Chemotherapy & targeted therapy in brain tumors

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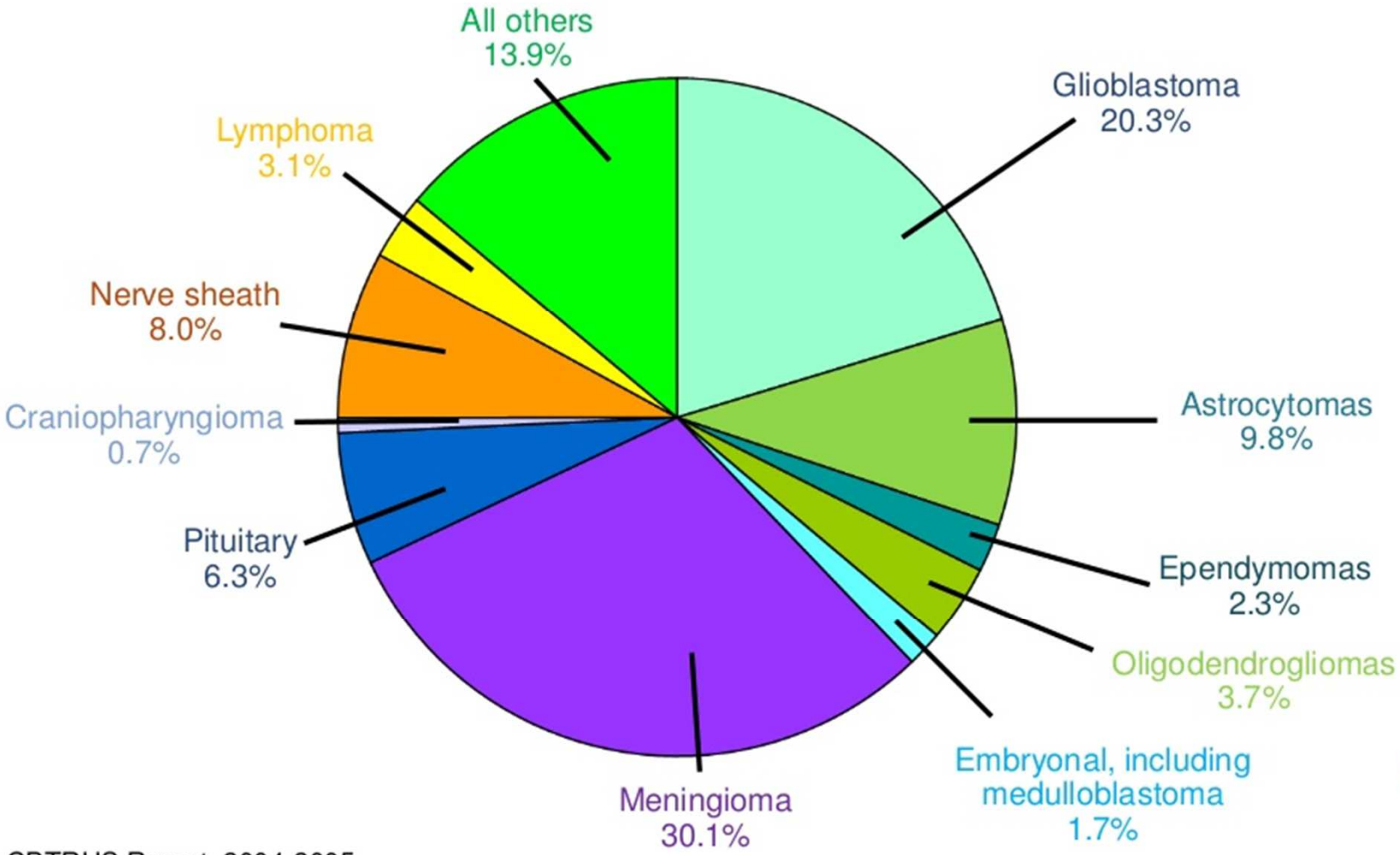
Distribution of primary CNS Tumors by Histology



