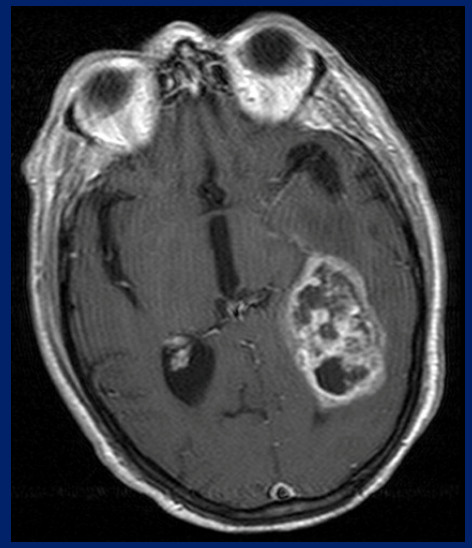
MANAGEMENT OF GLIOBLASTOMA



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EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

AGENDA

1. Glioblastoma Classification: 2021 WHO CNS Updates
2. MGMT Methylation as a Biomarkers
3. “Stupp Protocol”
4. Tumor Treating Fields
5. Recurrent GBM: Bevacizumab

CLASSIFICATION OF GLIOBLASTOMA

Classification of adult gliomas has evolved over time, and now requires integration of histologic characterization along with molecular characterization

Three major concepts integrated in diagnosing glioblastoma

1. WHO Grade
2. Isocitrate Dehydrogenase Mutation (IDH1/2)
3. Molecular Characterization

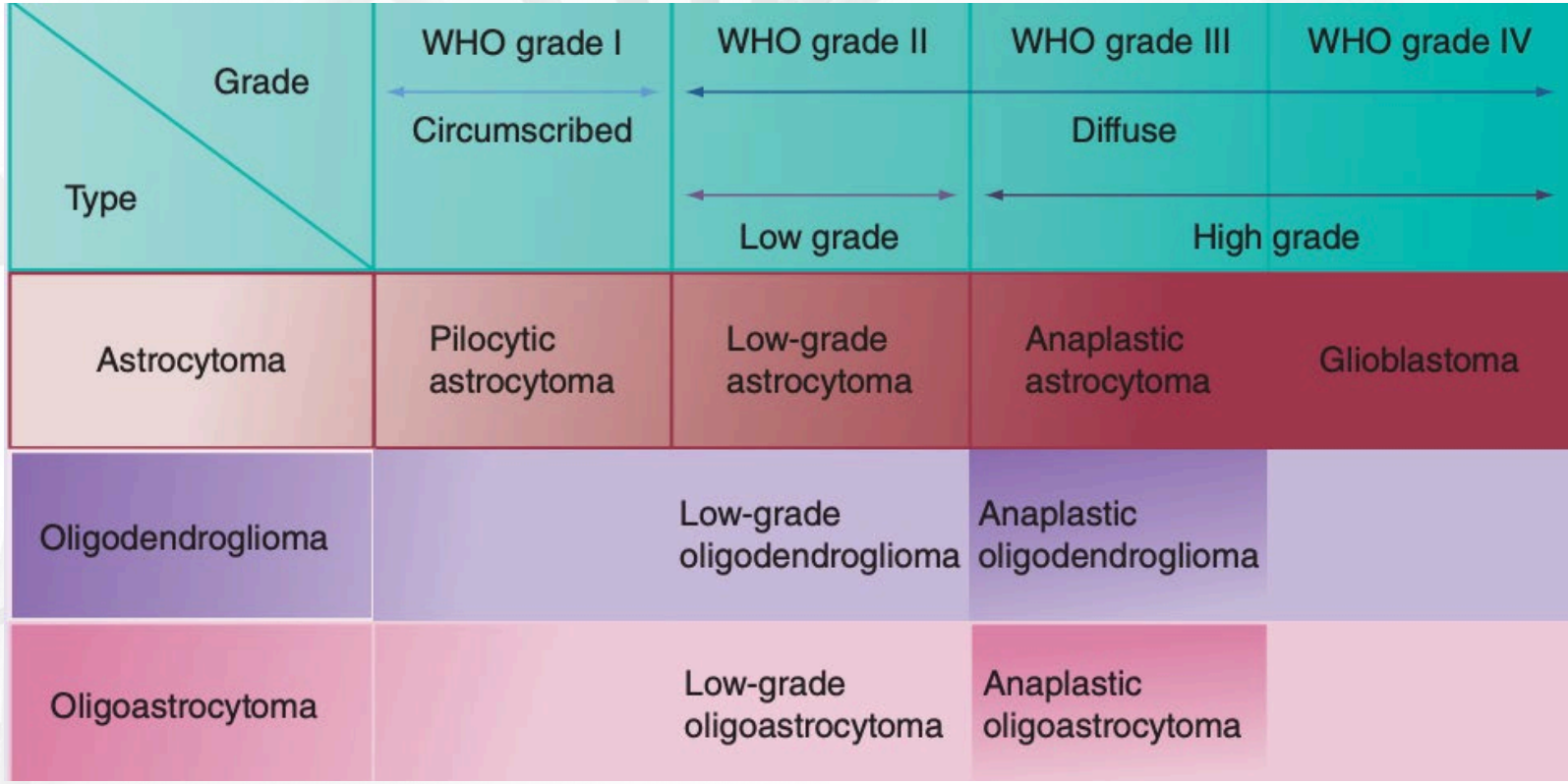
Kristensen BW, Priesterbach-Ackley LP, Petersen JK, Wesseling P. Molecular pathology of tumors of the central nervous system. Ann Oncol. 2019;30(8):1265-1278. doi:10.1093/annonc/mdz164

