Updates on the Identification & Management of Common Brain Tumors

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Objectives

- Describe the most common presenting symptoms for Gliomas.
- Describe new molecular genetic markers that assist in defining glioma subtypes by the new WHO 2016 classification scale.
- Outline the updated NCCN Guidelines for treatment of malignant gliomas.
- Identify novel treatments currently in clinical trials for gliomas including immune therapies and precision medicines.

Incidence

- Central Brain Tumor Registry United States (CBTRUS) database
- 62,930 new cases of malignant and non-malignant brain tumors in 2007
- Estimated 21,810 new cases of malignant CNS tumors in 2008, estimated deaths 13,070
- Relative risks: 1.38 Men vs Women
- 3.18 Elderly vs Young adults
- 1.86 Caucasian vs. African-American
- Malignant brain tumors (22,070 cases estimated in 2009) account for 1.42% of all primary malignant cancers in the US (American Cancer Society 2009) but account for a disproportionate share of cancer morbidity and mortality (CDC 2008).

PRESENTATION OF GLIOMAS

Presentation of a Brain Tumor

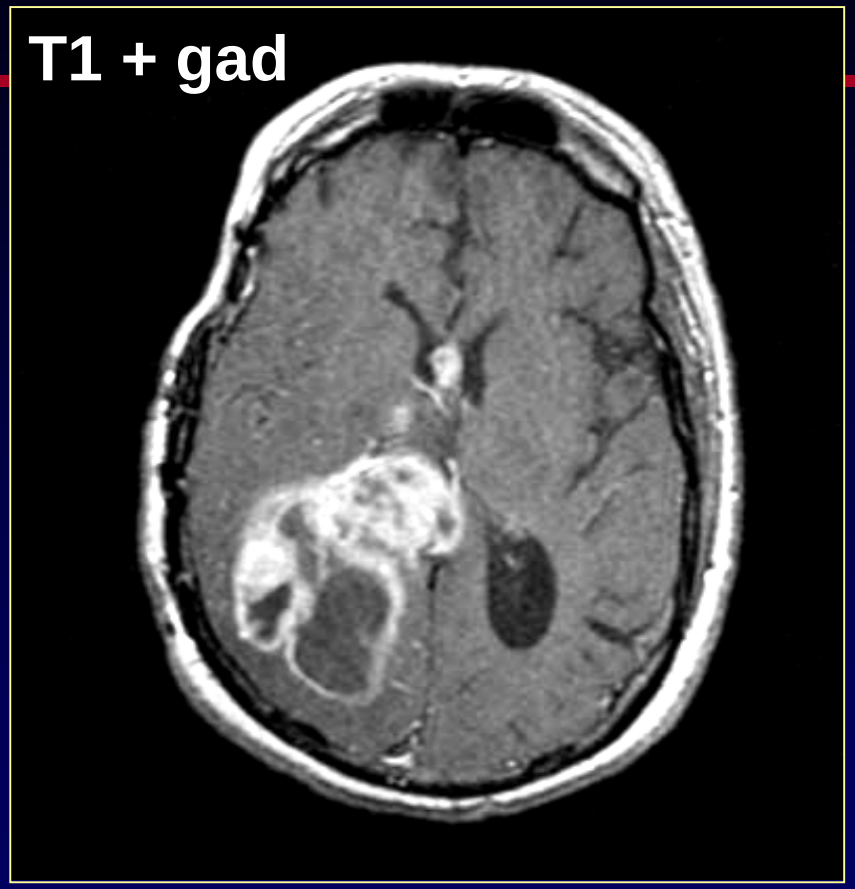
- 1/3 Asymptomatic
- Generalized
  - ICP, vasogenic edema
  - Headaches, lethargy, nausea/vomiting, confusion
  - Personality Changes
- Focal (or multi-focal)
  - Seizures
  - Hemiparesis
  - Visual field deficits
  - Aphasia
  - Ataxia
  - Etc.

Not one single pathognomonic presenting sign or symptom.
Look for clinical picture.

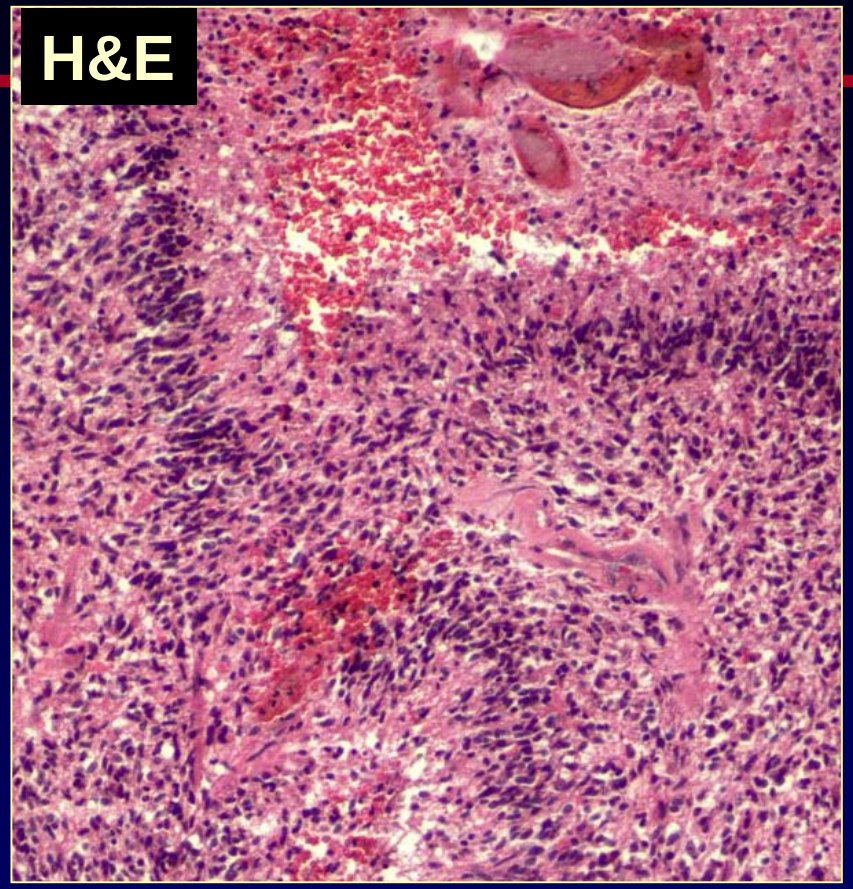
Diagnosis

- Imaging
  - MRI with gad, (most sensitive)
    - Perfusion
    - Spectroscopy
  - CT: hypodense lesion (usually edema)
  - PET scan
- Biopsy
  - Gold Standard
  - Therapeutic potential (resection)
  - (Post-op MRI 24-48 hours)

Glioblastoma (WHO Grade IV)



Enhancing mass, cystic components, variable necrosis



Highly cellular, pseudo-palisading necrosis, microvascular prolif.

Median survival: 14 months

MOLECULAR MARKERS AND CLASSIFICATION OF GLIOMAS

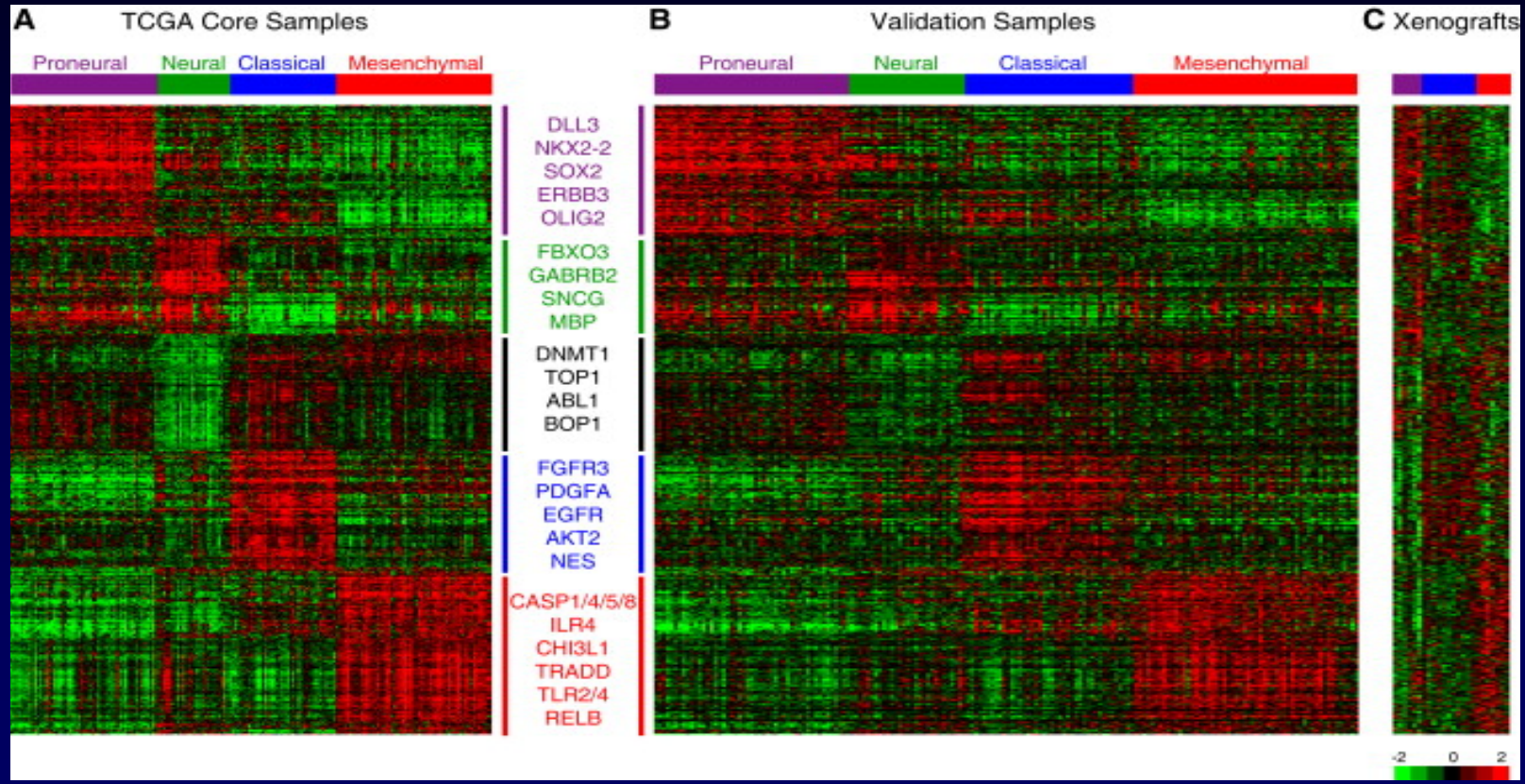
Gliomas (previous classification)

	Tumor cell of origin or differentiation sub-type		
	Oligodendroglioma	**Mixed: Oligoastrocytoma**	**Astrocytoma**
Grade I, “benign”			Pilocytic Astrocytoma
Grade II, Low grade glioma (LGG)	Oligodendroglioma	LGG oligoastrocytoma	Astrocytoma
Grade III, anaplastic	Anaplastic oligodendroglioma	Anaplastic oligoastrocytoma	Anaplastic Astrocytoma
Grade IV	GBM with oligodendroglia features		GBM

New WHO Molecular Classification of Gliomas

- WHO 2016
  - New classification of Primary Brain Tumors

The Cancer Genome Atlas (TCGA)



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

Cancer Cell Volume 17, Issue 1 2010 98 - 110

Biomarkers

Important Biomarkers:

- 1p/19q co-deletion
- IDH1/IDH2 mutation
- MGMT methylation status
- ATRX
- H3K27M mutation

