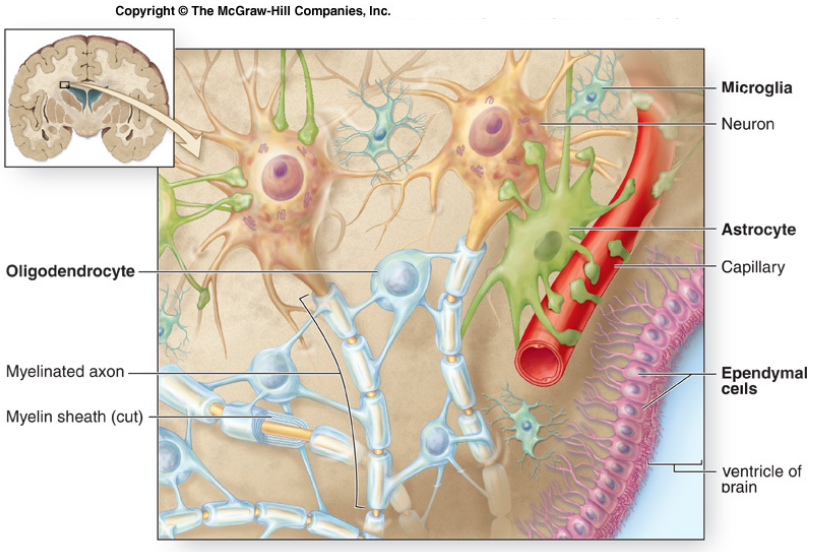
Neuro-oncology



MCBO Core Lecture II

Guido Wollmann

Division of Virology

March 12 2020

What is Neuro-oncology?

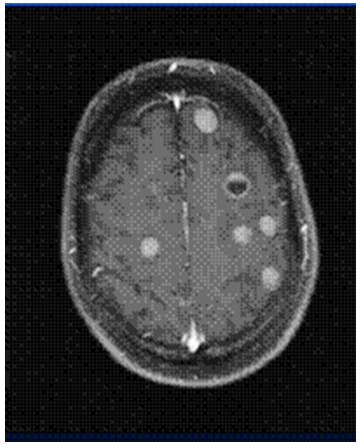
Primary brain tumors

Secondary brain tumors

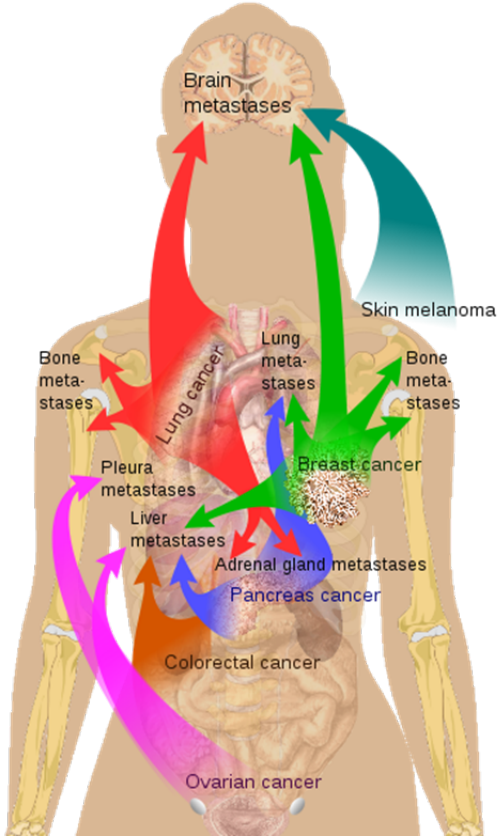
Neurological symptoms of general cancer

Neuro-oncology – Terminology

SECONDARY brain tumors = brain metastasis of non-brain cancers



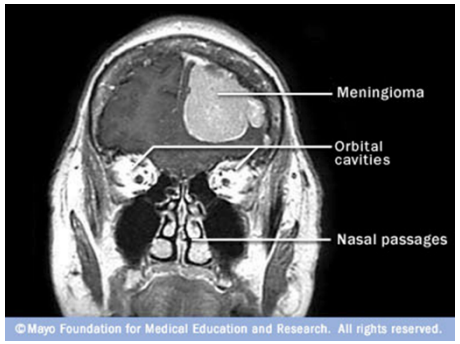
- Most common
- Often multiple lesions
- 25-45% of cancer patients
  - Lung: >50% of all; most common in men
  - Breast: Most common in women
  - Melanoma: Highest risk for brain mets
  - Renal Cell
  - Colorectal

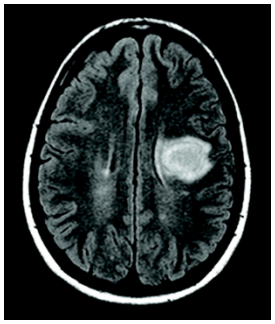


www.abta.org

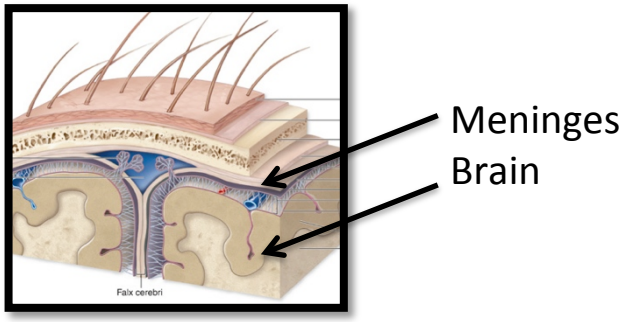
Neuro-oncology – Terminology

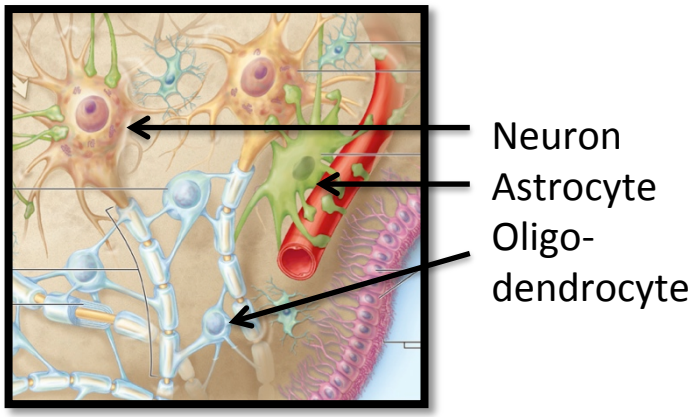
PRIMARY brain tumors = originating from brain tissue





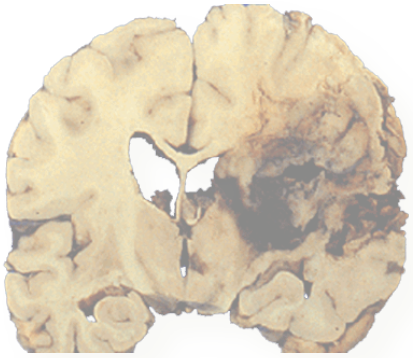
- Meningioma (35%)
- Glioma (30%)
  - Astrocytoma
    - Glioblastoma
  - Oligodendroglioma
  - Oligoastrocytoma
  - Ependymoma
- Pituitary Adenoma (13%)





www.abta.org

Glioma – Classification



WHO classification

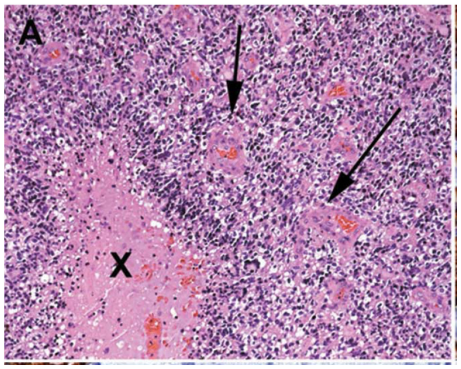
(classical classification)

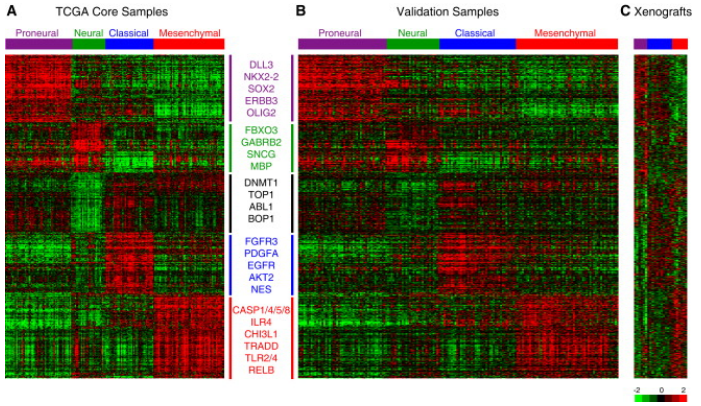
- Based on histopathology
- Grading I, II, III, IV

Molecular classification

(new classification – since 2010)

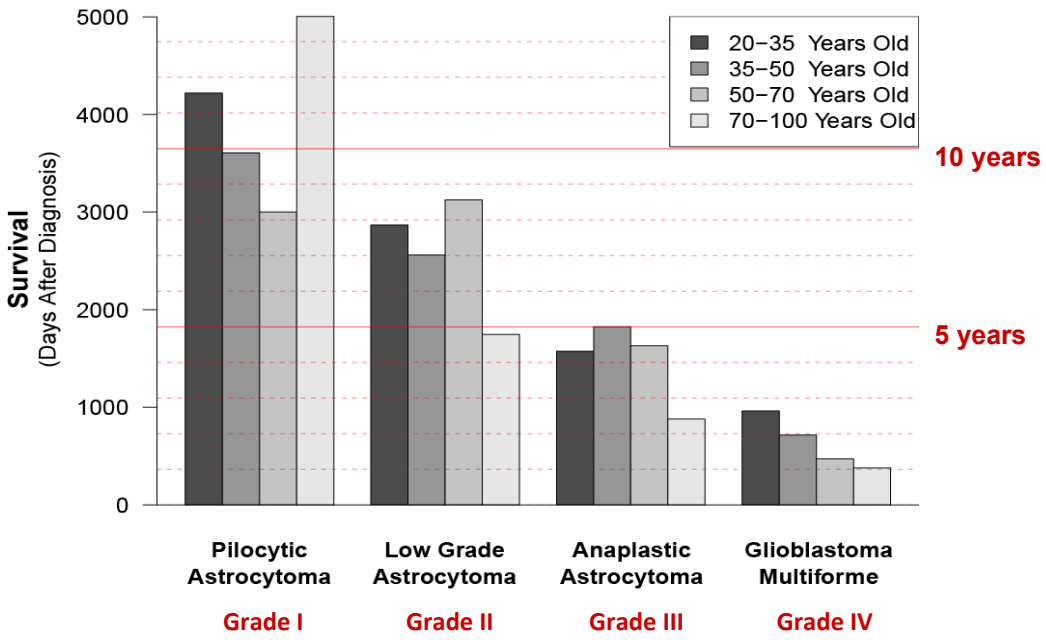
- Based on molecular profile
- Optimized treatment