WHO GRADE REFLECTS PRESENCE OF AGGRESSIVE FEATURES

WHO Grading refers to pathologic assessment on H and E of a glioma to determine it's potential for aggressive behavior

Graded 1-4, with grade 1 being least aggressive, and grade 4 being most aggressive

Glioblastoma were historically defined as WHO Grade 4 astrocytic tumors with characteristic histologic criteria of microvascular proliferation and necrosis



Taal W, Bromberg JE, van den Bent MJ. Chemotherapy in glioma. CNS Oncol. 2015;4(3):179-92. doi: 10.2217/cns.15.2. Epub 2015 Apr 23. PMID: 25906059; PMCID: PMC6088309.

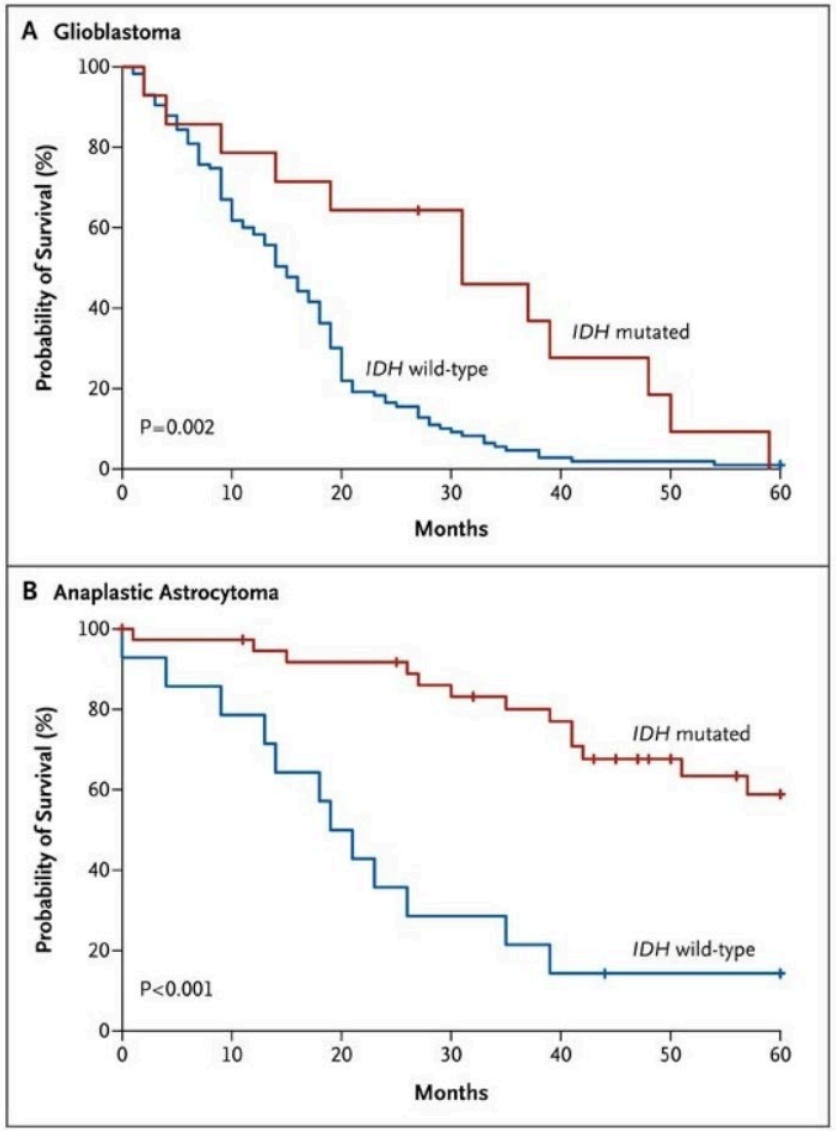
IDH MUTATION STATUS CONFERS BETTER PROGNOSIS AMONGST GLIOMAS

A common molecular aberration amongst glioma is the presence of a mutation in the genes *IDH1/2*