Secondary

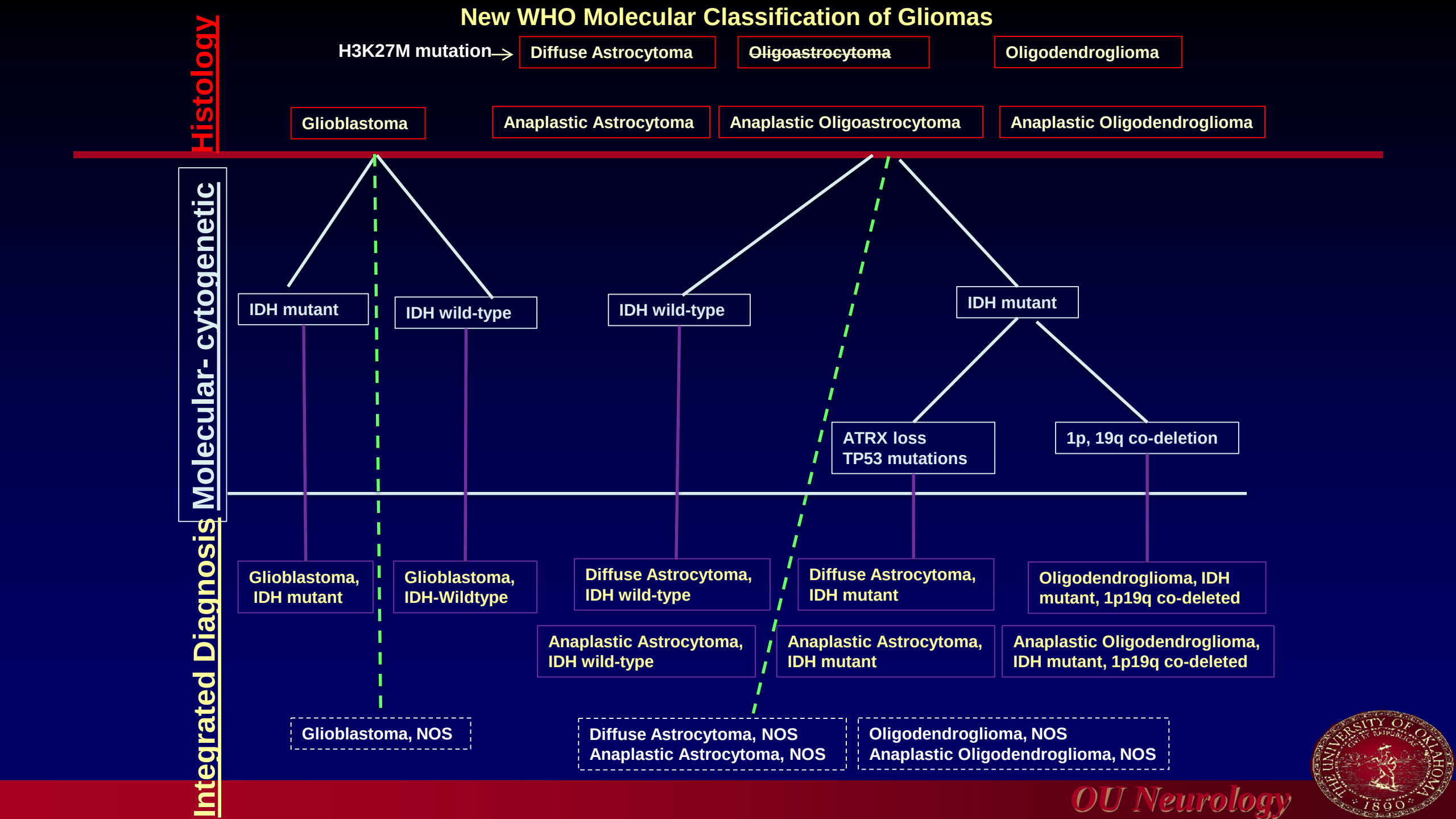
- EGFR vIII & EGFR alterations
- cMet alterations

Molecular pathology in adult gliomas: diagnostic, prognostic, and predictive markers. Jansen M, Yip S, Louis DN, Lancet Neurol. 2010;9(7):717

Table 1.3 Immunohistochemical markers commonly used in brain tumor classification

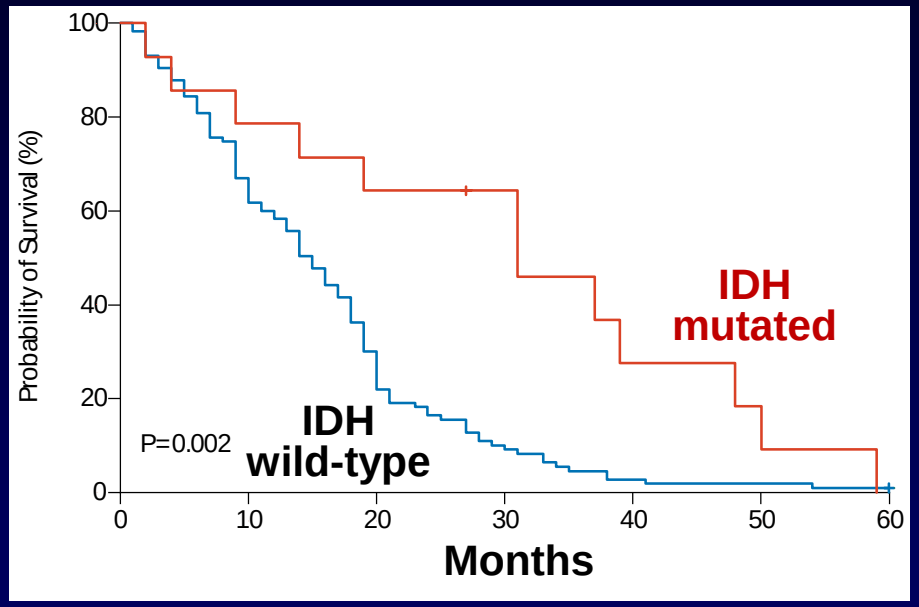
Neuronal and neuroendocrine markers
Synaptophysin, neurofilament proteins, NeuN, chromogranin A
Glial markers
Glial fibrillary acidic protein (GFAP), S-100 protein, MAP2
Epithelial markers
Cytokeratins, epithelial membrane antigen (EMA)
Melanocytic markers
Melan A, HMB-45
Mesenchymal markers
Vimentin, desmin, smooth muscle actin (SMA), myoglobin
Blood cell markers
CD45 (pan-leukocytes), CD20 (B cells), CD3 (T cells), CD68, HLA-DR (monocytes, macrophages, microglia), CD138 (plasma cells)
Germ cell markers
ß-HCG, alpha-fetoprotein (AFP), placental alkaline phosphatase (PLAP), human placental lactogen (HPL), OCT4 (germinomas), c-Kit (germinomas), CD30 (embryonal carcinomas)
Pituitary hormones
Prolactin, ACTH, TSH, FSH, LH, GH
Proliferation marker
Ki-67 (MIB1)
Other useful markers
p53, CD34, thyroid transcription factor 1 (TTF1), Cdx2, prostate-specific antigen (PSA), thyreoglobulin, estrogen and progesterone receptors, HER2/Neu, EGFR, INI1

New WHO Molecular Classification of Gliomas



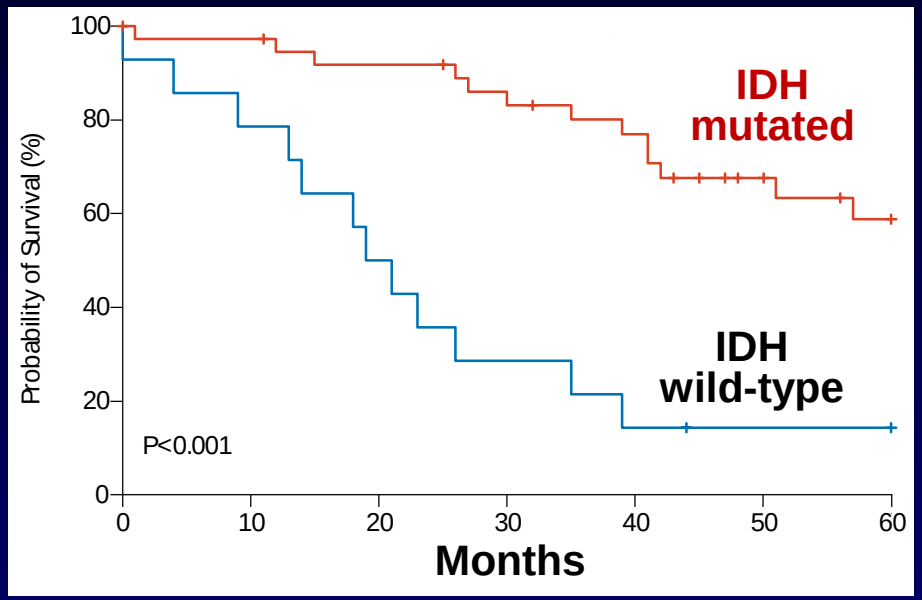
IDH mutations: Better overall survival
Excellent prognostic marker

Glioblastoma



(12% mutated)
Secondary GBM

Anaplastic astrocytoma

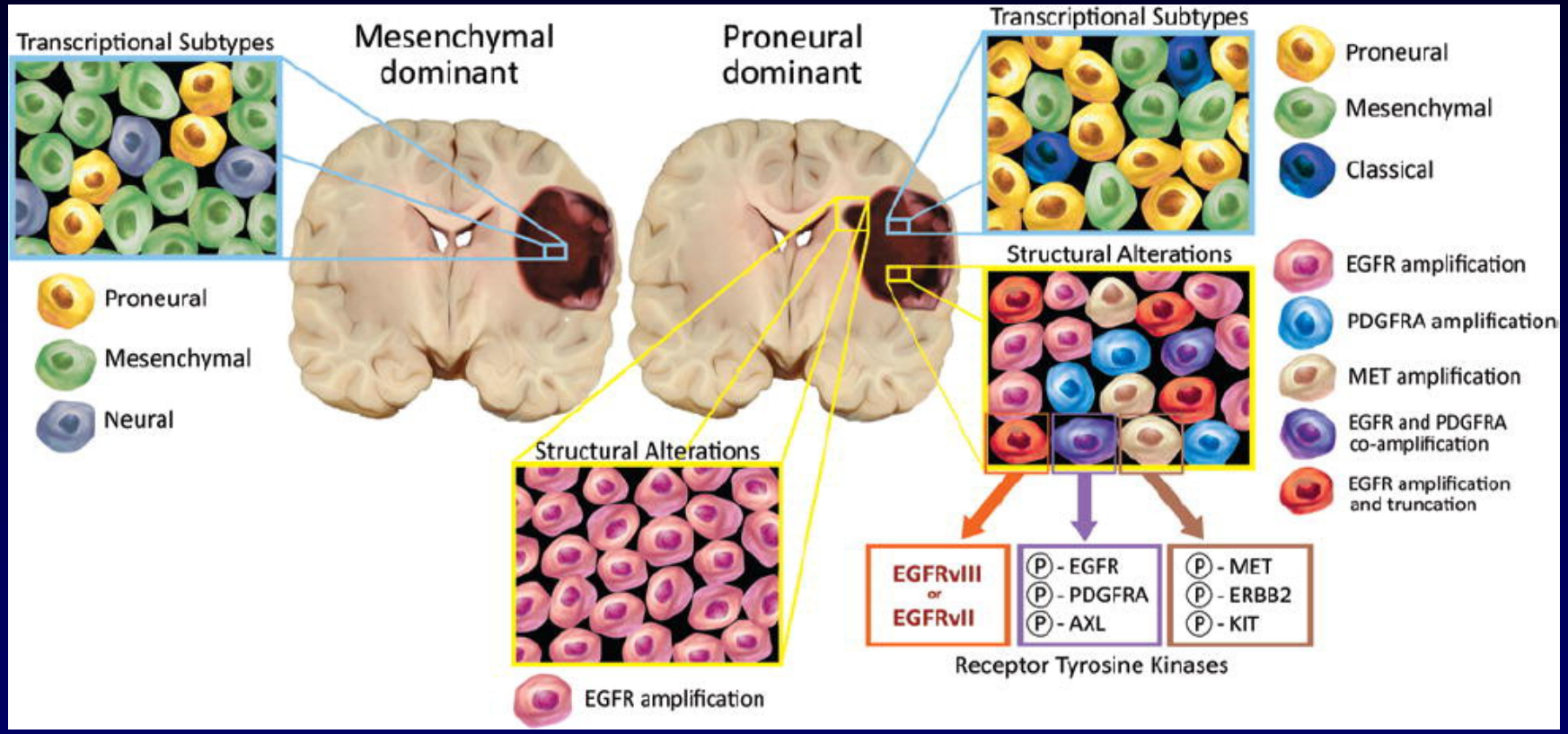


(70% mutated)

Yan *et al*, N Engl J Med 2009;360:765

OU Neurology

GBM Heterogeneity



Aum and Kim, et. al., Journal of Neurosurgery, 2014

TREATMENT OF GLIOMAS

Symptom management

- Steroids (next slide)
- AED’s
- Stimulants
- Anti-Depressants
- Monitor for clots: hypercoagulable state
- Autonomic instability
- Etc.

Edema

- Steroids
  - Vasogenic edema can cause/worsen symptoms
  - Dexamethasone best choice
    - Minimal mineralocorticoid effect
  - Acute:
    - 10 mg IV bolus
    - 4 mg IV q6hr
  - Chronic:
    - PO dosing, long half life
      - Plasma: 2-4 hours,
      - Biological effect 36-54 hours
    - Divide BID or TID
    - Slow taper, changes q3 days, q7 days, or q2weeks
      - Long tail, decreasing only by 1 mg.
    - Monitor symptoms to tailor therapy.