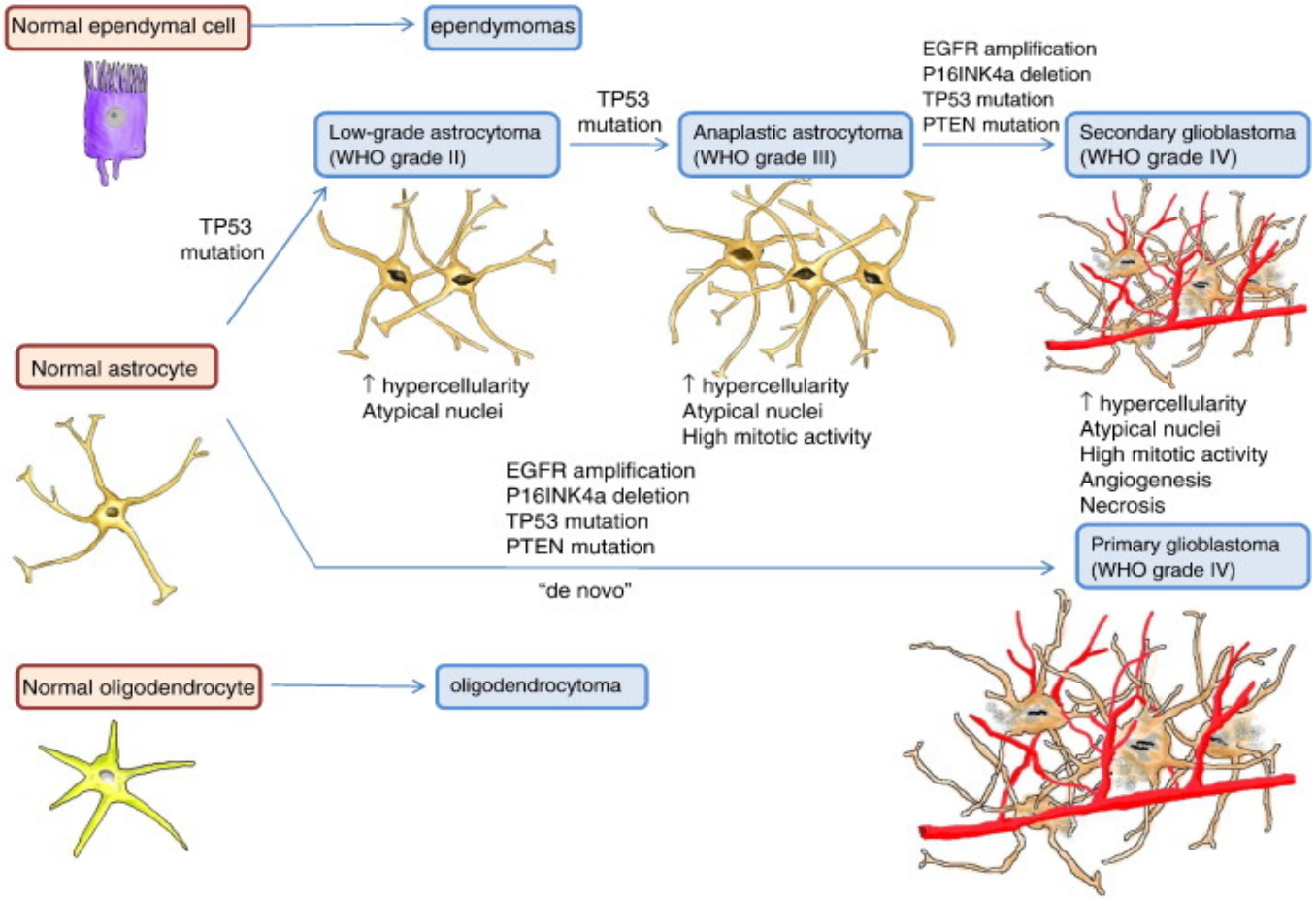
Glioma – WHO Classification Relative Frequencies

Grade	Tumor Type	Glioma %
I/II	Well-differentiated (low-grade) astrocytoma	15 to 20
III	Anaplastic astrocytoma	30 to 35
IV	Glioblastoma multiforme	40 to 50



http://www.neurooncology.ucla.edu/

Primary vs Secondary GBM



⇒ PRIMARY GBM emerges de-novo as a GBM upon first diagnosis

⇒ SECONDARY GBM evolve from lower grade gliomas first diagnosed years earlier

BBA - Reviews on Cancer, 2013, 1836:158–165

Primary vs Secondary GBM

Table 1. Primary and secondary glioblastomas: comparison of clinical versus genetic diagnosis

	Primary glioblastoma		Secondary glioblastoma		
	Clinical criteria[a]	Genetic criteria (*IDH1*^{wt})	Clinical criteria[a]	Genetic criteria (*IDH1*^{mut})	References
Fraction in a population	94.7%	91.2%	5.3%	8.8%	(7, 13)
Mean age, y	59–62	56–61	33–45	32–48	(7, 12, 13, 67, 70)
Male/female ratio	1.33–1.5	1.2–1.46	0.65–2.3	1.0–1.12	(7, 12, 13, 70)
Mean clinical history, mo	6.3	3.9	16.8	15.2	(7, 13)
Median overall survival, mo					(7, 12, 13)
Surgery + radiotherapy	4.7[b]	9.9	7.8[b]	24	(7, 13)
Surgery + radio/chemotherapy		15		31	(12)
Histologic features					
Oligodendroglial comp.	18%	20%	42%	54%	(13, 80)
Necrosis	89%	90%	63%	50%	(13, 80)
Genetic alterations					
IDH1 mutations	4–7%	0%	73–88%	100%	(10, 12, 13)
TP53 mutations	17–35%	19–27%	60–88%	76–81%	(7, 10, 12, 13, 67, 91)
ATRX mutations	4–7%		57–80%		(36, 37)
EGFR amplification	36–45%	35–39%	0–8%	0–6.5%	(7, 10, 12, 13, 91)
CDKN2A deletion	31–52%	30–45%	19–20%	7–22%	(7, 12, 13, 91)
PTEN mutations	23–25%	24–26%	4–12%	0–8%	(7, 12, 13)
19q loss	6%	4%	54%	32%	(9, 13)
1p/19q loss	2–8%		0–13%		(10, 12, 67)
10p loss	47%		8%		(8)
10q loss	70%	67%	63%	73%	(7, 13)

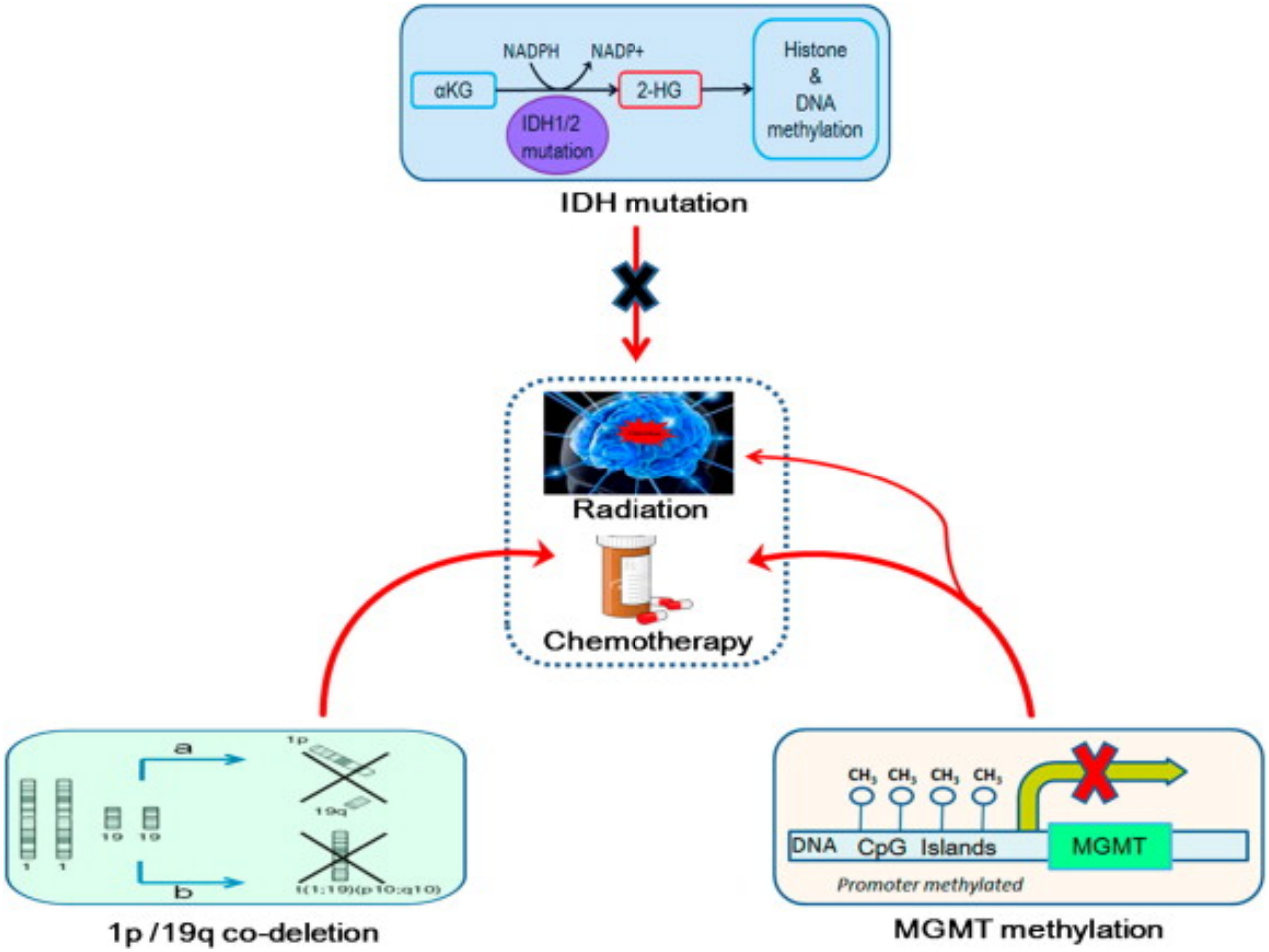
[a]Tumors were considered to be primary if the diagnosis of glioblastoma was made at the first biopsy, without clinical or histological evidence of a preexisting, less malignant precursor lesion, whereas the diagnosis of secondary glioblastoma required histological and/or clinical (neuroimaging) evidence of a preceding low-grade or anaplastic astrocytoma.