Mutations in *IDH1/2* lead to production of 2-Hydroxyglutarate, an oncometabolite

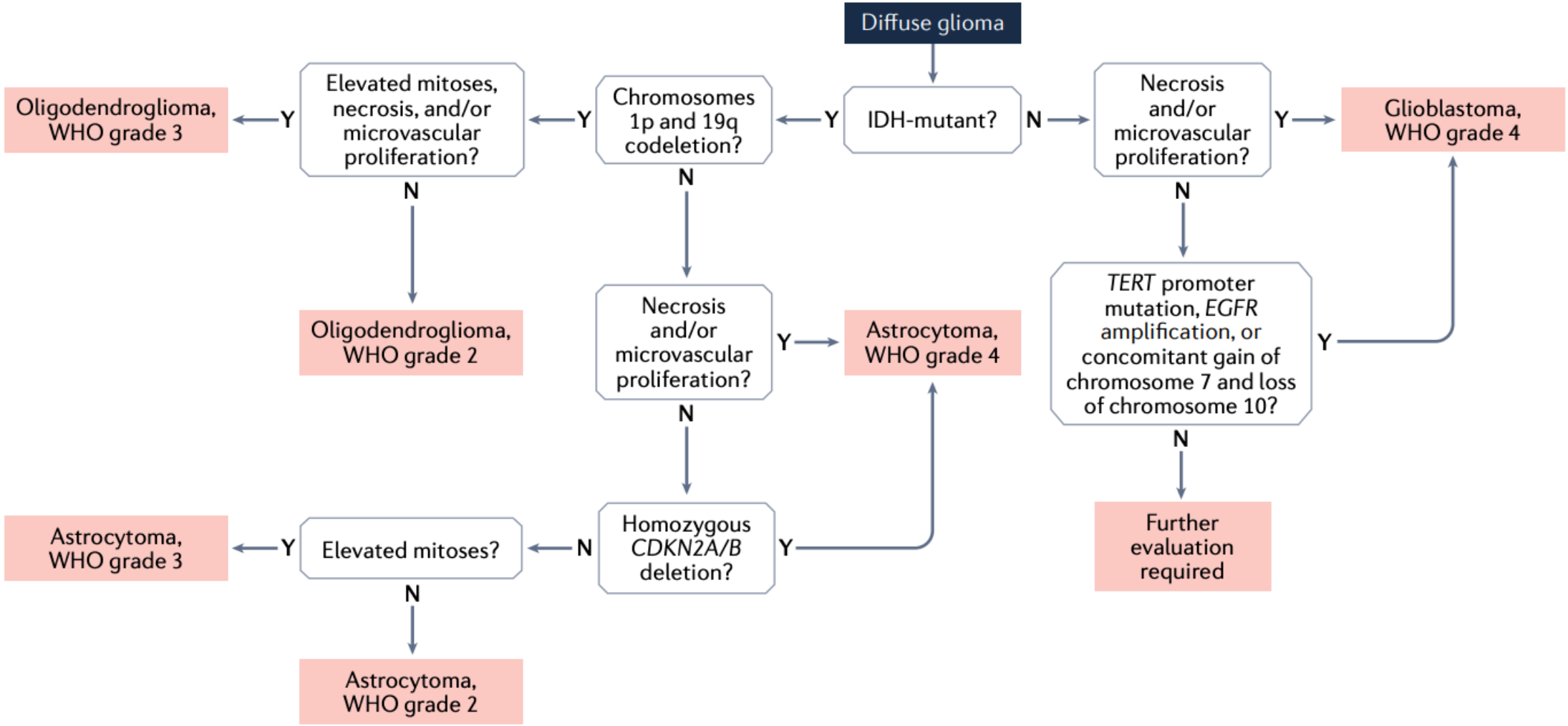
IDH mutations in gliomas confer better prognosis as compared to IDH – WT gliomas

Historically, IDH-mutant tumors with grade 4 histologic features were glioblastomas, but given significant difference in survival, glioblastomas are now exclusively IDH-WT



Yan H et al, IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009 Feb 19;360(8):765-73. doi: 10.1056/NEJMoa0808710. PMID: 19228619; PMCID: PMC2820383.