Grade III Anaplastic Oligodedroglioma
Grade III Anaplastic Astrocytoma
Grade IV Glioblastoma

Treatment

- Maximal resection
- Concurrent Radiation and Temodar
- Adjuvant Temodar

- Avastin at recurrence

Time frame

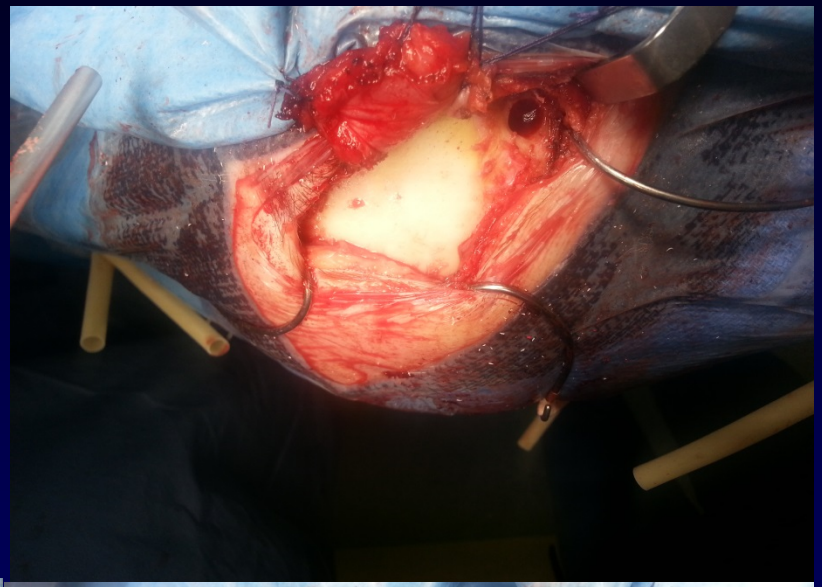
- Initial diagnosis
- ~6 weeks (IMRT)

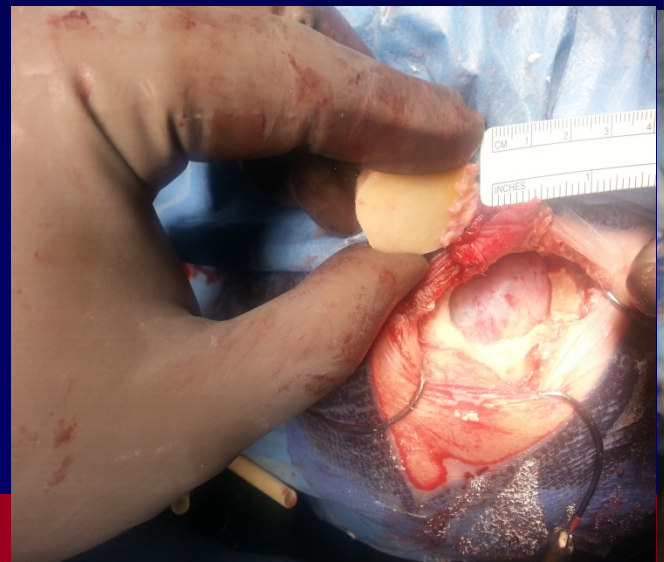
- 4 week cycles, plan for 12 cycles minimum

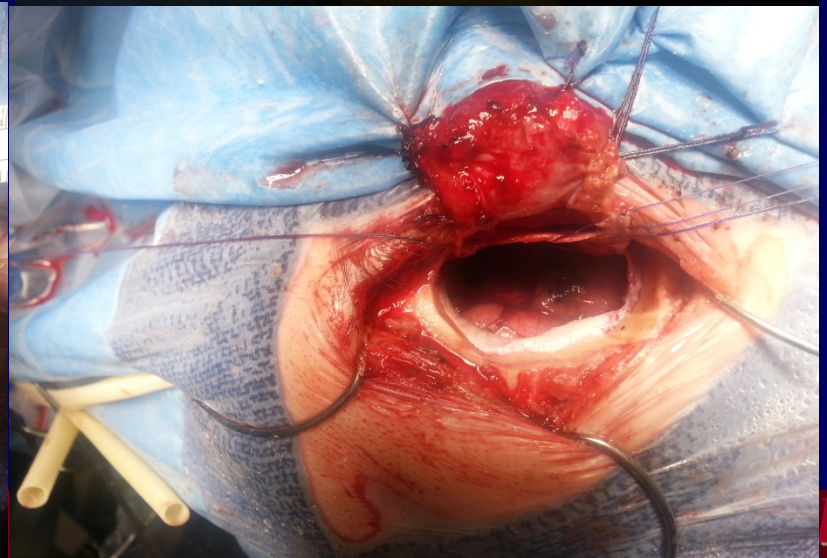
- IV infusion every 2 weeks

Surgical Resection

The very small hole through which it was taken out.







Gross Total Resection

- General principle:
  - Cytoreduction
  - Improve effectiveness of adjuvant therapy.
  - Balance with excision of eloquent areas

Gross Total Resection

TABLE 5

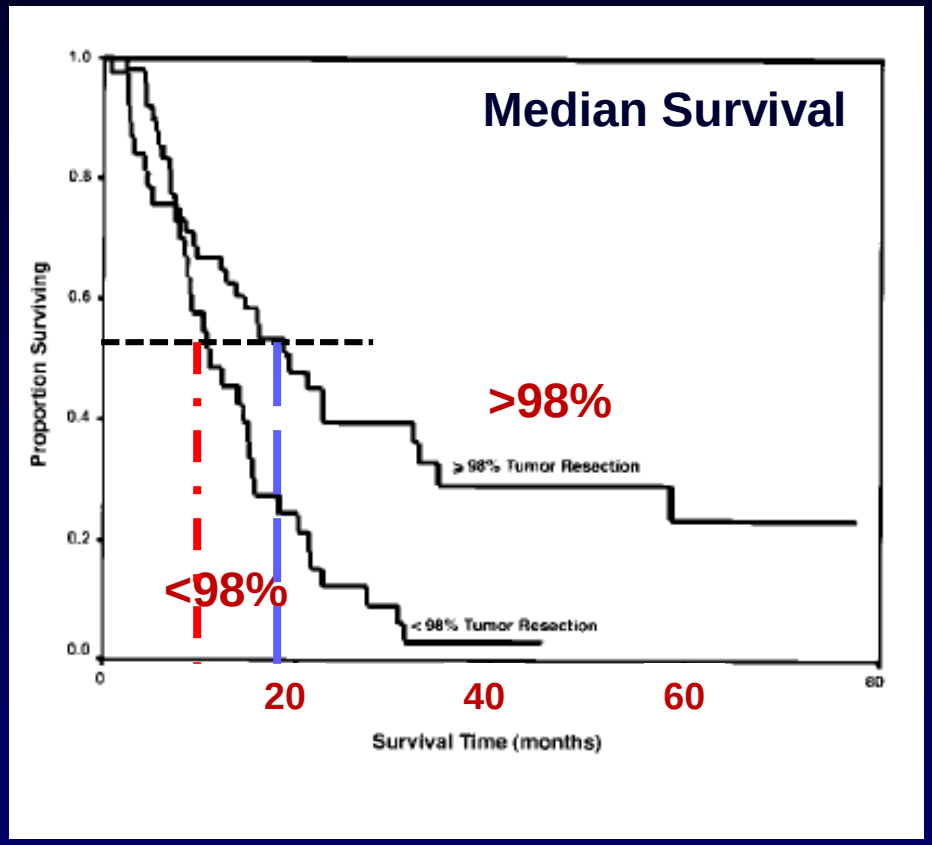
*Survival compared with extent of tumor resection**

Extent of Tumor Resection (%)	Median Survival in Mos (95% CI)	Rate Ratio (95% CI)	p Value
all 416 patients w/ GBM†			
≥85	10.9 (9.7–12.2)	1.2 (0.9–1.5)	0.22
≥87	10.8 (9.4–12.2)	1.2 (0.9–1.5)	0.15
≥89	10.9 (9.6–12.1)	1.3 (1.1–1.6)	0.04
≥90	10.9 (9.8–12.0)	1.4 (1.1–1.7)	0.02
≥93	11.2 (9.6–12.8)	1.3 (1.1–1.6)	0.01
≥94	11.3 (9.9–12.7)	1.4 (1.2–1.7)	0.01
≥95	11.6 (10.2–13.0)	1.4 (1.1–1.7)	0.005
≥96	12.6 (11.0–14.3)	1.5 (1.2–1.9)	0.0001
≥97	13.0 (11.4–14.6)	1.6 (1.3–2.0)	<0.0001
≥98	13.0 (11.4–14.6)	1.7 (1.4–2.1)	<0.0001
≥99	13.1 (11.6–14.6)	1.7 (1.4–2.1)	<0.0001
100	13.1 (11.6–14.7)	1.7 (1.4–2.2)	<0.0001
233 untreated patients w/ GBM‡			
≥85	10.8 (9.5–12.1)	0.9 (0.6–1.3)	0.61
≥90	10.9 (9.4–12.4)	1.1 (0.8–1.5)	0.62
≥93	11.6 (10.0–13.2)	1.1 (0.8–1.5)	0.48
≥94	11.9 (10.1–13.6)	1.2 (0.8–1.6)	0.36
≥95	12.1 (10.3–13.9)	1.2 (0.9–1.7)	0.15
≥96	12.6 (11.0–14.2)	1.3 (1.0–1.8)	0.06
≥97	12.6 (11.1–14.2)	1.4 (1.1–1.8)	0.04
≥98	13.0 (11.4–14.6)	1.4 (1.17–1.9)	0.02
≥99	13.1 (11.2–15.1)	1.5 (1.1–2.0)	0.006
100	13.1 (10.9–15.3)	1.5 (1.1–2.0)	0.006

* Comparing ≥ 85% with < 85%, ≥ 90% with < 90%, and so forth.

† Less than 89% tumor resection was not associated with increased survival time in this subgroup.

‡ Less than 97% tumor resection was not associated with increased survival time in this subgroup.



Lacroix, et al, J Neurosurg. 2001 Aug;95(2):190-8.

Grade III Anaplastic Oligodedroglioma
Grade III Anaplastic Astrocytoma
Grade IV Glioblastoma

Treatment

- Maximal resection
- Concurrent Radiation and Temodar
- Adjuvant Temodar

- Avastin at recurrence

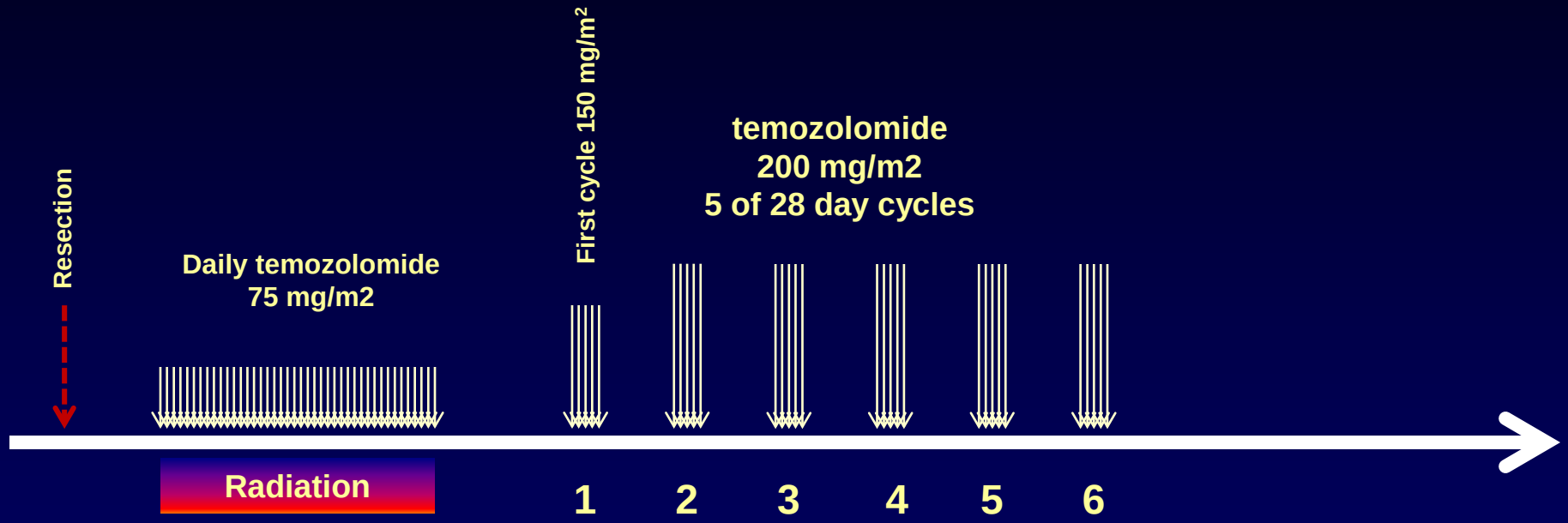
Time frame

- Initial diagnosis
- ~6 weeks (IMRT)