[b]Data from population-based study: all the patients who were treated in different ways were included.

Clin Cancer Res 2013;19:764-772

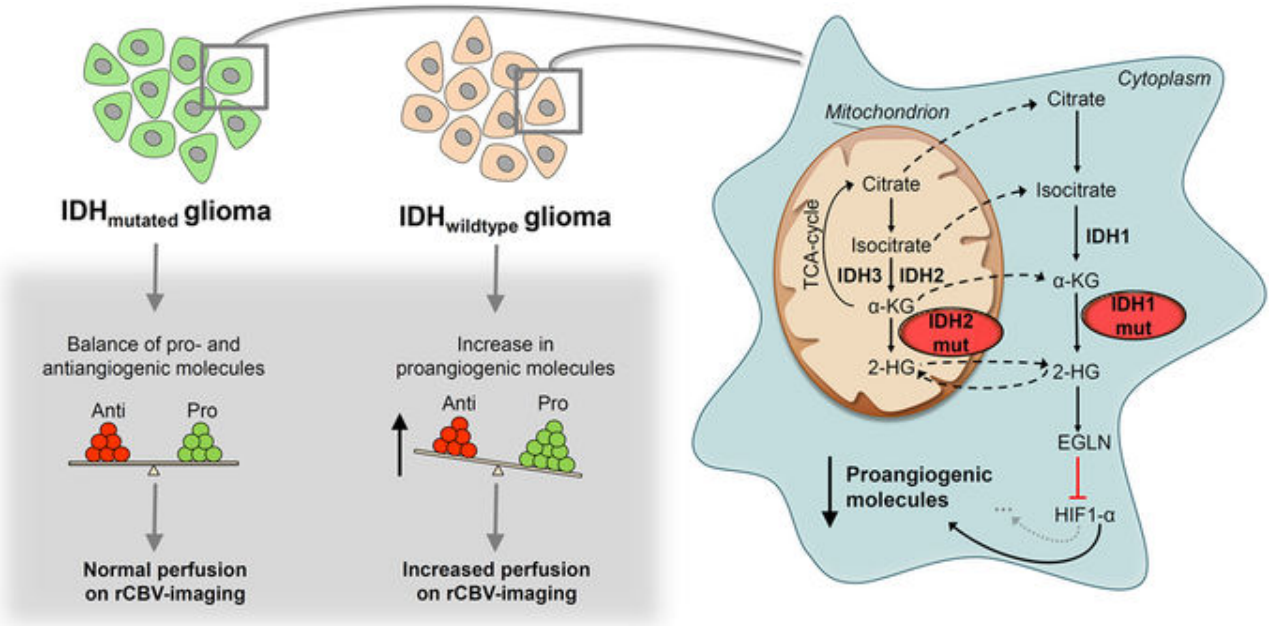
Molecular Biomarkers

Biomarker: *„A functional biochemical or molecular indicator of a biological or disease process that **has predictive, diagnostic, and/or prognostic** utility.“*



Cancer Letters, Volume 331, Issue 2, 2013, 139–146

Molecular Biomarkers: IDH Mutation

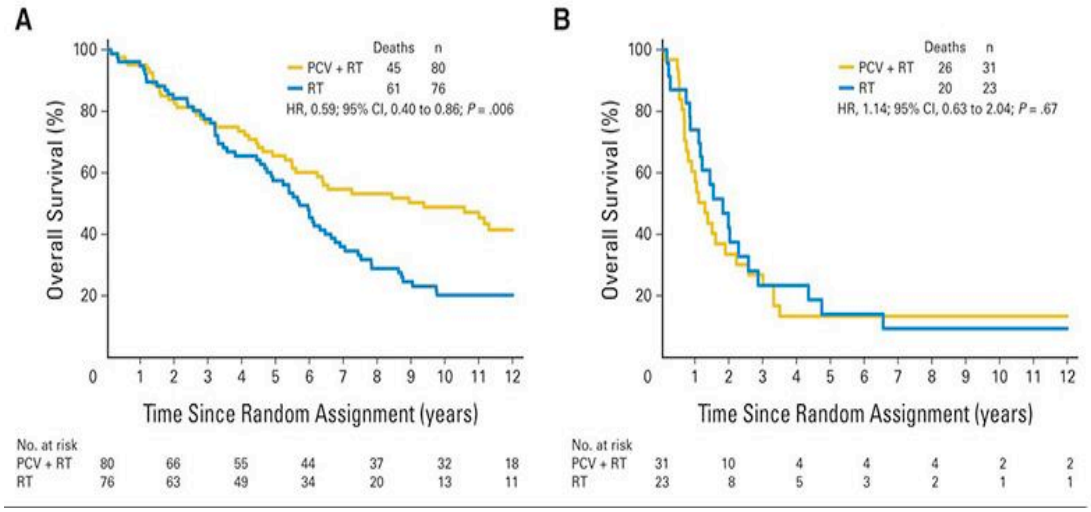


-> IDH mutation interferes with hypoxia-inducible factor HIF signaling

⇒ **MOLECULAR marker** for diffusely infiltrating glioma (II and III)
⇒ **PROGNOSTIC marker** for better survival
⇒ **PREDICTIVE marker** for better response to treatment

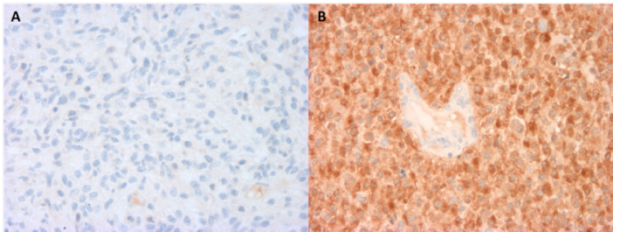
Scientific Reports 5:16238

Molecular Biomarkers: IDH Mutation



IDH mutant IDH wild type

IDH wt IDH mutant



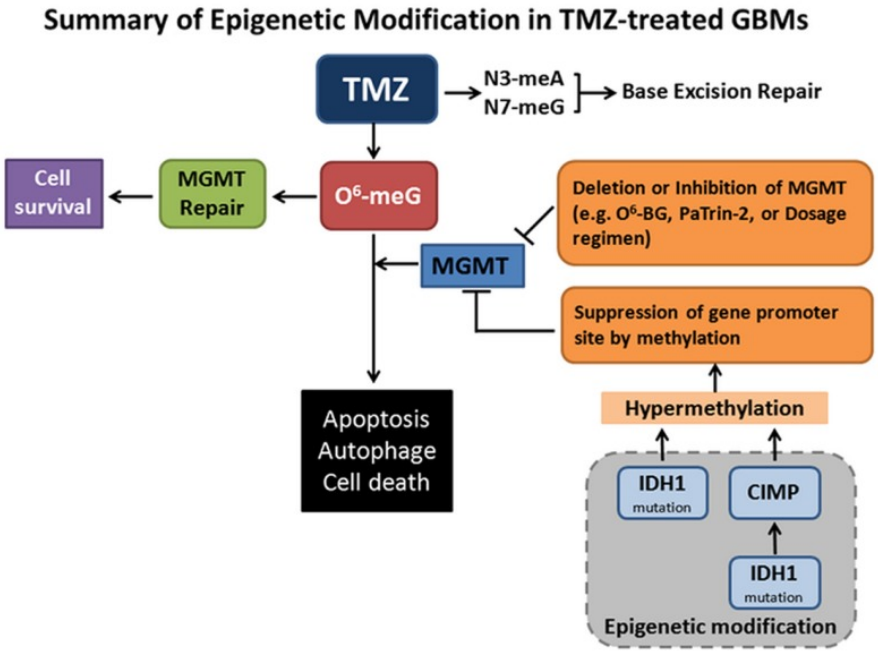
Better prognosis and better response to chemotherapy in patients with IDH mutation.

J Clin Oncol 2014; 32(8):783-90.

IDH1/2 Mutations in Glioma: ESMO Biomarker Factsheet

Molecular Biomarkers: MGMT Methylation

O6-methylguanine-DNA methyltransferase (MGMT) => DNA repair protein



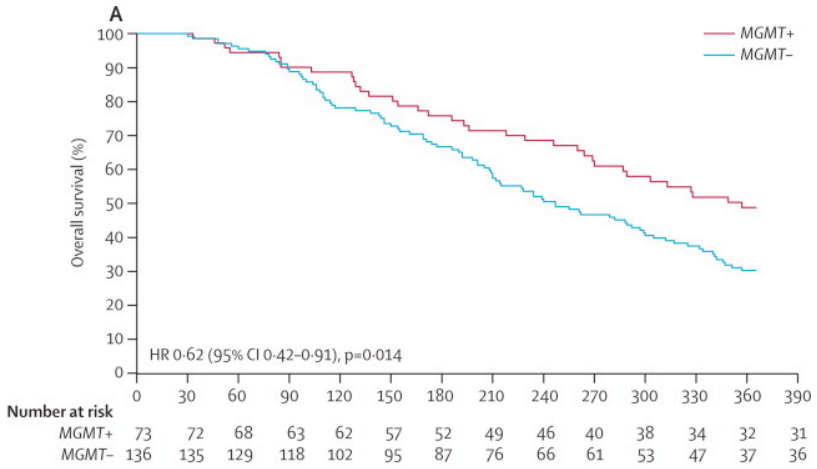
MGMT counteracts the alkylating drug TMZ. Hypermethylation of MGMT promoter region inhibits MGMT repair function and facilitates better chemo-therapeutic responses.

Front Oncol. 2013; 3: 59.