INCORPORATION ON MOLECULAR SUBTYPES: 2021 WHO CNS CLASSIFICATION



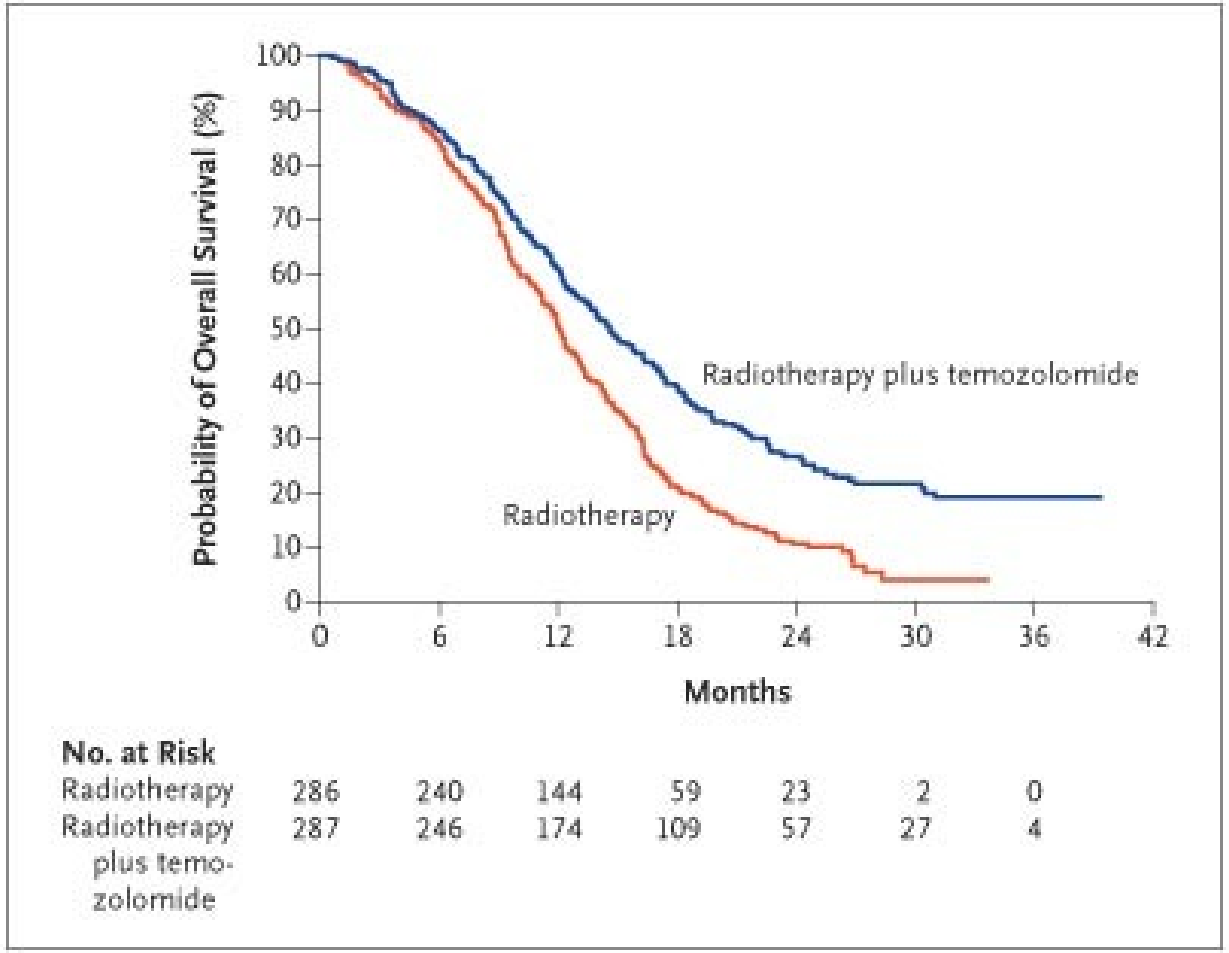
Horbinski C, Berger T, Packer RJ, Wen PY. Clinical implications of the 2021 edition of the WHO classification of central nervous system tumours. Nat Rev Neurol. 2022 Jun 21. doi: 10.1038/s41582-022-00679-w. Epub ahead of print. PMID: 35729337.