- 4 week cycles, plan for 12 cycles minimum

- IV infusion every 2 weeks

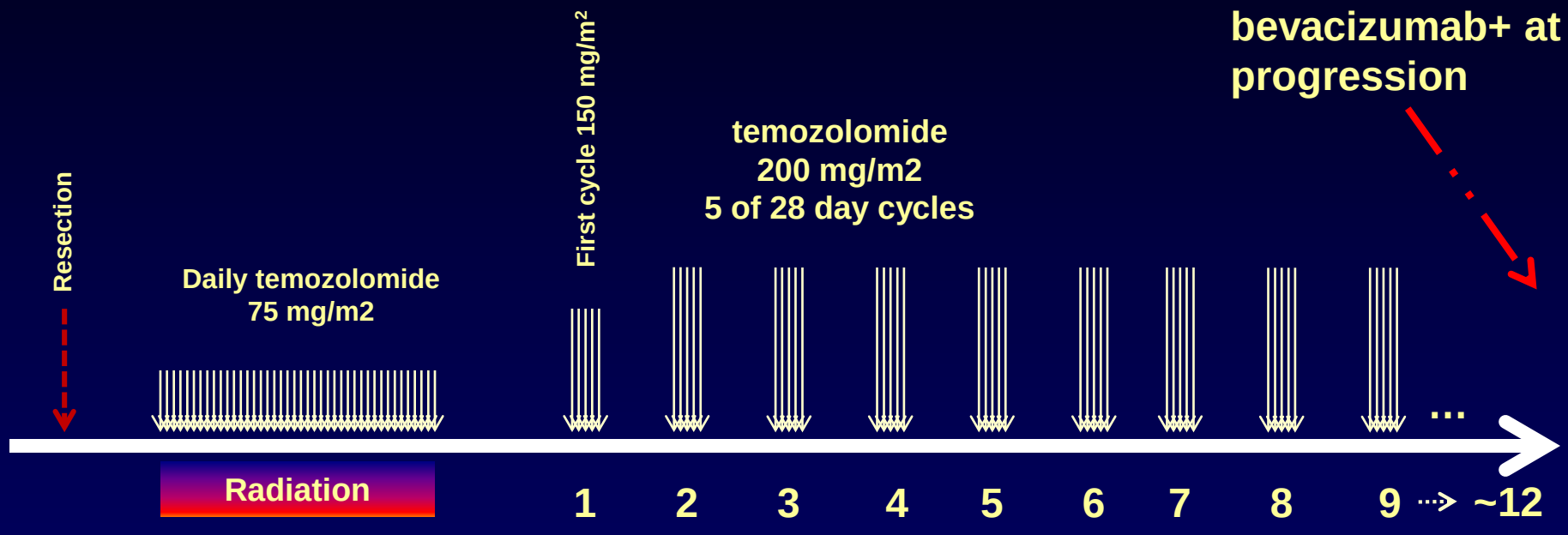
GBM Treatment: Stupp protocol, 2005



30 fractions
~60 Gy
IMRT
2-3 cm margin

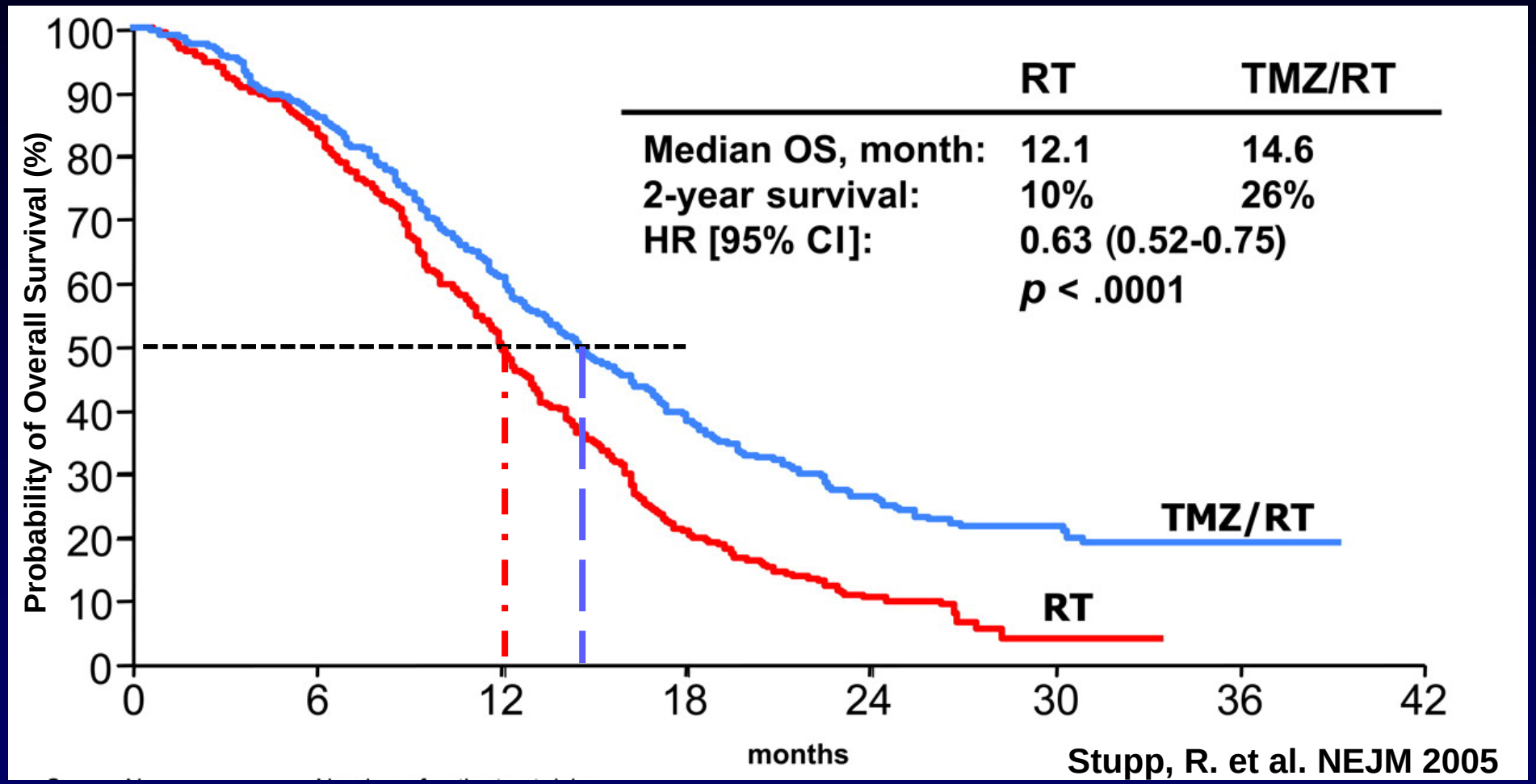
OS = 14.5 months

GBM Treatment: New Standard 2015/2017



OS = 22.4 months

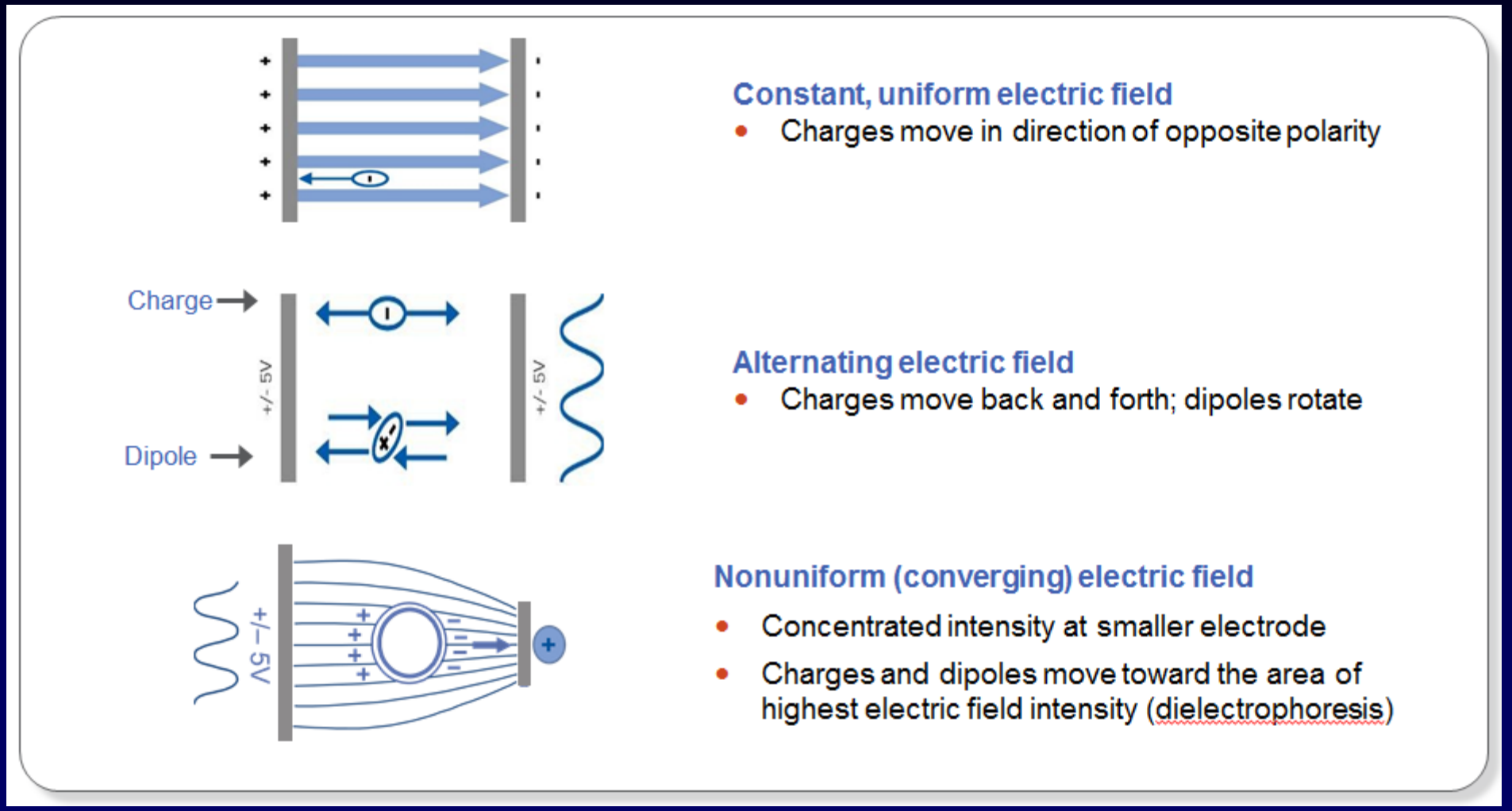
Standard Therapy: Concurrent daily Temozolomide and Radiation + 6 cycles Temozolomide (5 of 28 days)



Alternating Electrical Field Treatment Device (Tumor Treating Fields = TTF)

NCCN: Level 1 evidence for initial treatment

Alternating Electrical Fields – Mechanism of Action



Constant, uniform electric field

- Charges move in direction of opposite polarity

Alternating electric field

- Charges move back and forth; dipoles rotate

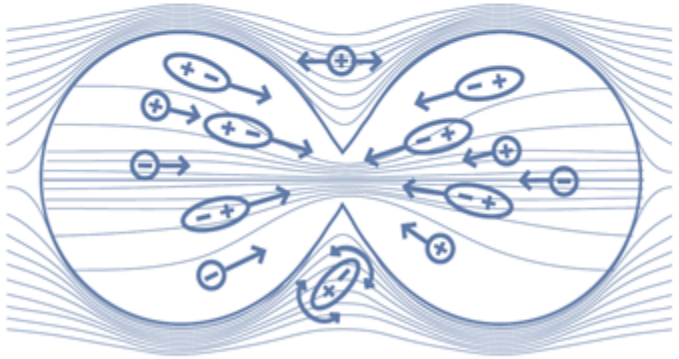
Nonuniform (converging) electric field

- Concentrated intensity at smaller electrode
- Charges and dipoles move toward the area of highest electric field intensity (dielectrophoresis)

Alternating Electrical Fields – Mechanism of Action

Metaphase—alternating electric fields (TTFields)

- Disrupt alignment of highly polarized tubulin subunits
- Disrupt microtubule spindle formation during mitosis and may ultimately lead to apoptosis

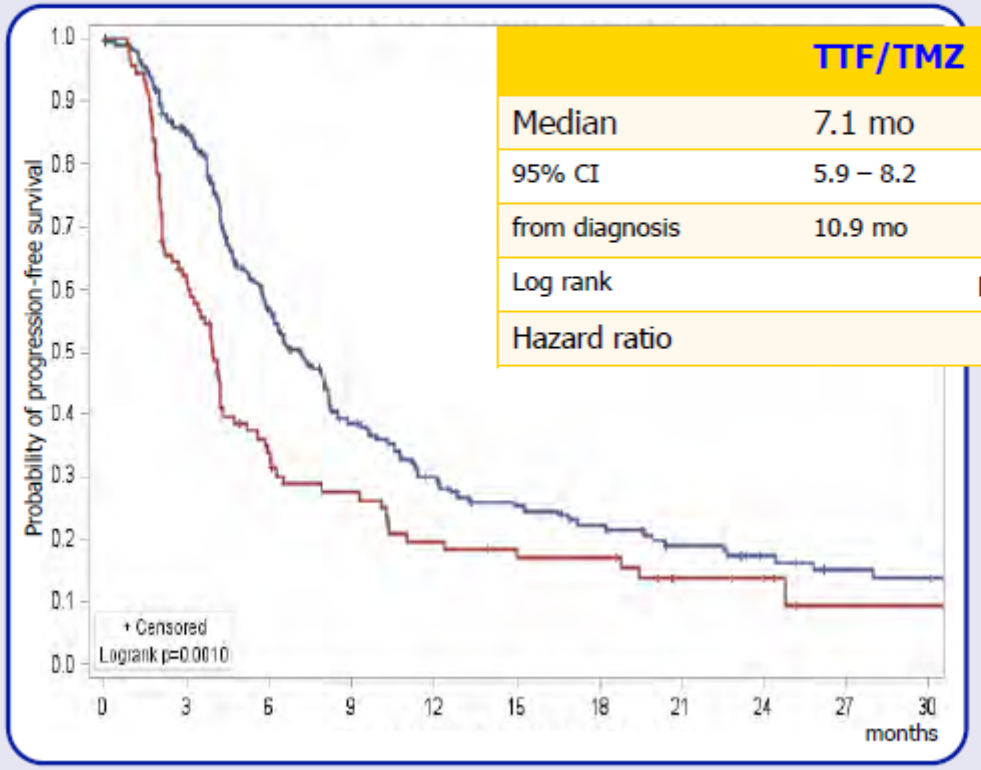


Telophase—nonuniform electric field

- A change in cell shape during telophase causes a nonuniform electric field
- Polar components move to cleavage furrow
- Cell cannot divide properly, which may ultimately lead to apoptosis