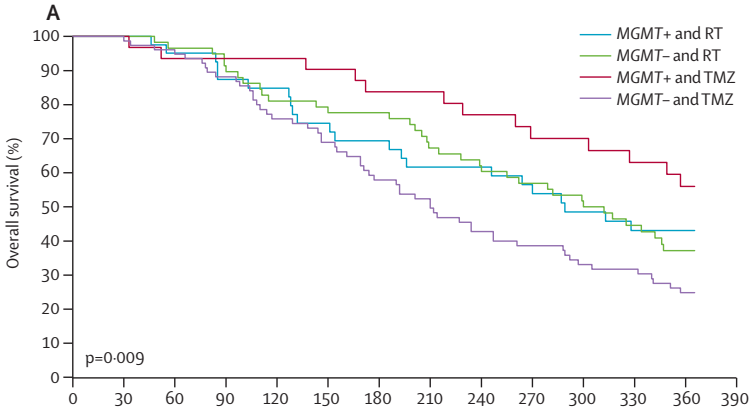
Molecular Biomarkers: MGMT Methylation

MGMT hypermethylation:

Prognostic marker



Predictiv marker

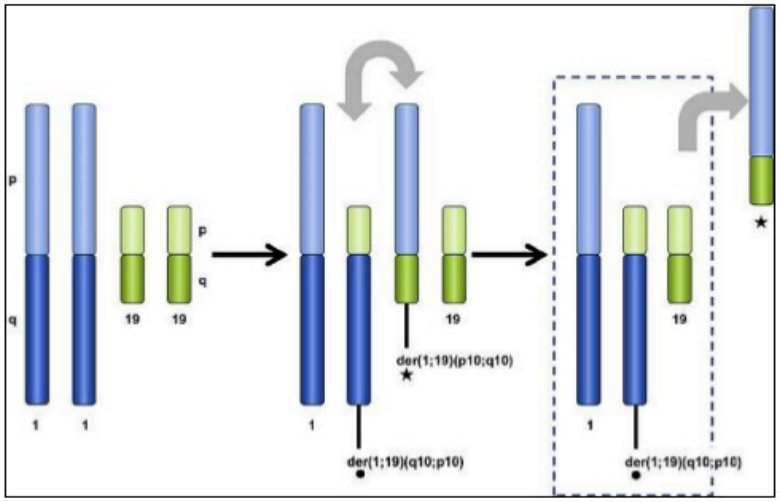


Better prognosis and better response to chemotherapy in patients with MGMT hypermethylation.

Lancet Oncol. 2012 13:707-15.

Molecular Biomarkers: 1p/19q co-deletion

Co-deletion => loss of heterozygosity

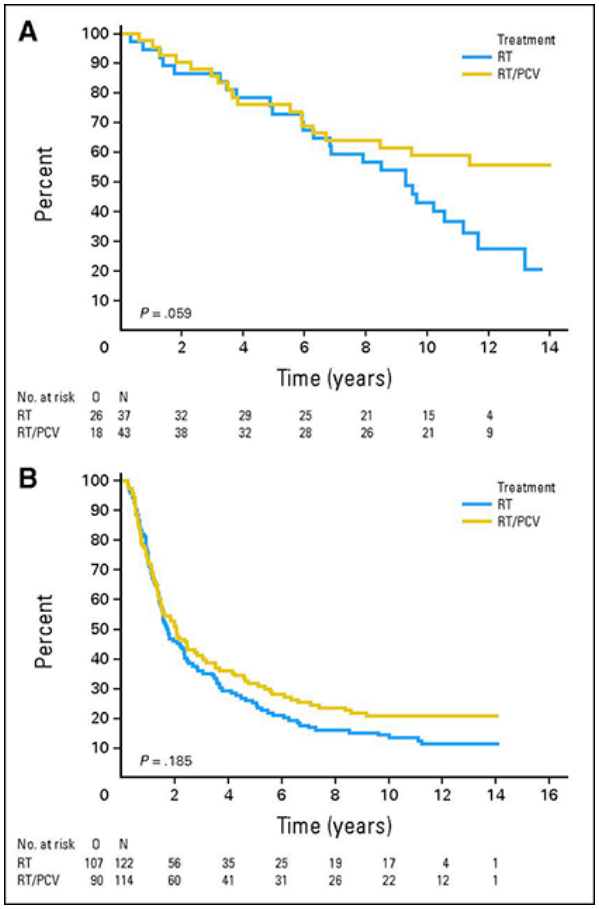


- The first allele is lost (**1st Hit**) due to an imbalanced reciprocal translocation between chromosomes 1 and 19
- The second allele is disrupted (**2nd Hit**) by a somatic mutation capable of inhibiting protein function

⇒ **MOLECULAR marker** for oligodendrogliomas (up to 70% positive for LOH 1p:19q)
⇒ **PROGNOSTIC marker** for better survival
⇒ **PREDICTIVE marker** for better response to treatment

Clinical Oncology 2015, 27:445-453

Molecular Biomarkers: 1p/19q co-deletion



<= LOH 1p:19q

Better prognosis and better response to chemotherapy in patients with LOH 1p/19q

<= normal 1p:19q status

J Clin Oncol 2013; 31:344–50

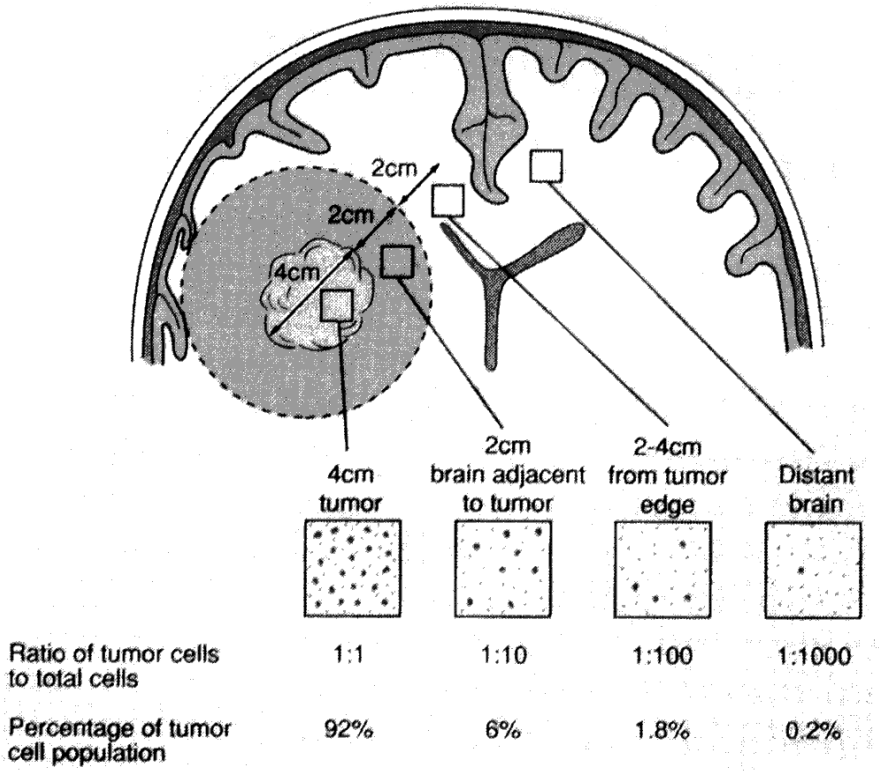
Glioblastoma – Clinical Challenge

- Mean survival 12-14 months from diagnosis (3 months w/o treatment)
- Mean survival 4-5 months from recurrence
- 2 year survival 10%
- 5 year survival 5%

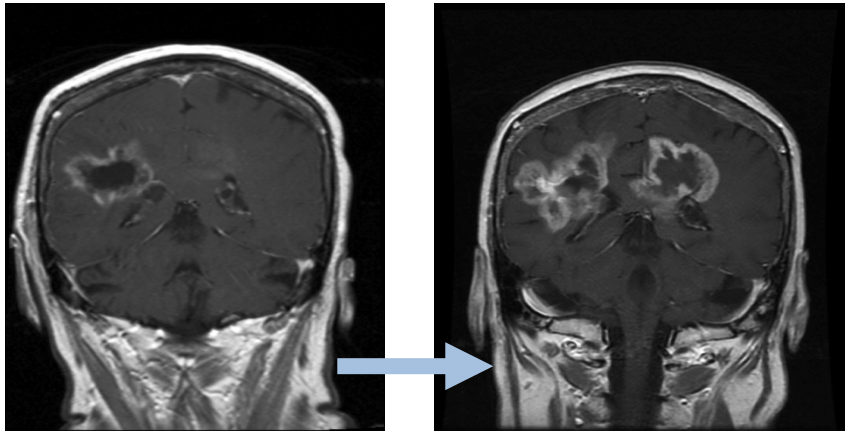
- Treatment options:
  - Surgery (recurrence within 2 cm of debulking margin in 80% of patients)
  - Radiation (rarely radiosurgery)
  - Chemotherapy:
    - Nitrosureas, PCV, **temozolomide, thalidomide, avastin**

Glioblastoma – Clinical Challenge

GBM is a “non-surgical disease” => a knife cannot remove the entire tumor



GBM always recurs



12’2010 3’2011

Clin Neurosurg. 1992;38:32.