TREATMENT OF GLIOMAS – STUPP PROTOCOL

”Stupp Protocol”

The primary treatment modality for gliomas was established in a randomized clinical trial in 2005 demonstrating an overall survival benefit for glioma patients with a three staged regimen combining:

- Maximal Surgical Resection
- Radiation therapy
- Chemotherapy agent: temozolomide



Stupp, R. *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N. Engl. J. Med.* **352**, 987–996 (2005).

TREATMENT OF GLIOBLASTOMA - THREE PHASES

"Stupp Protocol"

1. Maximal Surgical Resection
2. Radiation + Concurrent Temozolomide
3. Adjuvant Temozolomide

Stupp NEJM 2005

PHASE 2: CONCURRENT XRT + LOW DOSE TMZ

2

Radiation + Concurrent Temozolomide

Temozolomide 75mg/m2 Oral Pill taken daily x 6 weeks with RT

RT Monday - Friday x 6 weeks
Dose: 60 Gy x 30 Fractions

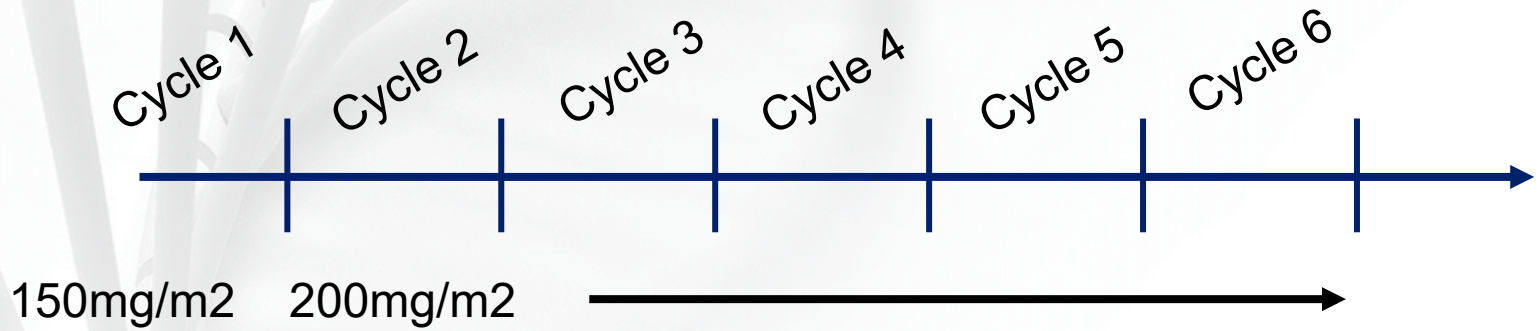
Stupp NEJM 2005

PHASE 3: ADJUVANT TMZ

3

Adjuvant Temozolomide

Temozolomide 150-200mg/m2
Day 1-5
Every 28 days; 6 cycles



If 150mg/m2 tolerated in first cycle, dose increases to 200mg/m2 for duration of treatment