EF-14, Tumor Treating Field Therapy

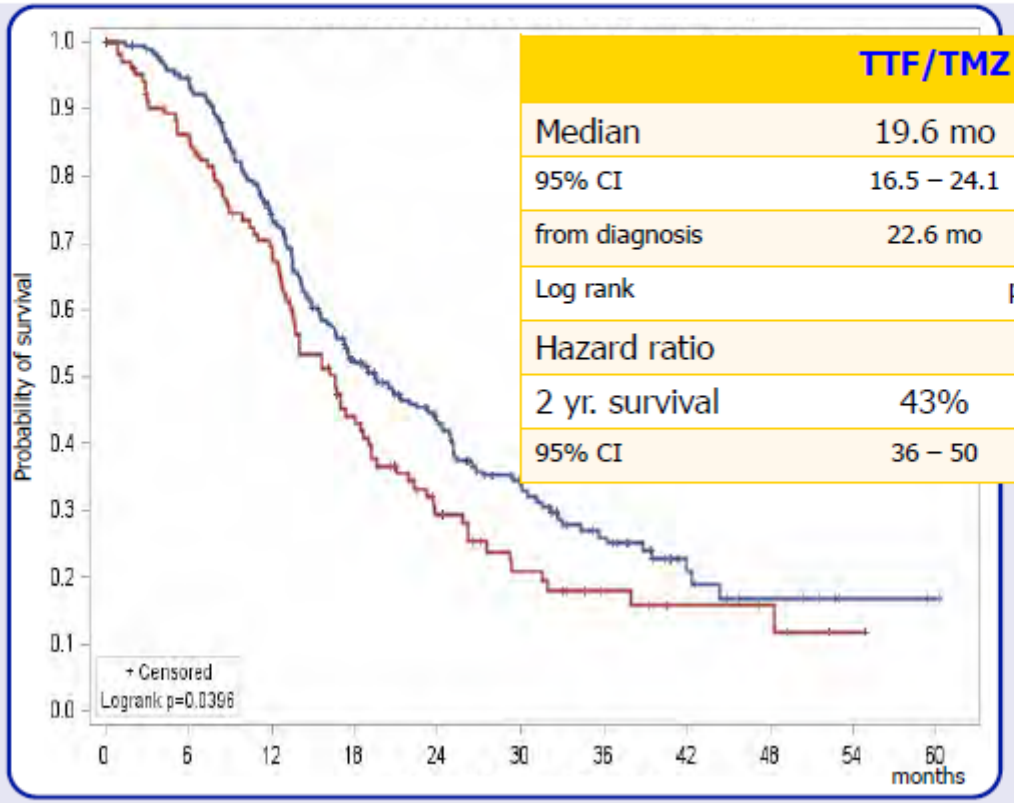
Progression-free survival
(1° endpoint, ITT population)



	TTF/TMZ	Adj. TMZ
Median	7.1 mo	4.0 mo
95% CI	5.9 – 8.2	3.0 – 4.3
from diagnosis	10.9 mo	7.9 mo
Log rank	p = 0.0014	
Hazard ratio	0.63	

EF-14, Tumor Treating Field Therapy

Overall - survival
(2º endpoint, ITT population)

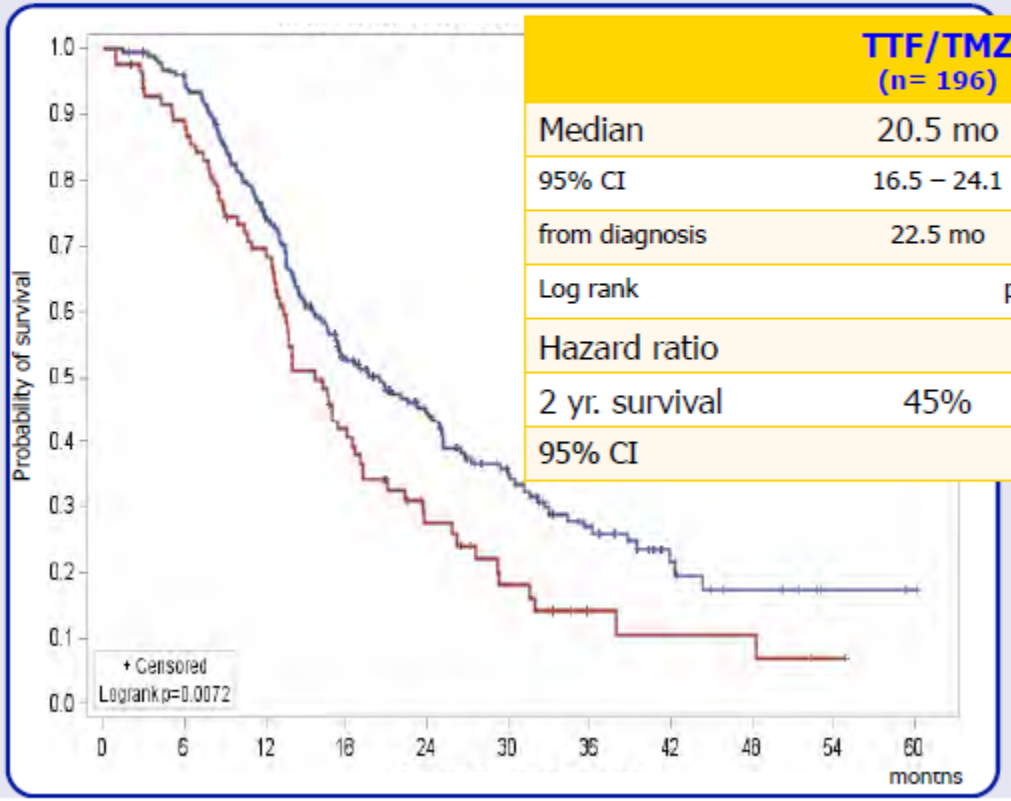


	TTF/TMZ	Adj. TMZ
Median	19.6 mo	16.6 mo
95% CI	16.5 – 24.1	13.5 – 19.1
from diagnosis	22.6 mo	19.6 mo
Log rank	p = 0.034	
Hazard ratio	0.75	
2 yr. survival	43%	29%
95% CI	36 – 50	21 – 39

EF-14, Tumor Treating Field Therapy

Overall - survival

(2º endpoint, as treated [crossover pts excluded])



	TTF/TMZ (n= 196)	Adj. TMZ (n=84)
Median	20.5 mo	15.5 mo
95% CI	16.5 – 24.1	13.5 – 19.1
from diagnosis	22.5 mo	18.5 mo
Log rank	p = 0.0072	
Hazard ratio	0.67	
2 yr. survival	45%	28%
95% CI		21 – 39

FDA Approved second-line treatment

- bevacizumab
- First line in recurrent Glioblastoma – approved in 2009
- Initial responses: ~60%
- More realistic: subgroups with short/long PRs
- Combinations: +TMZ; +Irinotecan
- If recurs after bevacizumab: Highly migratory phenotype in the recurrent setting
- No change in Overall Survival

bevacizumab

- Biological
- VEGF inhibitor antibody
- Anti-angiogenic
- IV infusion
- 10 mg/kg
- Every 2 weeks
  - basically for rest of life
  - Or, stop if a complication arises
- If recurs after bevacizumab: Highly migratory & aggressive phenotype

CLINICAL TRIALS AND OTHER ADVANCES

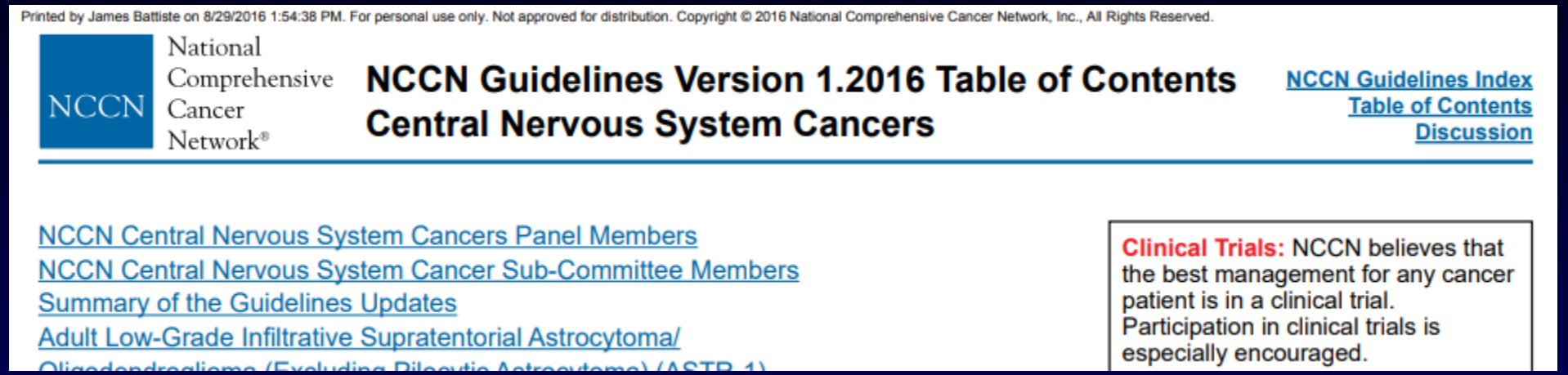
Therapies in the Pipeline (old slide)

- Cancer Vaccines
  - DCVax (still waiting on final data)
  - HSPPC-96 vaccination (trial closed…)
  - EGFR vaccination, (Rindopepimut, failed Phase III)
- Oncolytic Virus
  - Duke: PVS-RIPO (modified poliovirus)
  - MD Anderson: DNX2401
- Chemotherapy
  - OKN-007
  - TRC-105
- Higher Dose radiation and Proton Therapy

New Therapies Pipeline

- Bevacizumab plus INC-280 (cMET inhibitor)
- CXCR4 inhibitor
- REGN-2810 (PD-1 inhibitor) plus plasmid adjuvant
- Niraparib – IDH1 and IDH2 mutations induce HRD
- LITT plus chemo – opens BBB
- OKN-007 plus TMZ (OKN opens BBB and overcomes TMZ resistance

Clinical Trials



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016 Table of Contents
Central Nervous System Cancers

NCCN Guidelines Index
Table of Contents
Discussion

Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

BN-001: Dose Escalation of Photon vs. Proton Therapy

- Standard dose Photon 60 Gy of radiation
- High dose Photon 75 Gy of radiation
- Proton Therapy

- Results pending. Proton Therapy arm still open

RTOG 1205 – Recurrent Glioblastoma

- Repeat radiation and bevacizumab
- Bevacizumab, q2weeks
- Radiation, 30 Gy in 15 fractions
- Results still pending

OKN-007, Phase 1b (Nitrone compound)

- Recurrent GBM (heavily pre-treated)
- 3x3 Dose escalation trial with modified expansion phase
- Results
  - 18 patients treated
  - No DLT's
  - Only possible AE's: headache, increased BUN, generalized pain, nausea (n=1)
  - Partial response (n=2), stable disease (n=7), progressive disease (n=9).
  - Median PFS was 2.3 months, and median OS was 11.5 months
  - 6 month PFS of 15.38% and 6 month OS of 77% with a 1 year OS of 38%

OKN-007, Phase 1b

- Recurrent GBM (heavily pre-treated)

Additional salvage chemotherapy after bevacizumab failure was given to 19 patients. The median progression-free survival (PFS) among these 19 patients was 2 months, the median OS was 5.2 months, and the 6-month PFS rate was 0%.

***Neurology*® 2009;73:1200–1206**

  - Partial response (n=2), stable disease (n=7), progressive disease (n=9).
  - Median PFS was 2.3 months, and median OS was 11.5 months
  - 6 month PFS of 15.38% and 6 month OS of 77% with a 1 year OS of 38%

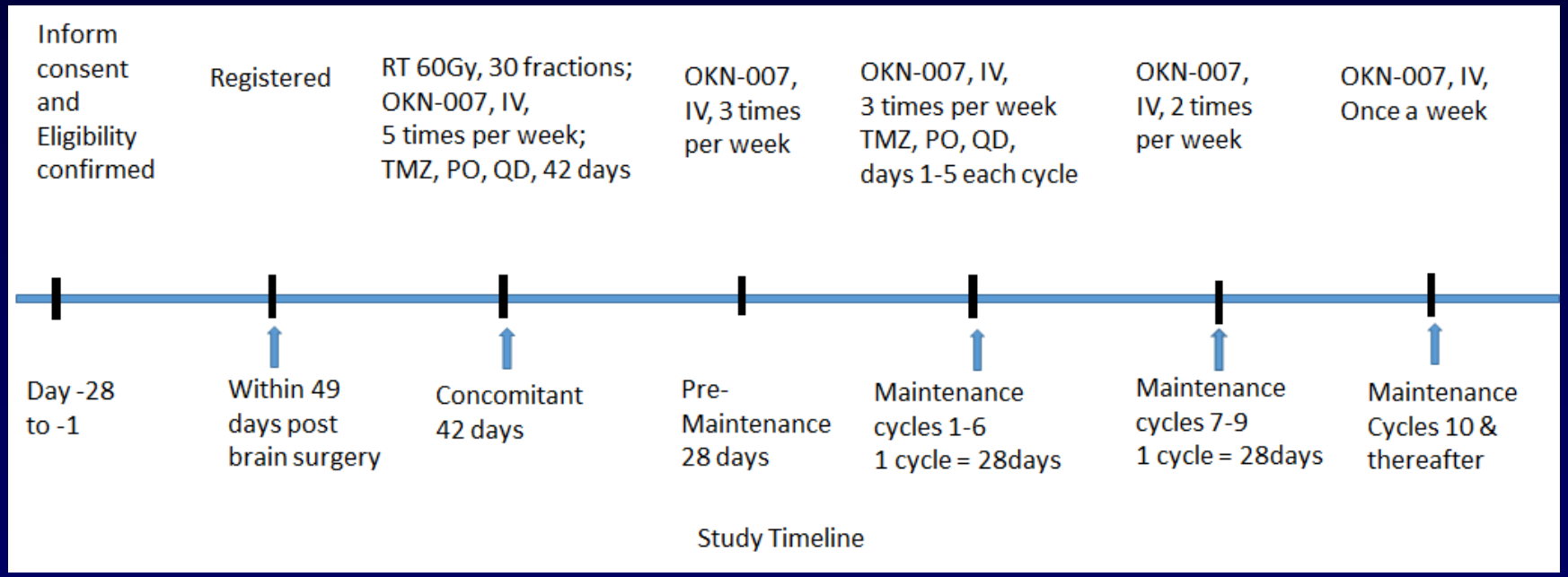
OKN-007 & TMZ & Radiation

- Feasibility Pilot Study of OKN-007 in Combination with Adjuvant Temozolomide Chemoradiotherapy in Patients with Newly Diagnosed Glioblastoma