E.A. Chiocca, 2017, Regis lecture

Glioblastoma – Standard Therapy

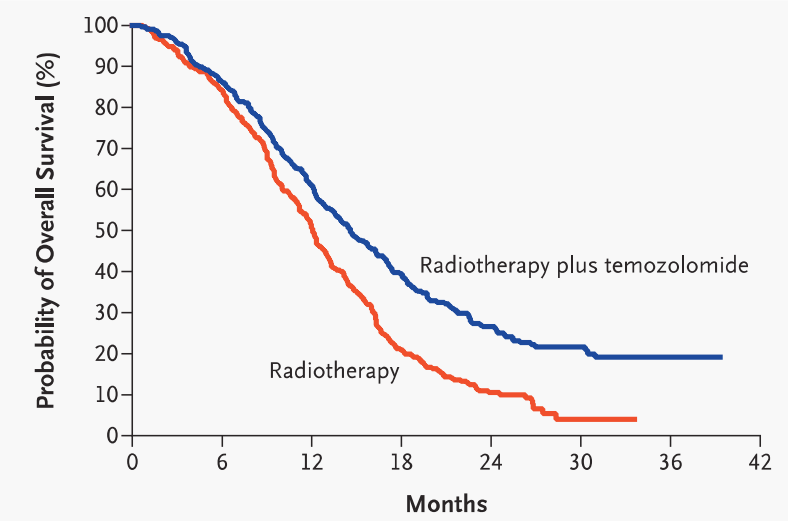
The NEW ENGLAND JOURNAL of MEDICINE

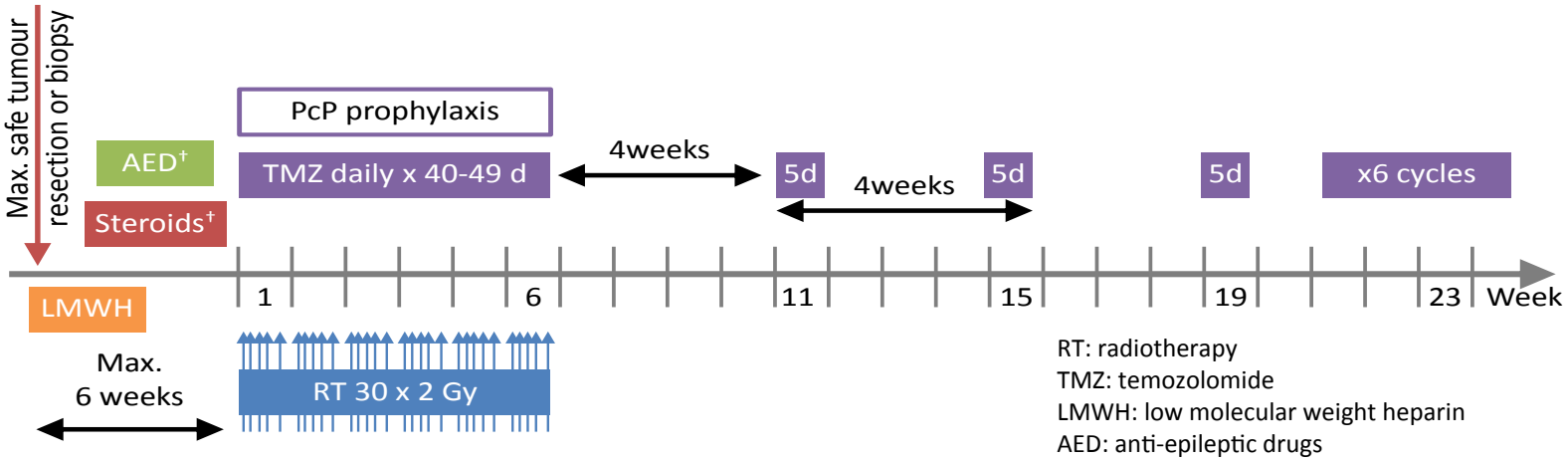
ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

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., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., 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*

N Engl J Med 352., 987-996

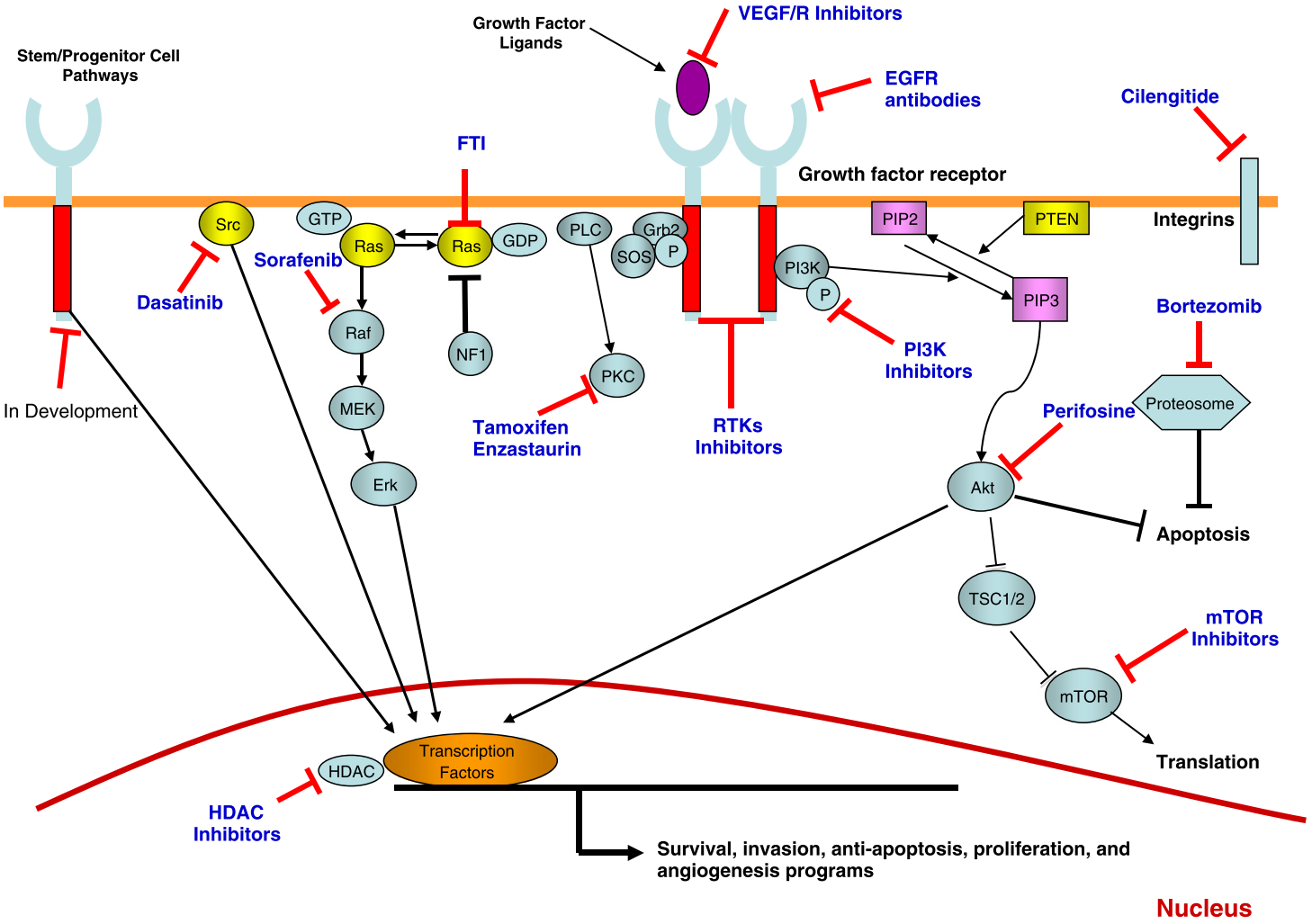




RT: radiotherapy
TMZ: temozolomide
LMWH: low molecular weight heparin
AED: anti-epileptic drugs
PcP: pneuomocystis jirovicii pneumonia prophylaxis

Ann Neurol 2011;70(1):9–21

Glioma – Molecular Targets



Hu and Kesari

The Cancer Journal • Volume 18, Number 1, January/February 2012

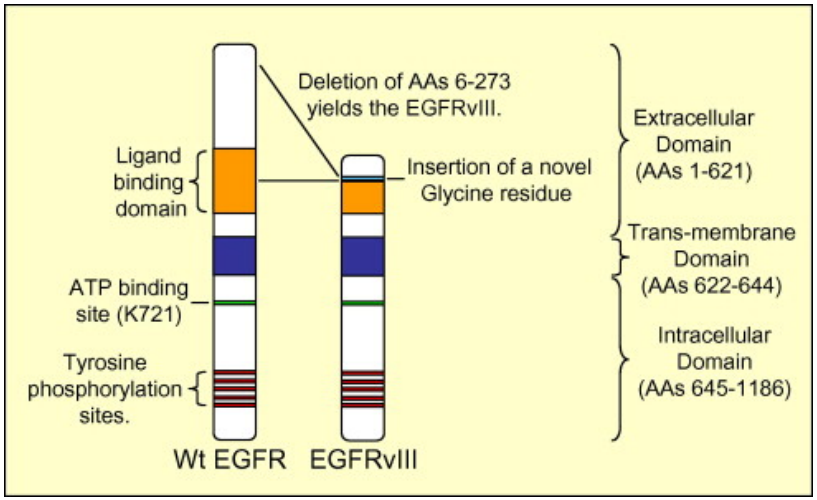
Glioblastoma – Targeted Therapy

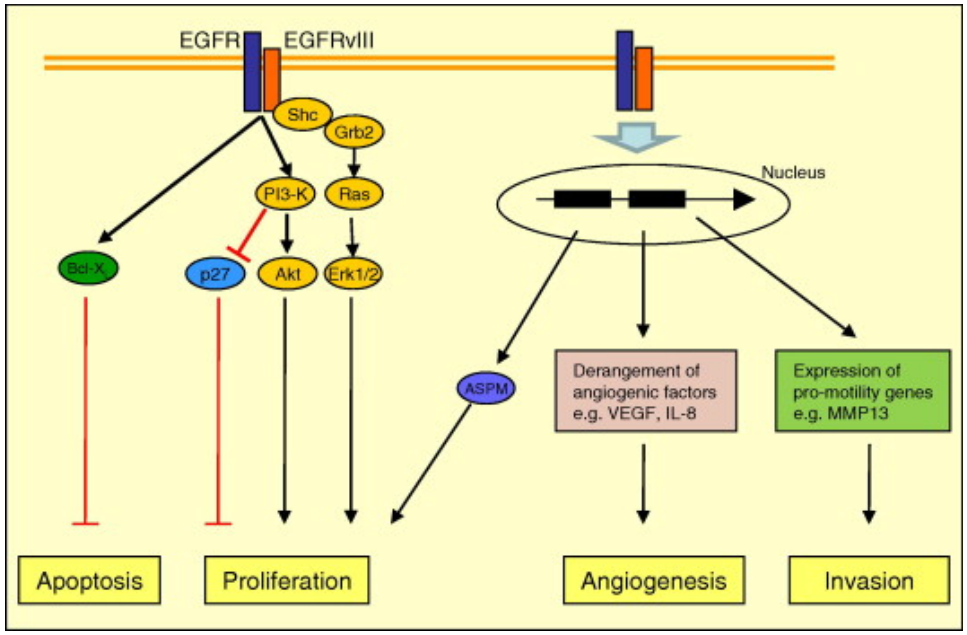
Challenges in GBM therapy:

- **Redundancy**
  - Not depending on one driver mutation, others can compensate
- **Heterogeneity**
  - Several different driver mutations present in same tumor
- **Resistance**
  - Tumors escape targeting by utilizing new driver mutations

=> Targeted therapy rarely shows a lasting effect

Glioblastoma – EGFR Targeted Therapy





The rationale for using erlotinib (EGFR blocker) to treat glioblastoma:

- High expression of EGFR in about 50% of GBM
- Blocking EGFR should block glioblastoma growth & invasion
- Small molecule tyrosine kinase inhibitor (TKI) - crosses blood-brain barrier

=> In trials, only 10-20% of patients respond

J Clin Neurosci. 2009 Jun;16(6):748-54.