Stupp NEJM 2005

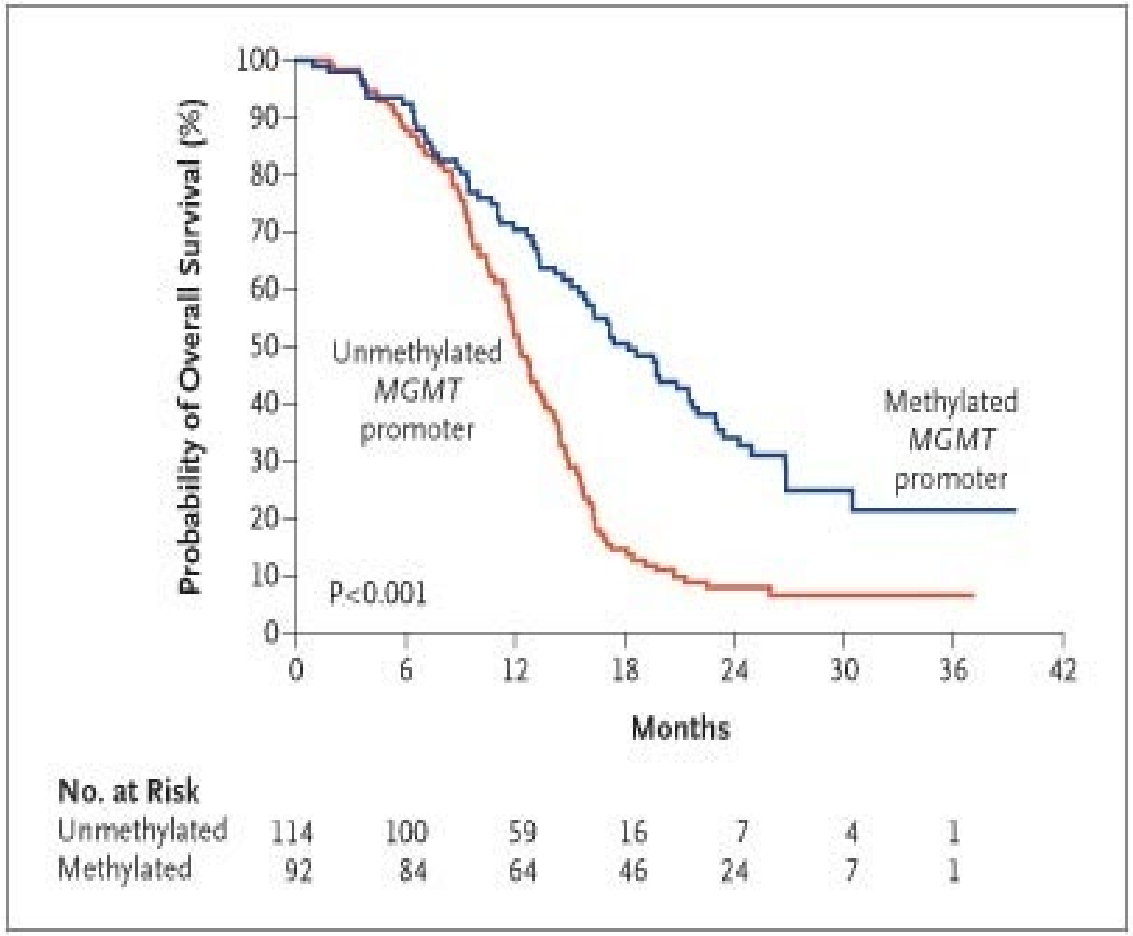
BIOMARKER OF TMZ RESPONSE: *MGMT* PROMOTER METHYLATION

*MGMT (*O6-methyl-guanine-methyltransferase) is a gene that encodes for an enzyme involved in repair of DNA damage induced by alkylating agents such as temozolomide

When this gene is silenced via methylation:

- the enzyme is not produced
- DNA damage induced by Temozolomide is not repaired

***MGMT* Promoter Methylation = Improved response to Temzolomide**



Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JE, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC, Stupp R. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005 Mar 10;352(10):997-1003. doi: 10.1056/NEJMoa043331. PMID: 15758010.

NUTS AND BOLTS OF TEMOZOLOMIDE

Most prominent adverse effects are lymphopenia (CD4+) and anemia:

- Prophylactic antibiotics often used, most commonly trimethoprim/sulfamethoxazole
- Need to monitor CBC at regular intervals
- Risk of developing therapy related hematologic malignancy so CBC should be monitored as part of survivorship

Nausea very common side effect. Need to prescribed prophylactic ondansetron

In addition to temozolomide mediated side effects, brain tumor patients have higher risk of other complications clinicians should monitor:

- Deep venous thrombosis
- Seizure disorders

Temozolomide capsules and injection (package insert). Whitehouse Station, NJ: Merck and Co., INC.; 2019 Nov.

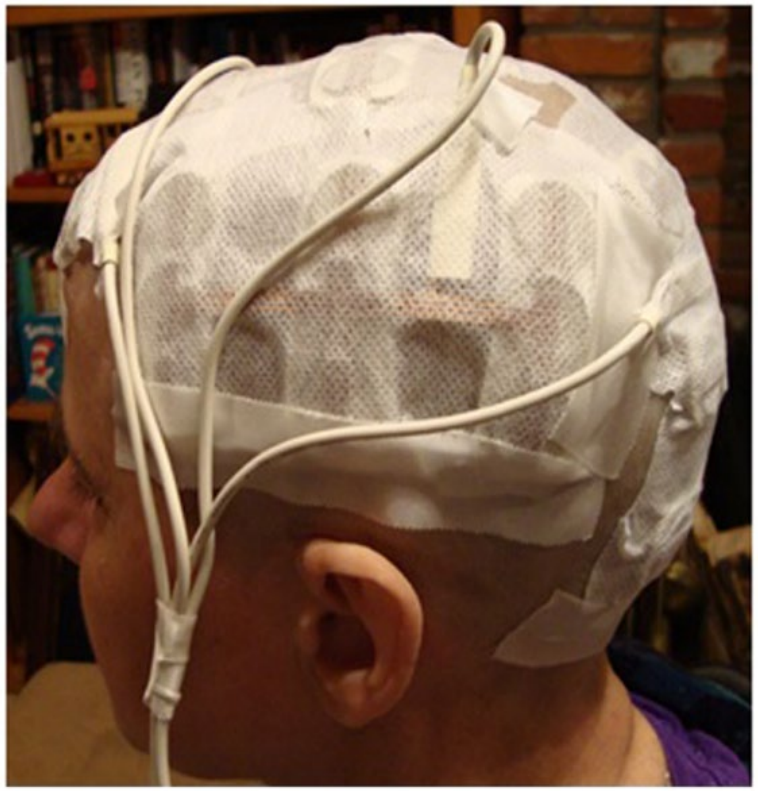
DeAngelis LM, Wen PY. Primary and Metastatic Tumors of the Nervous System. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. McGraw Hill; 2014

