. Armstrong, Ph.D., A.N.P.-B.C., Jeffrey S. Wefel, Ph.D., Deborah T. Blumenthal, M.D., Michael A. Vogelbaum, M.D., Ph.D., Howard Colman, M.D., Ph.D., +14, and Minesh P. Mehta, M.D. Author Info & Affiliations

Published February 20, 2014 | N Engl J Med 2014;370:699-708 | DOI: 10.1056/NEJMoa1308573
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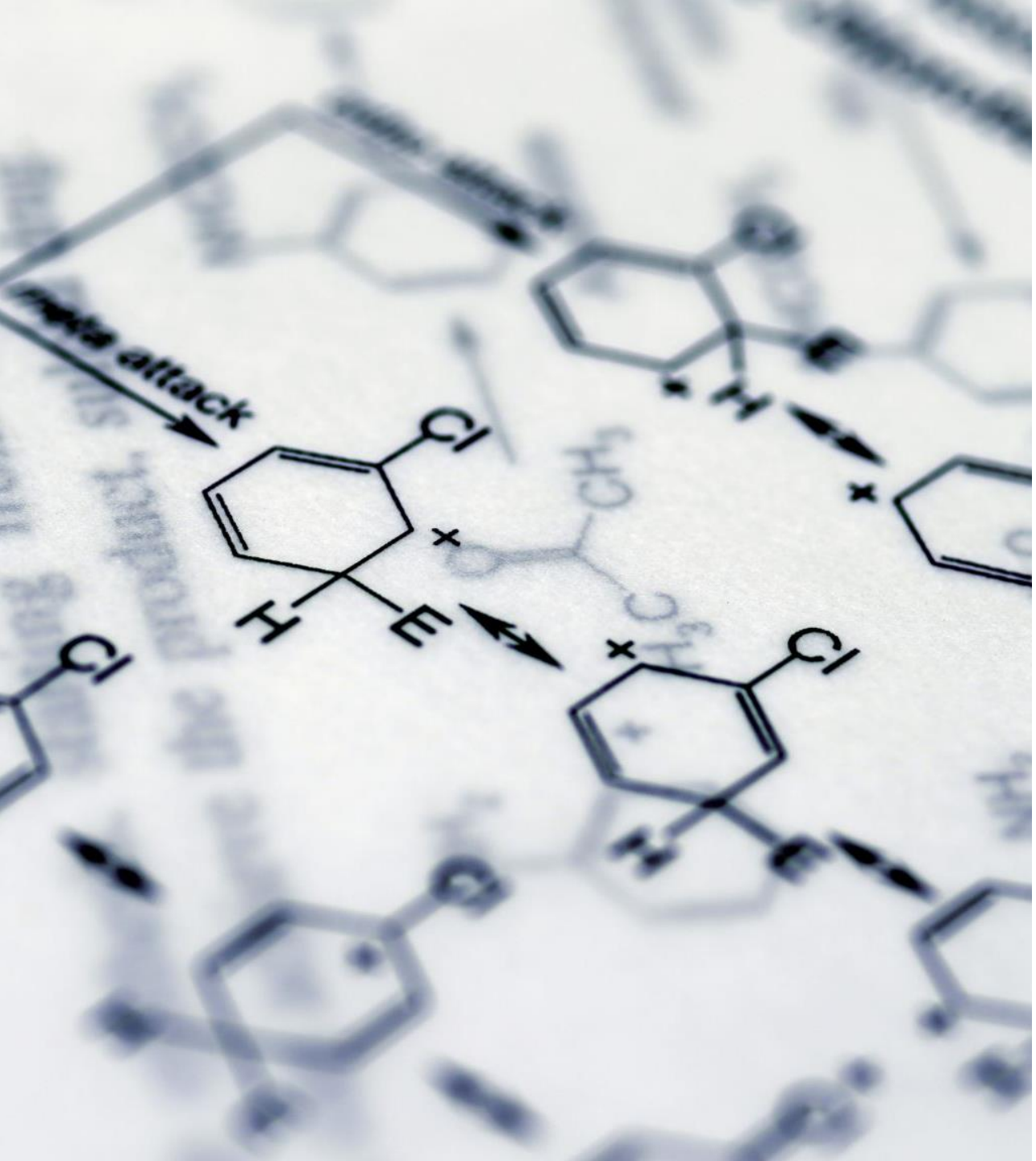
- Avaglio: improved PFS but not OS with addition of bev, but higher incidence of AE's
- RTOG 0825: No improvement in OS, and PFS prolonged