Glioblastoma – Immunotherapy

- Checkpoint modulation
- Antibody-drug conjugates
- Vaccines
- CAR-T-cells

Glioblastoma – Immunotherapy

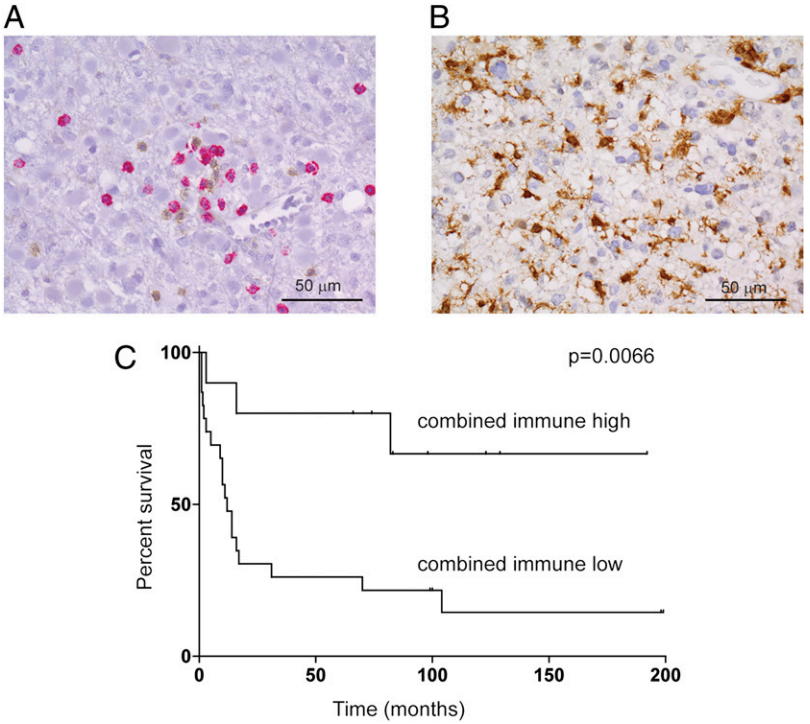


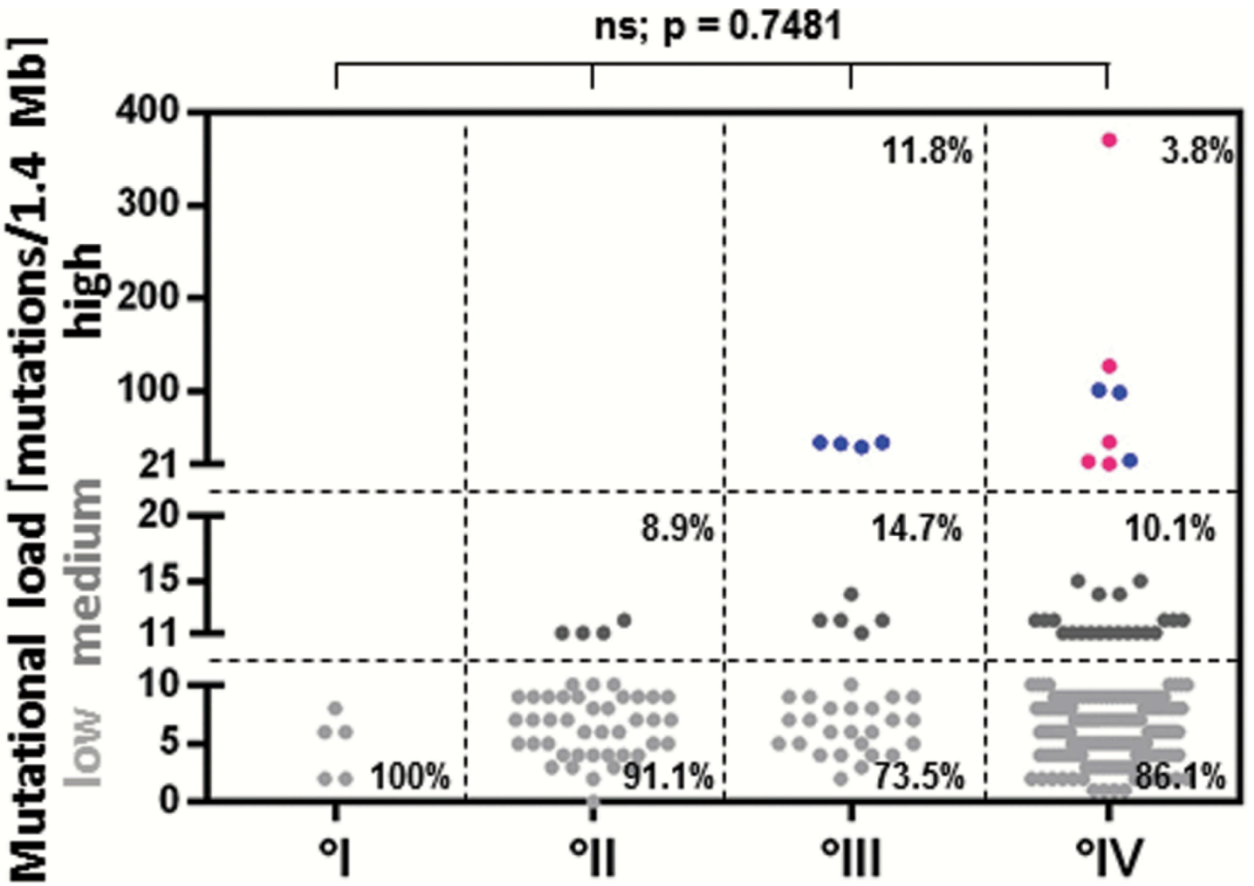
FIGURE 1. Representative histology of (**A**) greater than median tumor infiltration of cytotoxic T cells (CD8; red) and Th cells (CD4; brown) in long-term survivor HGA11, and (**B**) >75th percentile tumor infiltration of microglia/macrophages (AIF1; brown) in long-term survivor HGA12. IHC was performed using FFPE tumor sections with hematoxylin counterstaining (original magnification ×400). (**C**) Kaplan–Meier survival analysis of combined immune cell infiltration. High combined immune cell infiltration was defined as greater than median cytotoxic T cell or Th cell or >75th percentile microglia/macrophage infiltration. Thirty-three HGA samples were used.

⇒ **Higher immunoscore associated with better prognosis**

⇒ **Brain not excluded from immunotherapy approaches**

The Journal of Immunology, 2012, 189: 1920–1927.

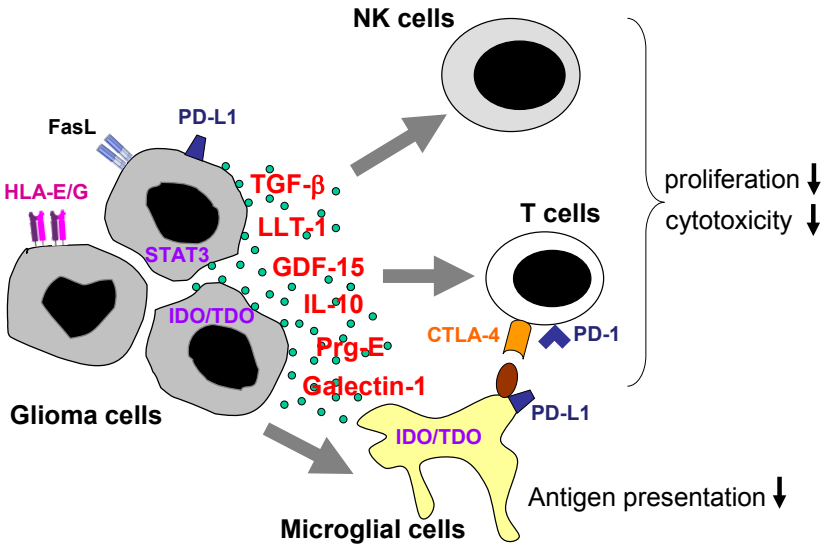
Mutational Load in Glioma



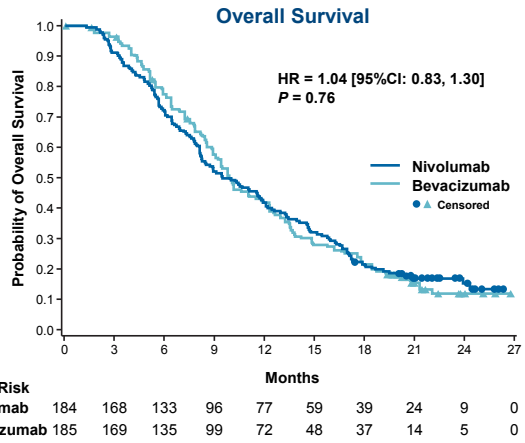
=> Higher grade glioma show higher mutational load

Neuro-Oncology,2017, 19:1047–1057

Checkpoint Immunotherapy



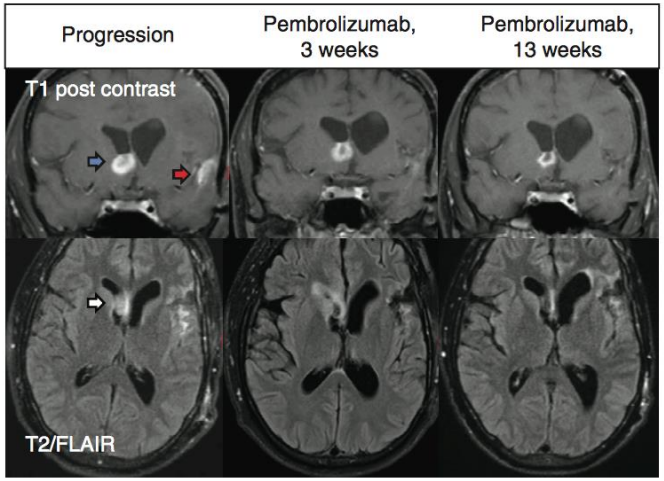
	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], months
Nivolumab	154	9.8 [8.2, 11.8]	41.8 [34.7, 48.8]
Bevacizumab	147	10.0 [9.0, 11.8]	42.0 [34.6, 49.3]



Reardon et al., WFNOS meeting 2017

- PD-L1 present in gliomas (in some)
- Anectodal evidence of succesful PD-1 inhibition in some cases
- **Phase III PD-1 inhibitor trial negative** in recurrent glioblastoma
- Clinical trials in newly diagnosed glioblastoma ongoing