New OKN-007 trial: Schema

Cohort A:
RT 60 Gy, 30 fractions
OKN-007, IV,
3 times per week;
TMZ, PO, QD, 42 days

Cohort B:



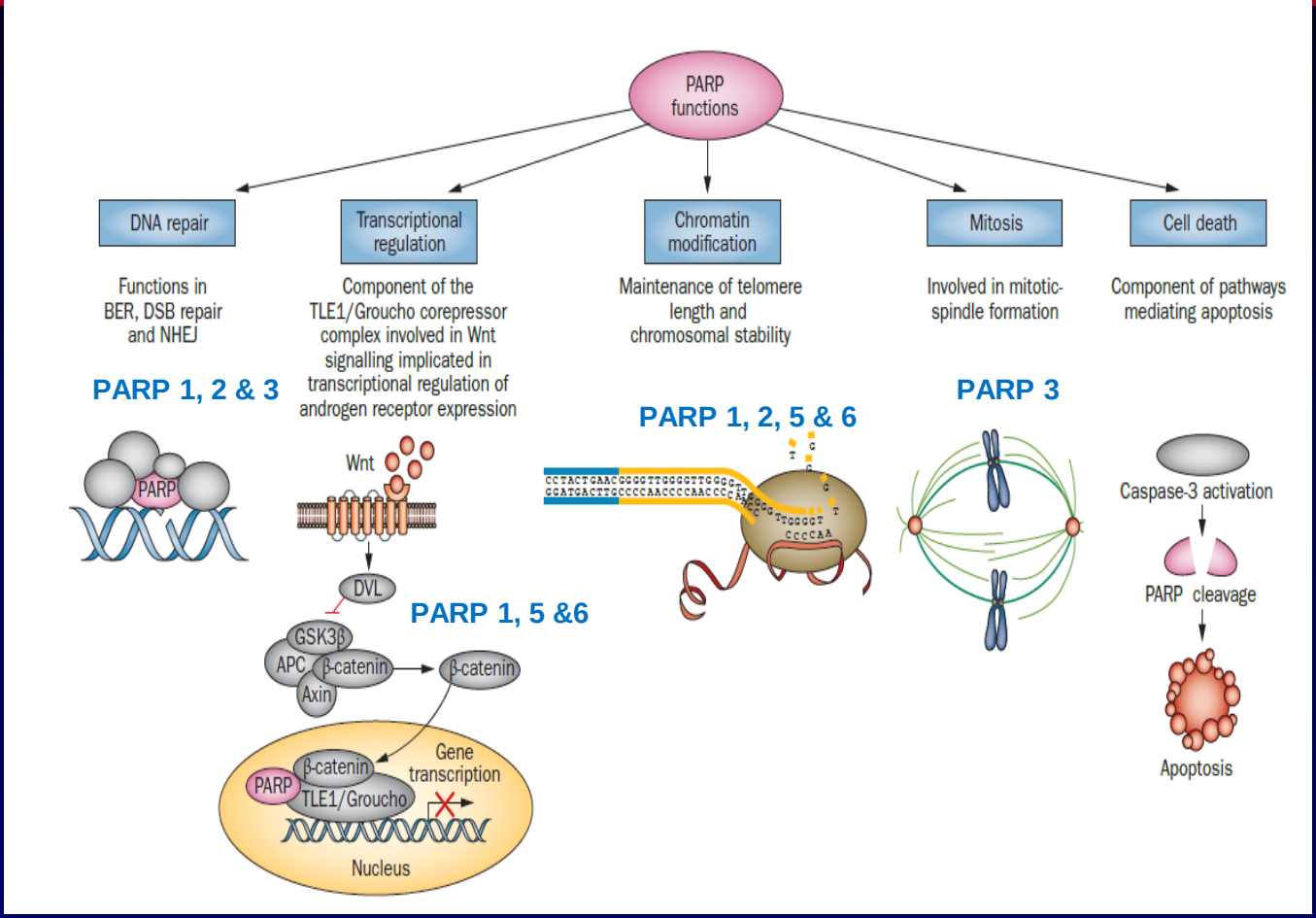
New Therapies – Precision Medicine

- PARP inhibitors
  - BGB-290-104
  - Niraparib
- PI3K inhibitors
  - GDC-0084

BGB-290-104 STUDY
CNS-26

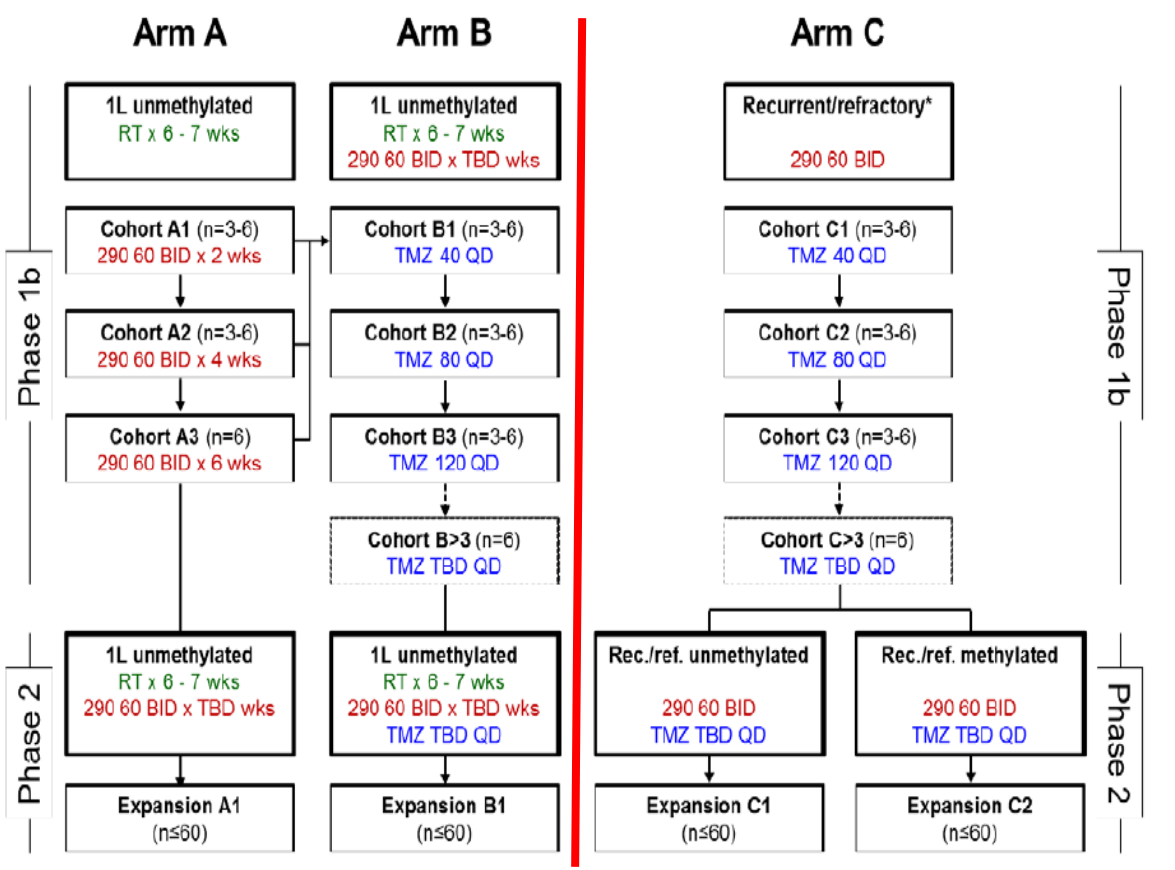
A Phase 1b/2 study to assess the safety, tolerability and efficacy of BGB-290 in combination with radiation therapy and/or temozolomide in subjects with first-line or recurrent/refractory glioblastoma

Different Biological PARP Functions



Sonnenblick et al Nat Rev Clin Oncol 12:27-41 (2015)

BGB-290-104 Study Design



* During dose escalation, unmethylated and methylated GB are allowed.
1L = first-line; methylated = glioblastoma with methylated *MGMT* promoter; rec./ref. = recurrent/refractory; RT = radiation therapy; TBD = to be determined; unmethylated = glioblastoma with unmethylated *MGMT* promoter; wks = weeks
BGB-290: 60 BID = BGB-290 60 mg twice daily; TMZ: 40/80/120/TBD QD = temozolomide 40/80/120/TBD mg once daily; in Arms A and B given for the time period of BGB-290 administration, in Arm C given on Days 1 to 21 of each 28-day cycle

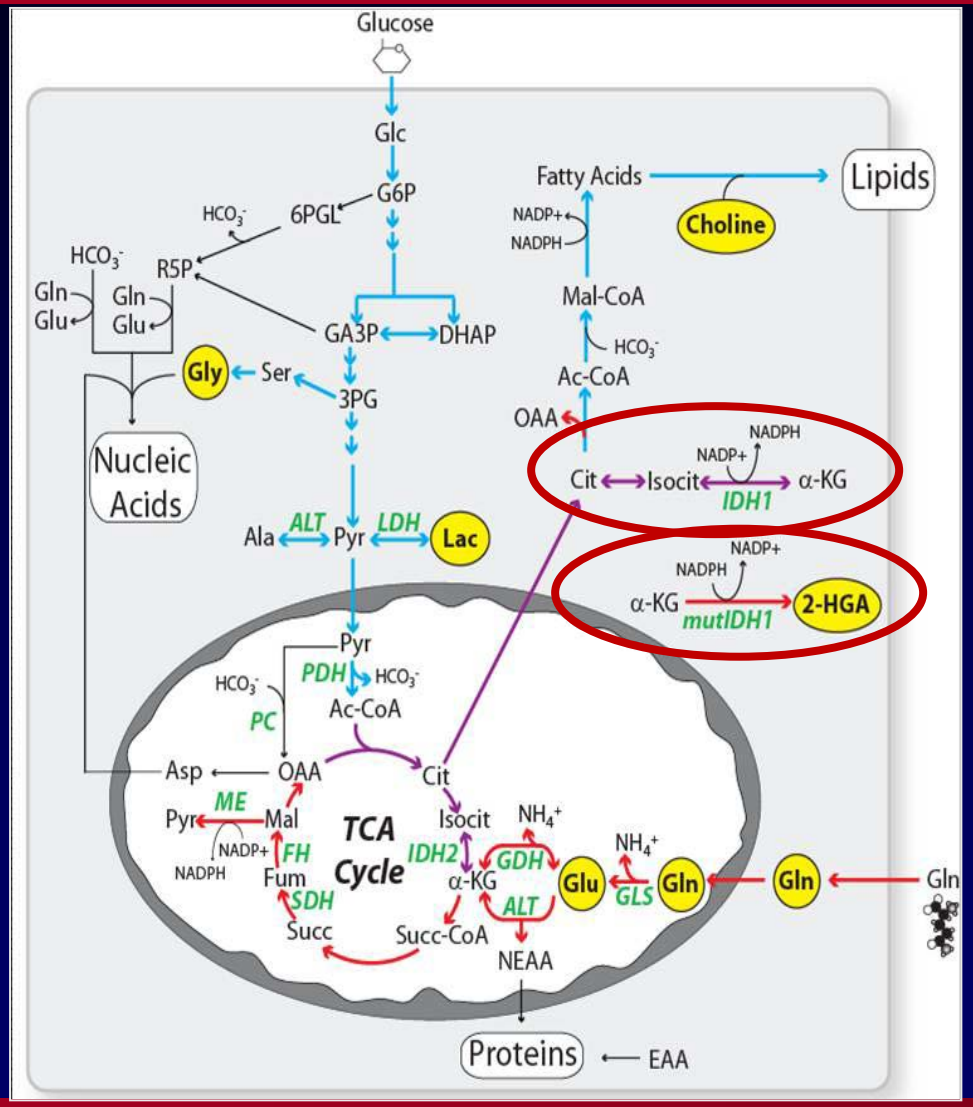
Patients with GBM diagnosis

1. **Initial diagnosis**
2. **Recurrent GBM**

Niraparib Trial, Recurrent Glioma

- PARP inhibitor, monotherapy
- Any recurrent glioma (Grade II-IV)
- Dose escalation
  - 3 dose levels
  - 6 patients each, with expansion phase
- Will be tracking IDH mutation status and LOH status (HRD), (potential for increased response).