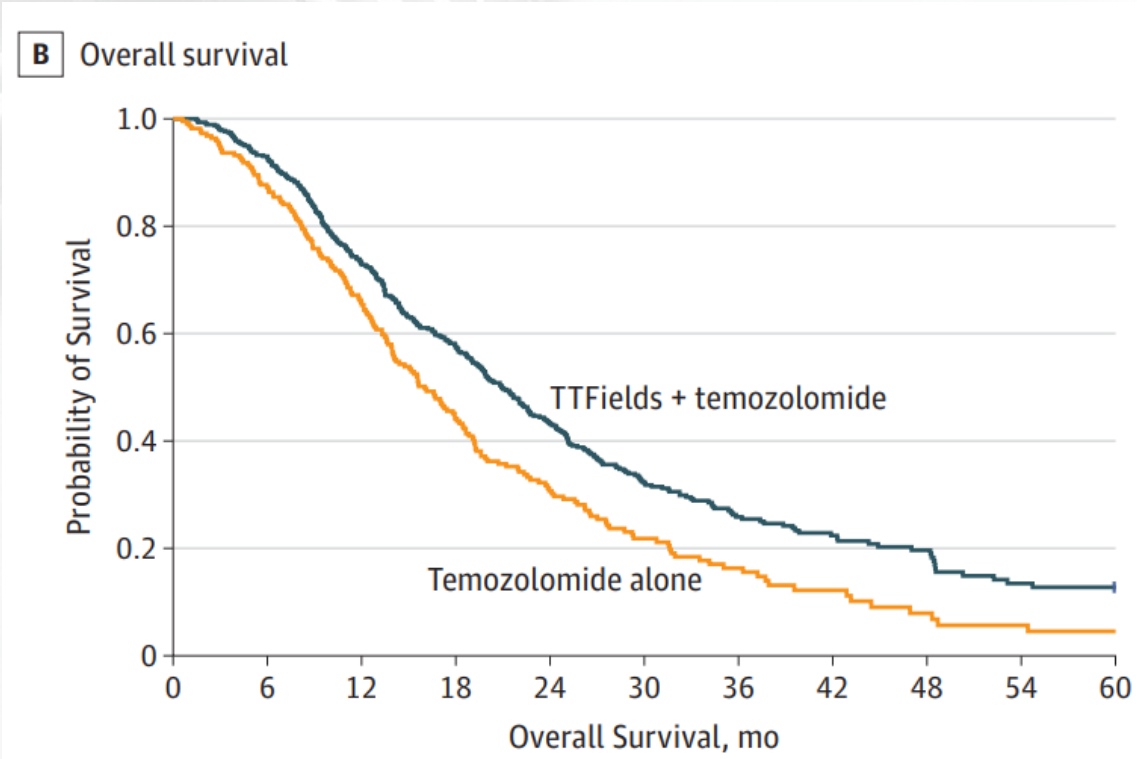
ADDITIONAL ADJUVANT OPTION: TUMOR TREATING FIELDS

In addition to temozolomide, there is randomized data supporting the use of a device called “Optune” which is a device worn on the head that generates electric fields thought to inhibit cell division

Optune is worn while adjuvant temozolomide is being taken

In Phase 3 RCT – goal was >18 hours/ day, this can be quite a commitment for patients





Stupp R, et al.Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. JAMA. 2017
Mrugala, M. M., Ruzevick, J., Zlomanczuk, P. & Lukas, R. V. Tumor Treating Fields in Neuro-Oncological Practice. *Curr Oncol Rep* **19**, 53 (2017).