Roth ESMO 2016



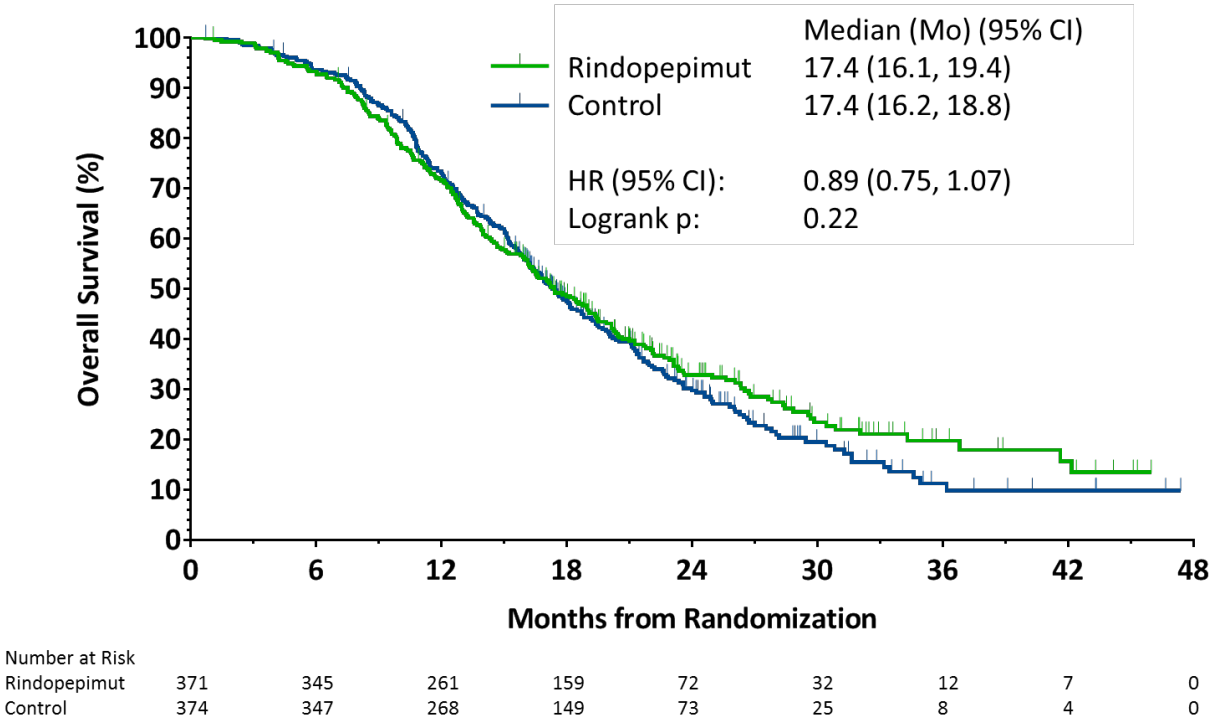
Johans, Cancer Discovery 2016

Glioblastoma Cancer Vaccination

- Vaccine approaches: tumor cell lysate, RNA, peptides, DC
- Strong adjuvants required
- Promising data from preclinical models
- Clinical trials dissapointing

Glioblastoma – EGFRviii vaccination

EGFRviii vaccination

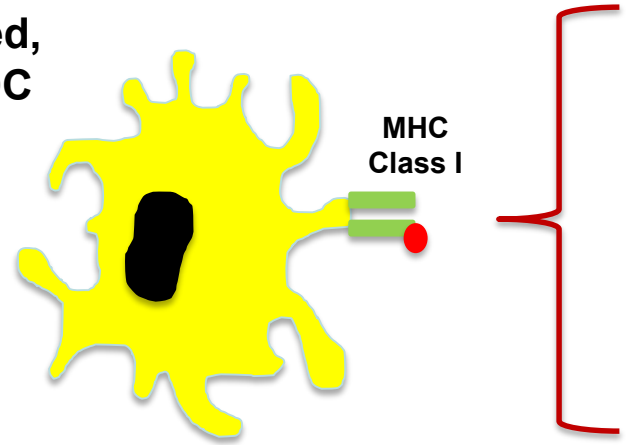


Weller et al., SNO meeting 2016

Glioblastoma – DC vaccine

Example for a DC based vaccine

Matured, activated, peptide-loaded DC



Six 9-10 amino acid antigen epitopes

- **MAGE-1 (HLA - A1)**
- **AIM-2 (A1)**
- **gp100 (HLA - A2)**
- **IL-13Rα2 (A2)**
- **HER2/neu (A2)**
- **TRP-2 (A2)**

- Targeting multiple antigens
- Promising data in a randomized phase II trial
- Phase III trial ongoing: ICT-107 or placebo in addition to temozolomide-based radiochemotherapy in patiens with newly diagnosed glioblastoma

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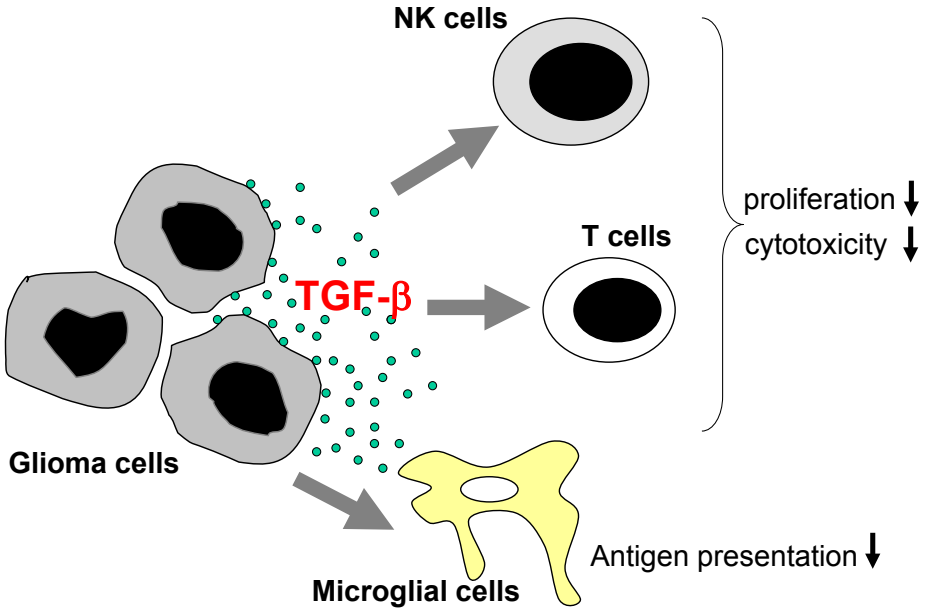
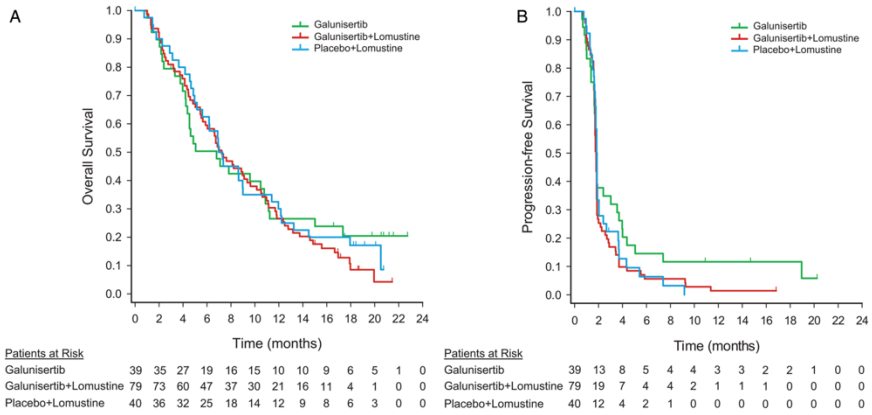
Glioblastoma – TGF-β inhibition





=> No impact on median survival in TGF-b targeting treatment groups

Roth ESMO 2016

Neuro Oncol. 2016;18(8):1146-1156

The Year 2010

Introduction of a novel GBM classification based on *molecular signatures*

Glioma – Molecular Classification

Cancer Cell
Article

Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in *PDGFRA*, *IDH1*, *EGFR*, and *NF1*

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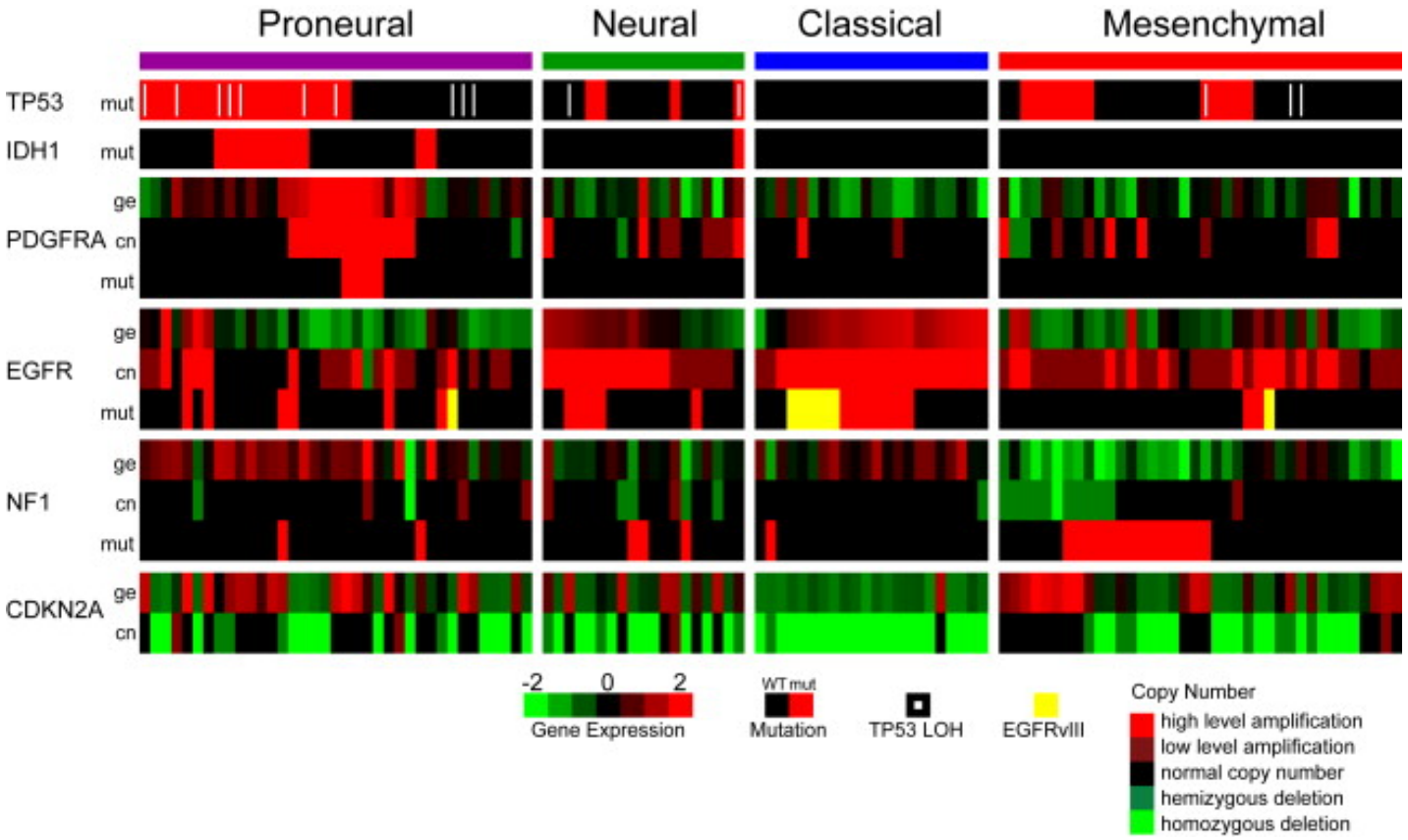
Cancer Cell *17*, 98–110, January 19, 2010