Accumulation of 2-Hydroxyglutarate (2HG) due to IDH mutation produces HRD



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces PARP inhibitor sensitivity

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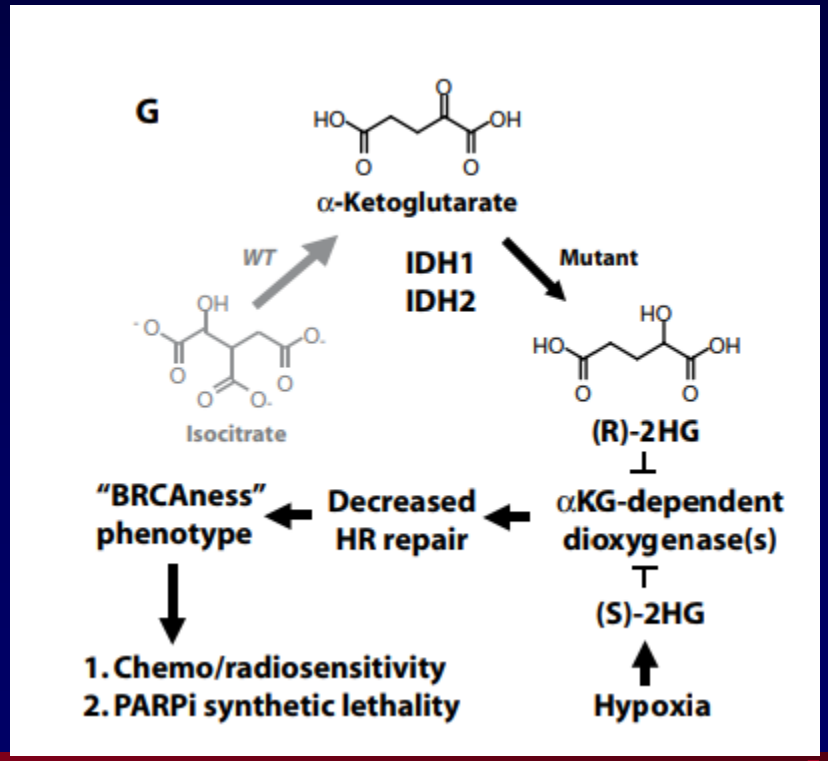

Choi, et al, Nat Med 2012

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GDC-0084

- A phase 2a study to evaluate the safety, pharmacokinetics and clinical activity of the PI3K/mTOR inhibitor GDC-0084 administered to patients with glioblastoma multiforme characterized by unmethylated O6-methylguanine methyltransferase promoter status
- Initially diagnosed GBM, MGMT unmethylated, can screen up to the end of radiation and Temodar.

GDC-0084

- Nonclinical studies have demonstrated that GDC-0084 inhibits proliferation of a large number of glioma cell lines in vitro and inhibits tumor growth in intracranial and subcutaneous mouse xenograft models of human glioblastoma.
- PI3K can promote tumor cell growth and migration/invasion of tissue

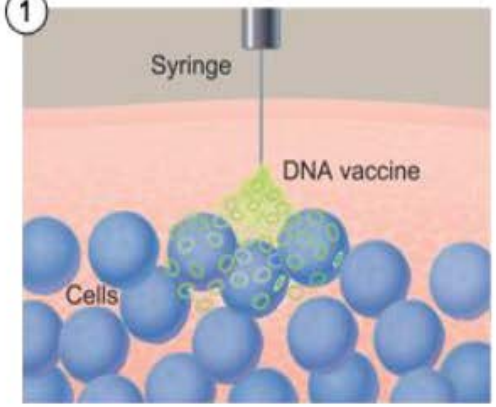
New Therapies – Immunotherapy

- Checkpoint Inhibitors
  - Checkmate – recurrent treatment failed
- Vaccines
  - Rindopepimut – failed
- New studies with combination therapies

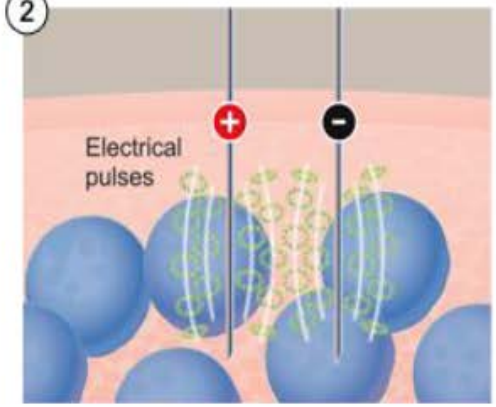
CNS-28 (GBM-001)
AN OPEN-LABEL, MULTI-CENTER STUDY OF INO-5401 AND INO-9012 DELIVERED BY ELECTROPORATION (EP) IN COMBINATION WITH REGN2810 IN SUBJECTS WITH NEWLY-DIAGNOSED GLIOBLASTOMA (GBM)

REGN2810 = cemiplimab

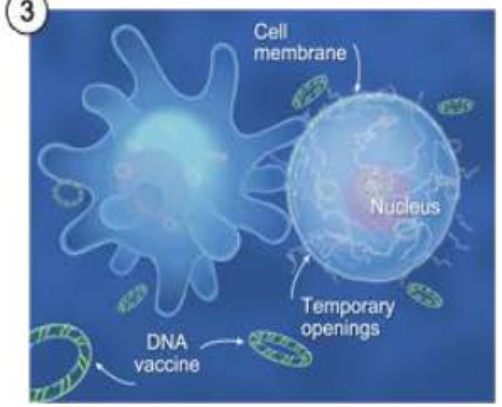
Enhanced DNA Delivery by *in vivo* Electroporation



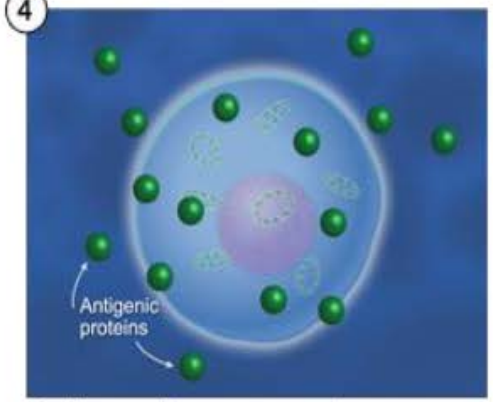
DNA vaccine delivered into muscle or skin.



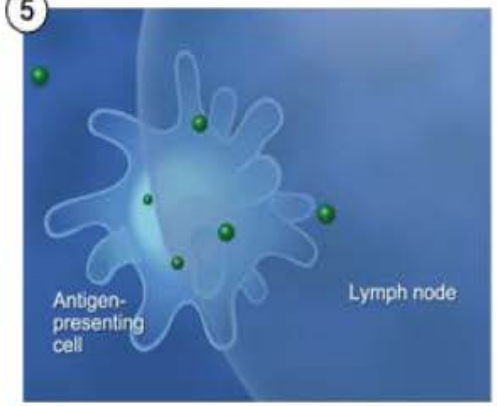
Electroporation: millisecond electrical fields applied.



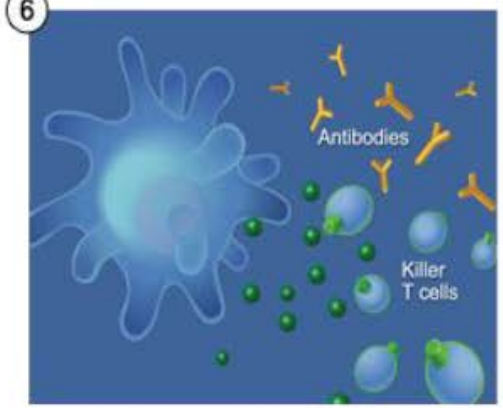
Temporary pores in cell membrane; significant cellular uptake of vaccine.



Cell membrane reseals. Cellular machinery uses the DNA code to produce one or more of the disease antigens coded by the DNA vaccine.



Antigen-presenting cells engulf the antigens and carry them to lymph nodes.



Antibodies or killer T-cells that can eliminate cancerous or infected cells are produced.