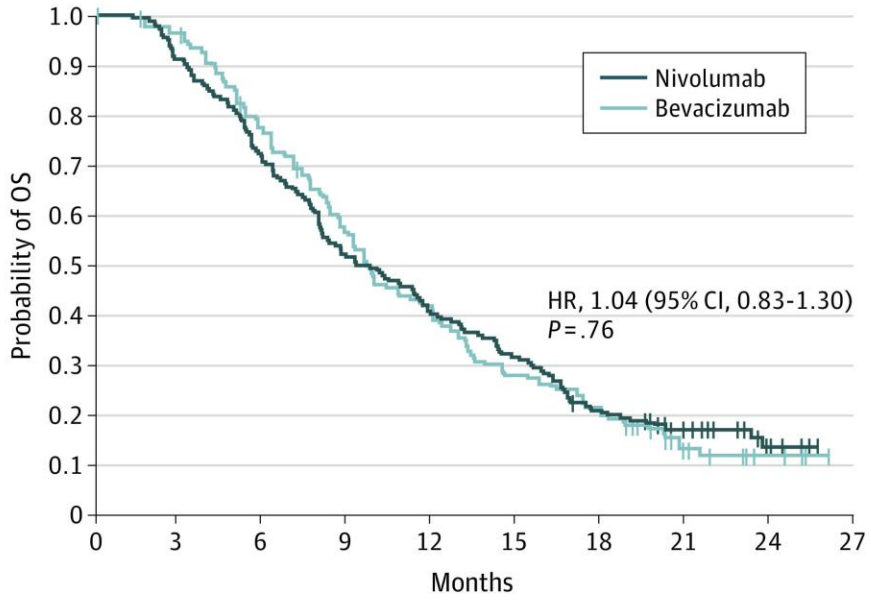
Immunotherapy

- CheckMate 143 phase 3 randomized trial
  - Nivolumab vs Bevacizumab for recurrent GBM
    - Niovlumab is an immunce checkpoint inhibitor to PD-1
    - Patients randomized to bev 10mg/kg q3w vs nivo 3mg/kg q3w
    - Overall no difference in OS between the two groups
    - Trend toward inferior OS with nivo in MGMT unmethylated patients
    - Trend toward improved OS with nivo in MGMT methylated patients not on steroids at baseline

Immunotherapy—Checkmate 143

A Probability of OS by intervention

Intervention	Events, No.	Median OS (95% CI), months	OS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	154	9.8 (8.2-11.8)	72.3 (65.2-78.2)	41.8 (34.7-48.8)	21.7 (16.1-27.9)
Bevacizumab	147	10.0 (9.0-11.8)	78.2 (71.2-83.6)	42.0 (34.6-49.3)	21.6 (15.8-28.0)

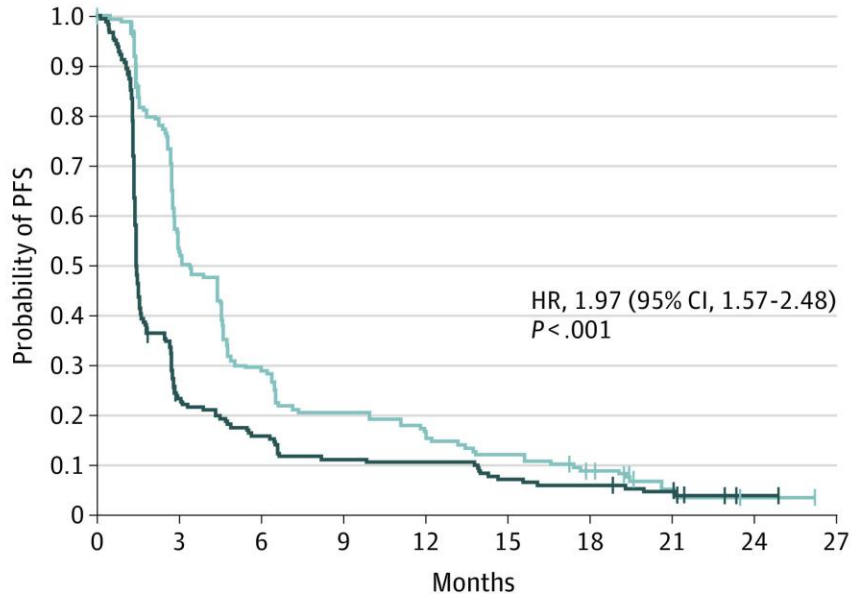


No. at risk

Nivolumab	184	168	133	96	77	59	39	24	9	0
Bevacizumab	185	169	135	99	72	48	37	14	5	0

B Probability of progression-free survival

Intervention	Events, No.	Median PFS (95% CI), months	PFS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	171	1.5 (1.5-1.6)	15.7 (10.8-21.5)	10.5 (6.5-15.5)	5.8 (3.0-10.0)
Bevacizumab	146	3.5 (2.9-4.6)	29.6 (22.7-36.9)	17.4 (11.9-23.7)	8.9 (5.1-14.1)



No. at risk

Nivolumab	184	41	27	19	18	12	10	7	1	0
Bevacizumab	185	88	46	32	27	19	12	3	1	0

Other considerations in treatment of brain tumors

- Brain tumors are incurable and in general lead to a poor outcome
- Supportive care/Palliative care should always be offered at time of diagnosis to help improve quality of life through treatment
- Patients with poor functional status who are not candidates for treatment should be offered hospice services if desired
- Clinical trials offer extra treatment options that may lead better overall survival, and should be considered at time of diagnosis as well as at times of progression.

Conclusion

- Brain tumors can either by primary or secondary (metastasis)
- Management of primary brain tumors includes surgery, radiation, and chemotherapy
- The most common primary brain tumors include meningioma and glioblastoma
- Radiation and temozolomide form the basis for the majority of brain tumor therapy

Questions?