Glioma – Molecular Classification

Analysis from The Cancer Genome Atlas (≈ 600 GBM tumors)



Cancer Cell *17*, 98–110, January 19, 2010

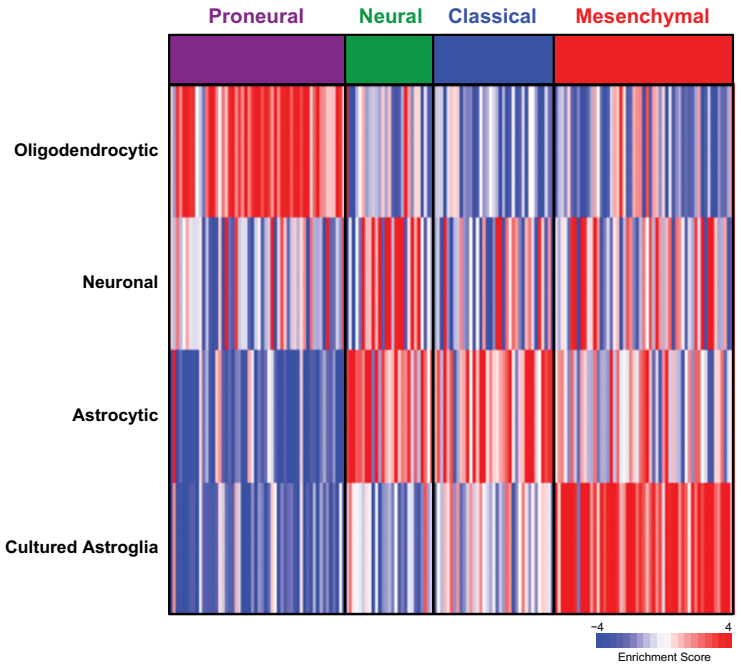
Glioma – Molecular Classification

Table 3. Distribution of Frequently Mutated Genes across GBM Subtypes

Gene	Proneural (n = 37)	Neural (n = 19)	Classical (n = 22)	Mesenchymal (n = 38)	Total No. of Mutations
TP53	**20 (54%)**	4 (21%)	**0 (0%)**	12 (32%)	36
PTEN	6 (16%)	4 (21%)	5 (23%)	12 (32%)	27
NF1	2 (5%)	3 (16%)	1 (5%)	**14 (37%)**	20
EGFR	6 (16%)	5 (26%)	7 (32%)	2 (5%)	20
IDH1	**11 (30%)**[a]	1 (5%)	0 (0%)	0 (0%)	12
PIK3R1	7 (19%)	2 (11%)	1 (5%)	0 (0%)	10
RB1	1 (3%)	1 (5%)	0 (0%)	5 (13%)	7
ERBB2	2 (5%)	3 (16%)	1 (5%)	1 (3%)	7
EGFRvIII	1 (3%)	0 (0%)	5 (23%)	1 (3%)	7
PIK3CA	3 (8%)	1 (5%)	1 (5%)	1 (3%)	6
PDGFRA	4 (11%)	0 (0%)	0 (0%)	0 (0%)	4

Significance of the difference in number of events between subtypes and remainder of the subtypes was determined using a two-sided Fisher's exact test, corrected for multiple testing using a Familywise Error Rate. Bold type indicates p values significant at an 0.1 level. Also see Figure S5 and Tables S2, S4, and S6.

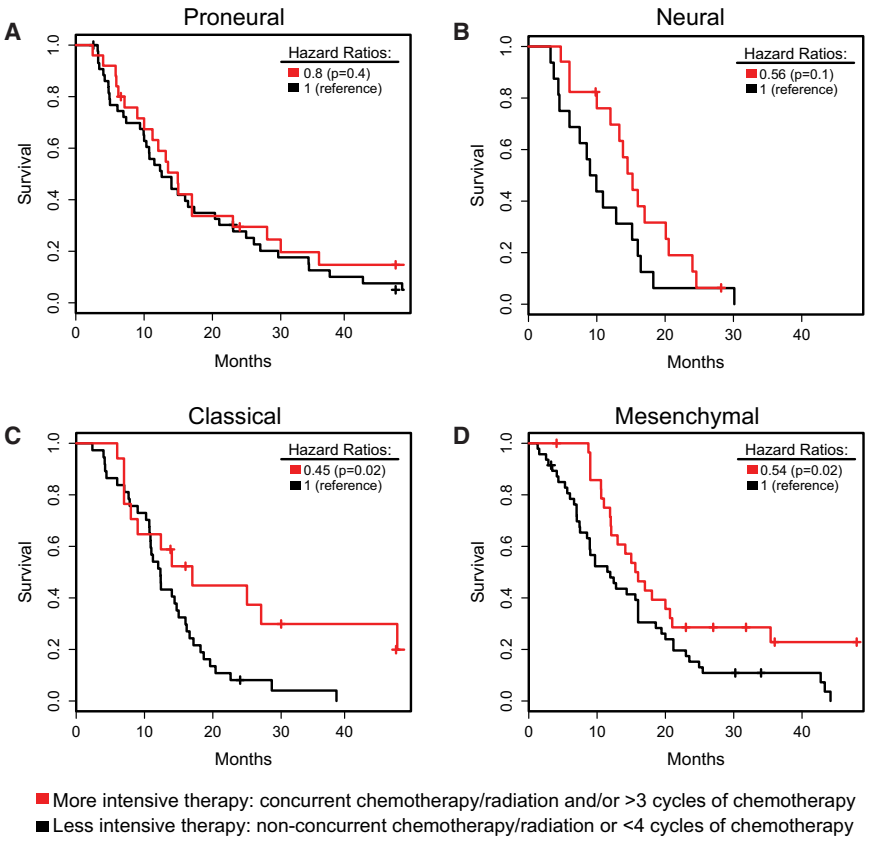
[a] p value significant at 0.01 level.



Correlation between GBM subtype and cultured cell types

Cancer Cell *17*, 98–110, January 19, 2010

Glioma – Molecular Classification



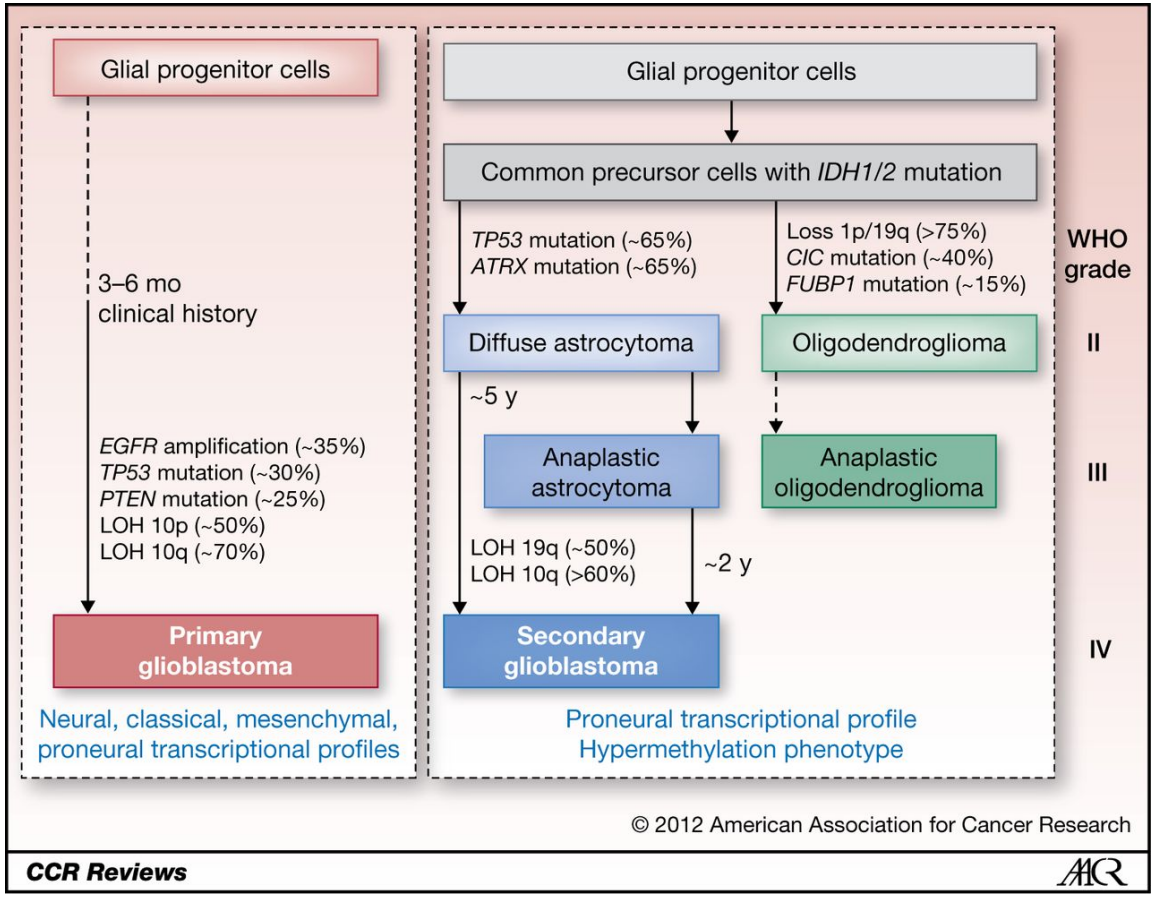
⇒ The "CLASSICAL" subtype responds best, the "PRONEURAL" subtype worst to intensified treatment.

⇒ Later studies found proneural to have best and mesenchymal subtype to have worst overall prognosis

Cancer Cell *17*, 98–110, January 19, 2010

Glioma – Molecular vs WHO Classification

Genetic pathways to primary and secondary glioblastomas



Clin Cancer Res 2013;19:764-772