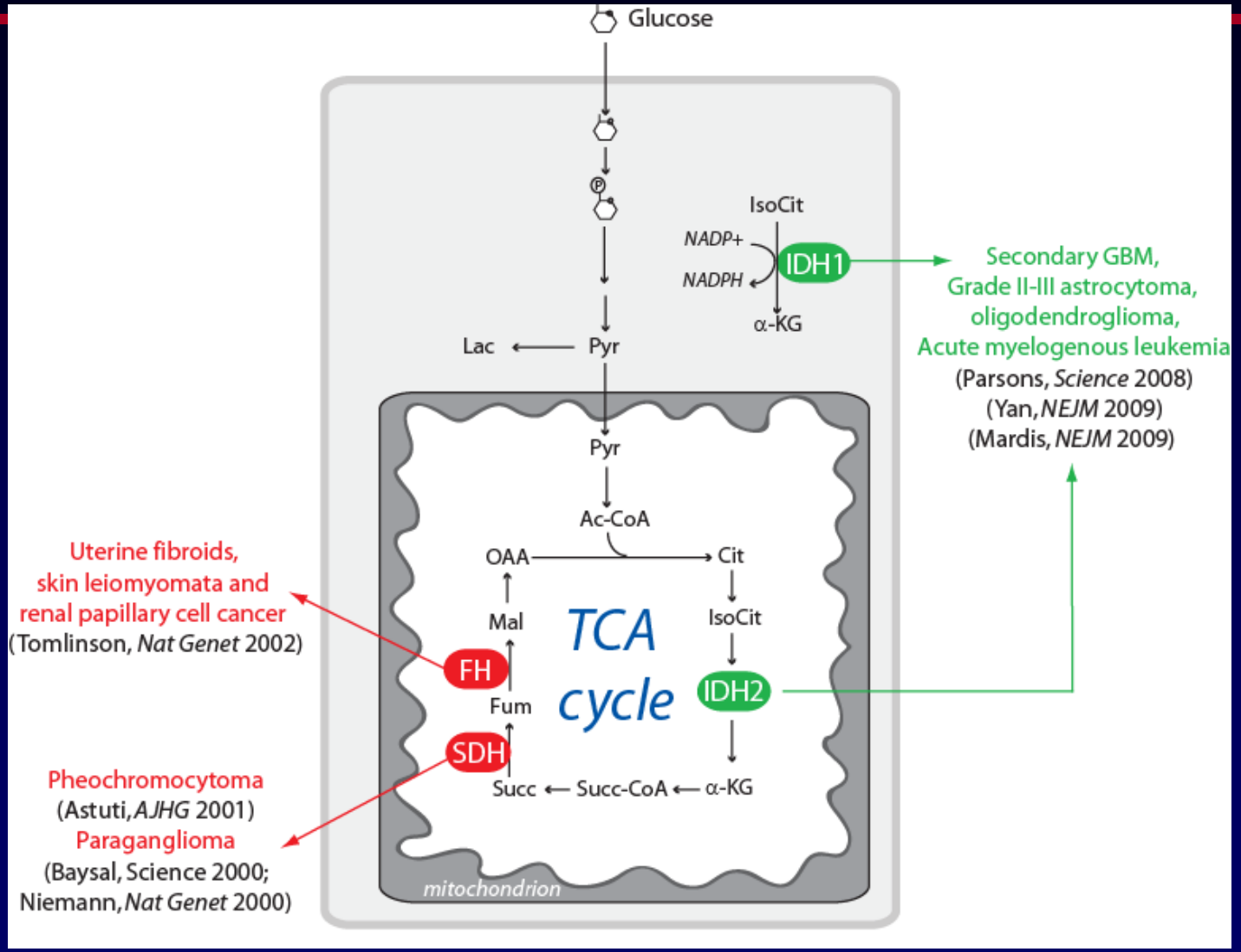
Treatment

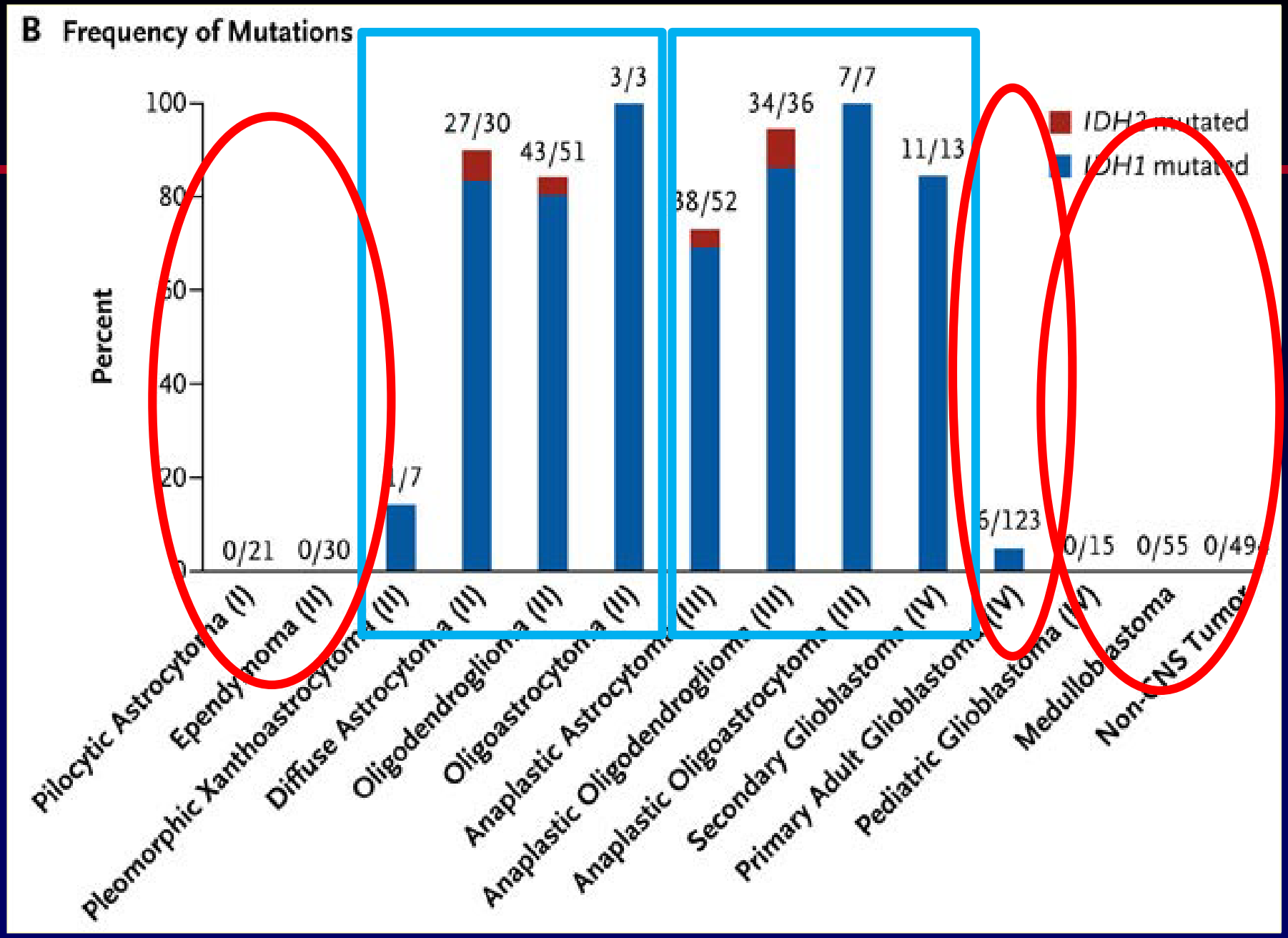
- **INO-5401** (3 mg of each WT-1, PSMA and hTERT plasmids) combined with 1 mg INO-9012, (total 10 mg of DNA) IM injection followed by EP given every three weeks for four doses, then every 9 weeks; and
- **REGN2810 (cemiplimab)** (350 mg/dose IV every three weeks)

- **Radiotherapy** (RT), given in a hypofractionated schedule (40 Gy over three weeks)
- **Temozolomide** (TMZ) concurrent with and following radiotherapy for 6 cycles, initially for all subjects and the remaining cycles for MGMT-methylated or indeterminate status

MOLECULAR DISCOVERIES APPLICATIONS IN GLIOMA

Sequencing of GBMs led to the discovery of mutations in Isocitrate Dehydrogenase (IDH)





Yan et al, *NEJM* 2009

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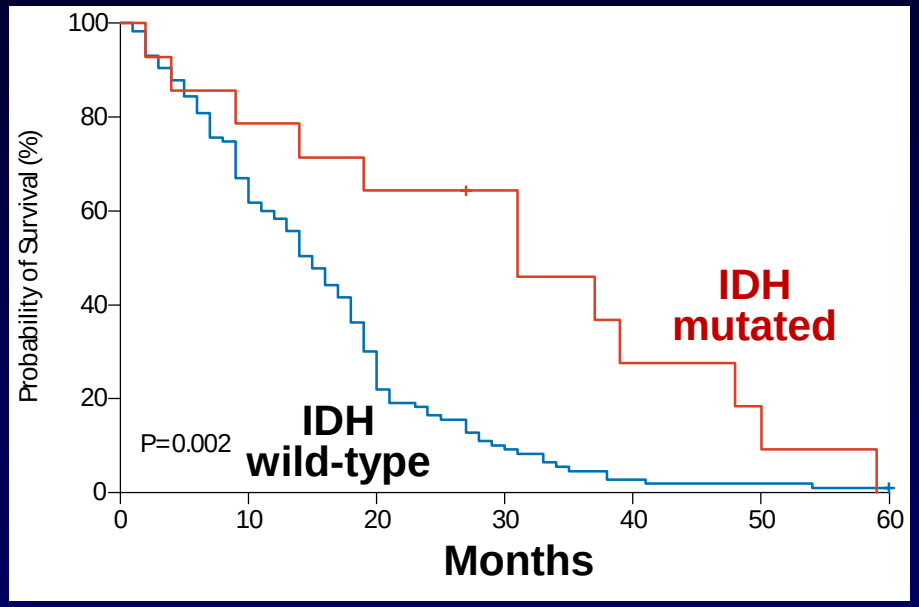
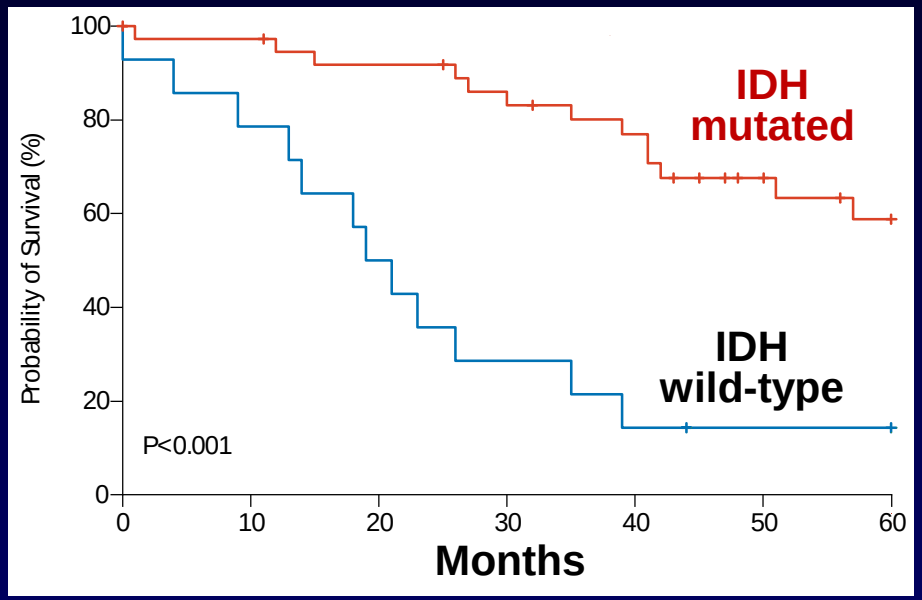
IDH mutations: Better overall survival
Excellent prognostic marker

Glioblastoma



(12% mutated)
Secondary GBM

Anaplastic astrocytoma



(70% mutated)

Yan *et al*, N Engl J Med 2009;360:765

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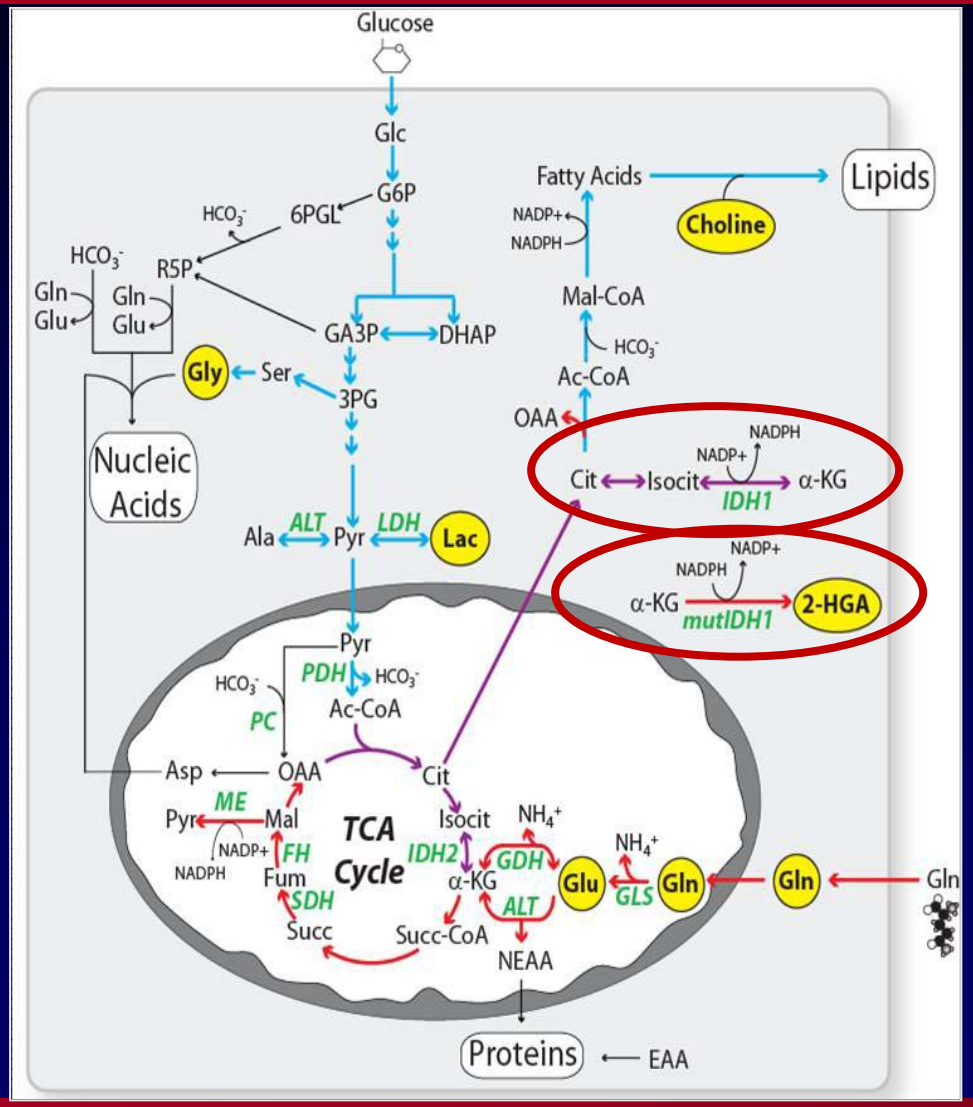
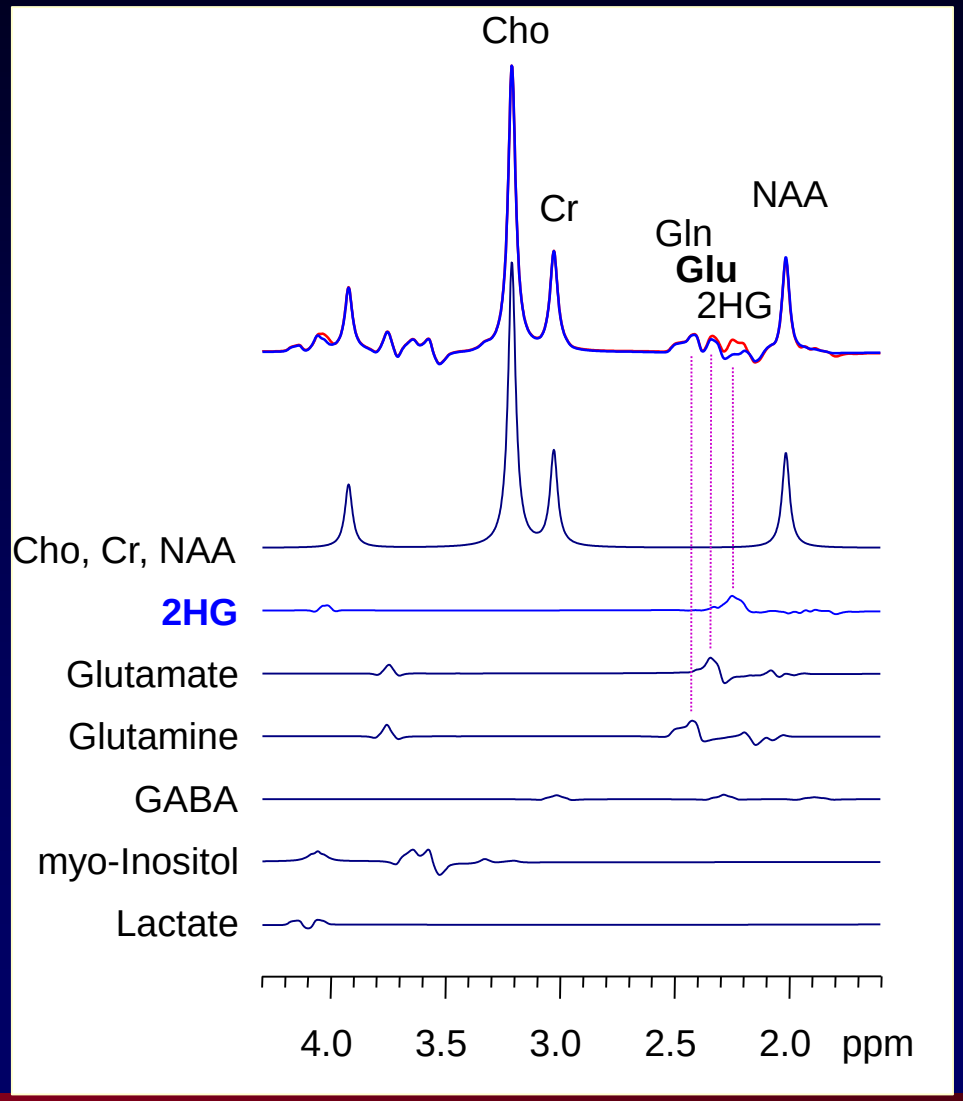
Accumulation of 2-Hydroxyglutarate (2HG)

2HG can be imaged by MR spectroscopy





Choi, et al, Nat Med 2012

THE END

SORT OF…
QUESTIONS…