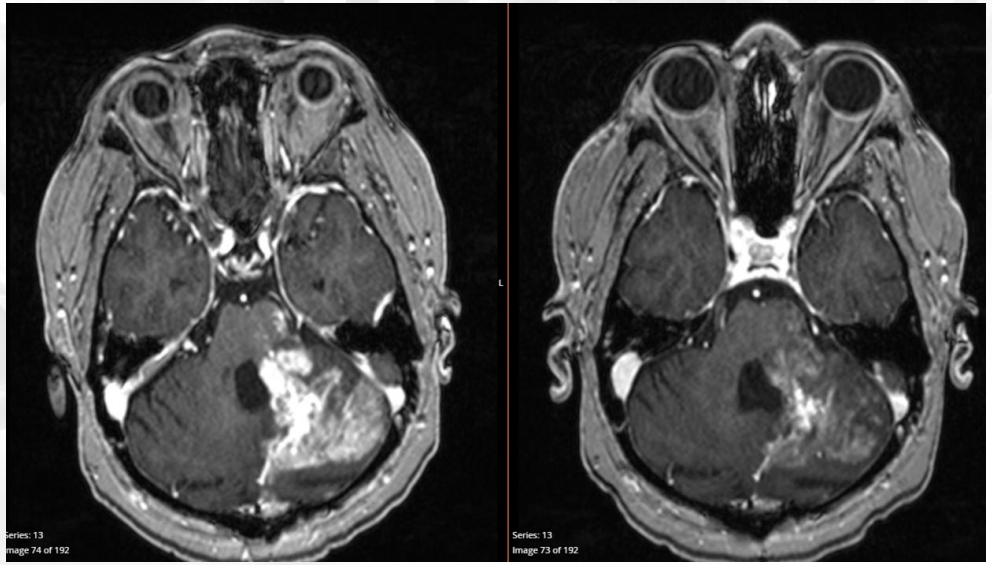
TREATMENT OF RECURRENT GLIOMA: BEVACIZUMAB

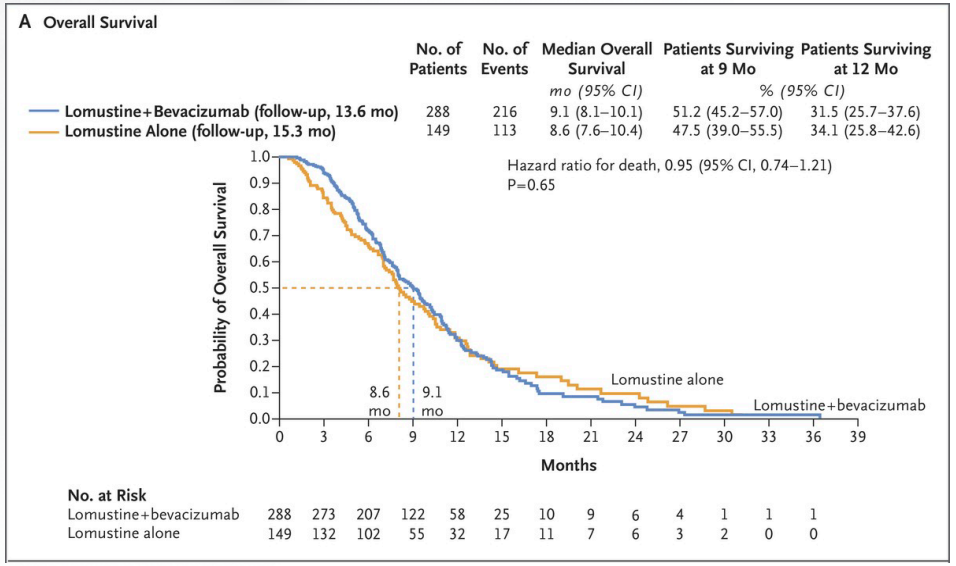
Bevacizumab is a monoclonal anti-body targeted against Vascular Endothelial Growth Factor A (VEGF-A)

The drug is thought to block abnormal blood vessel proliferation in the tumor and reduces local inflammation at site of progression leading to improvement in clinical symptoms and reduced steroid requirements

Standard dosing: 10mg/kg q2 weeks

<u>The drug has not been shown to prolong survival and so it is often paired with an alkylating agent: lomustine or temozolomide retreatment</u>





Wick W. et al. Lomustine and Bevacizumab in Progressive Glioblastoma. N Engl J Med. 2017 Nov 16;377(20):1954-1963.

Wick, W. *et al.* Lomustine and Bevacizumab in Progressive Glioblastoma. *N Engl J Med* **377**, 1954–1963 (2017).

THANK YOU!

Additional Reading:

1. Wen PY et al. ”Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions.” Neuro Oncol. 2020 32328653

2. Horbinski C et al. “Clinical implications of the 2021 edition of the WHO classification of central nervous system tumours.” Nat Rev Neurol. 2022