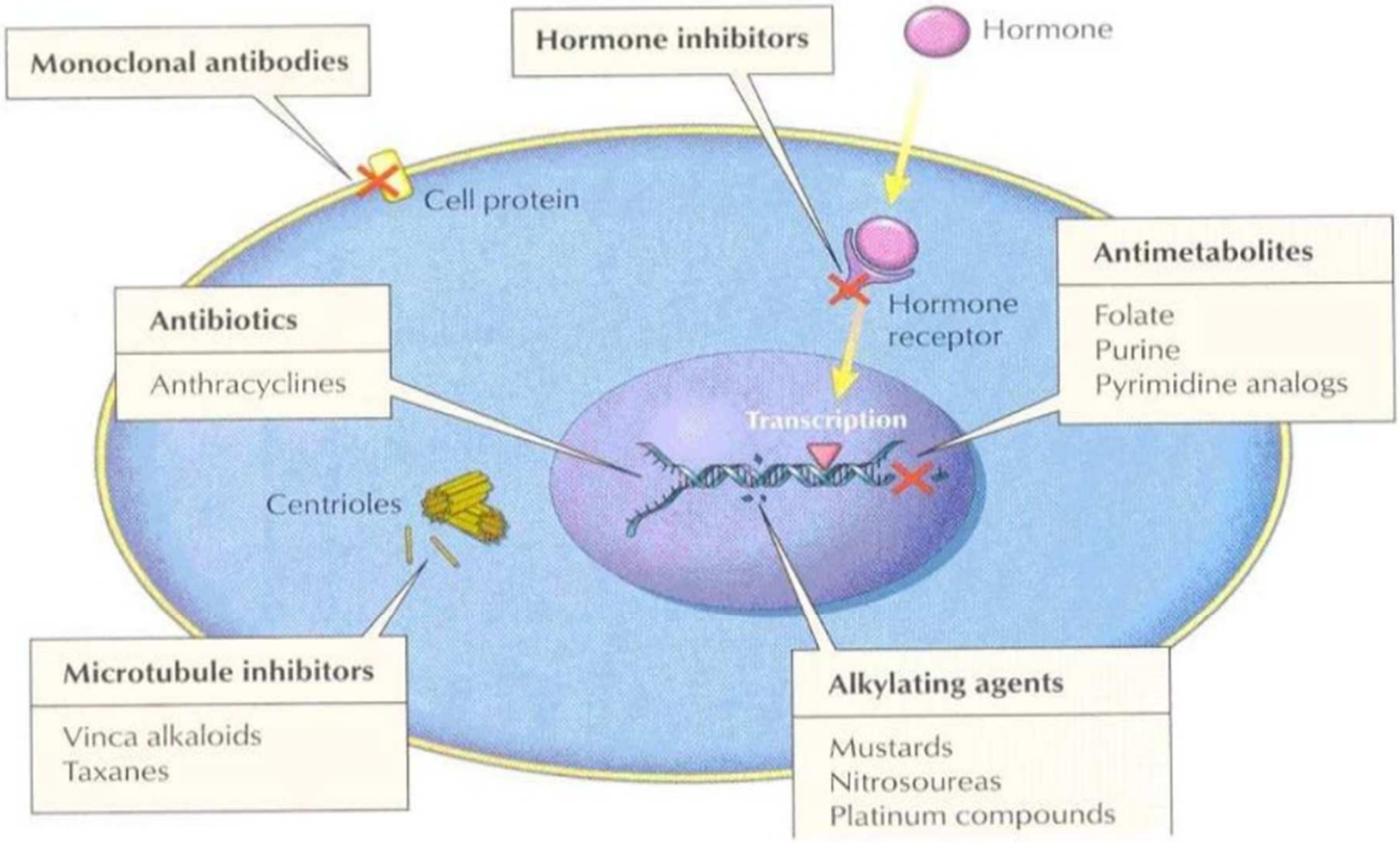
CBTRUS Report, 2004-2005.

A BIT OF HISTORY..

- Surgery and radiation mainstays of treatment (and still are)
- Chemotherapy options
  - PCV standard of care for many years
    - **P**rocarbazine 60 mg/sq. m PO D8-21
    - **C**armustine (BCNU) 130 mg/sq. m PO D1
    - **V**incristine 1.4 mg/sq. m IV D8 and D29
      - Significant side effects

    Repeat every 8 weeks for 6 cycles
  - Single agent nitrosurea(lomustine/carmustine) equivalent

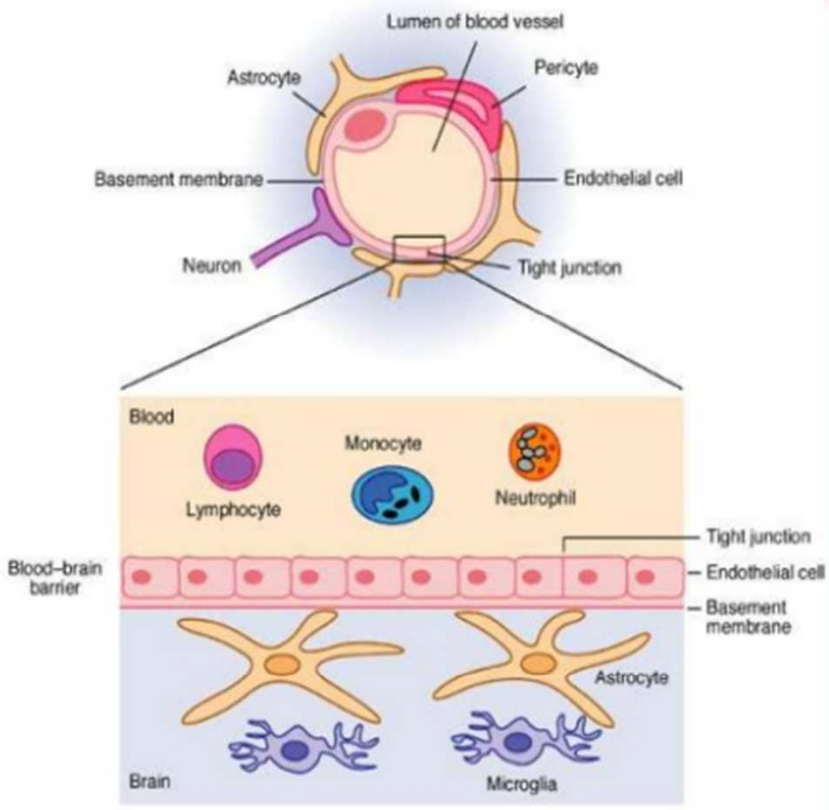
MECHANISM OF ACTION OF CHEMOTHERAPY AGENTS



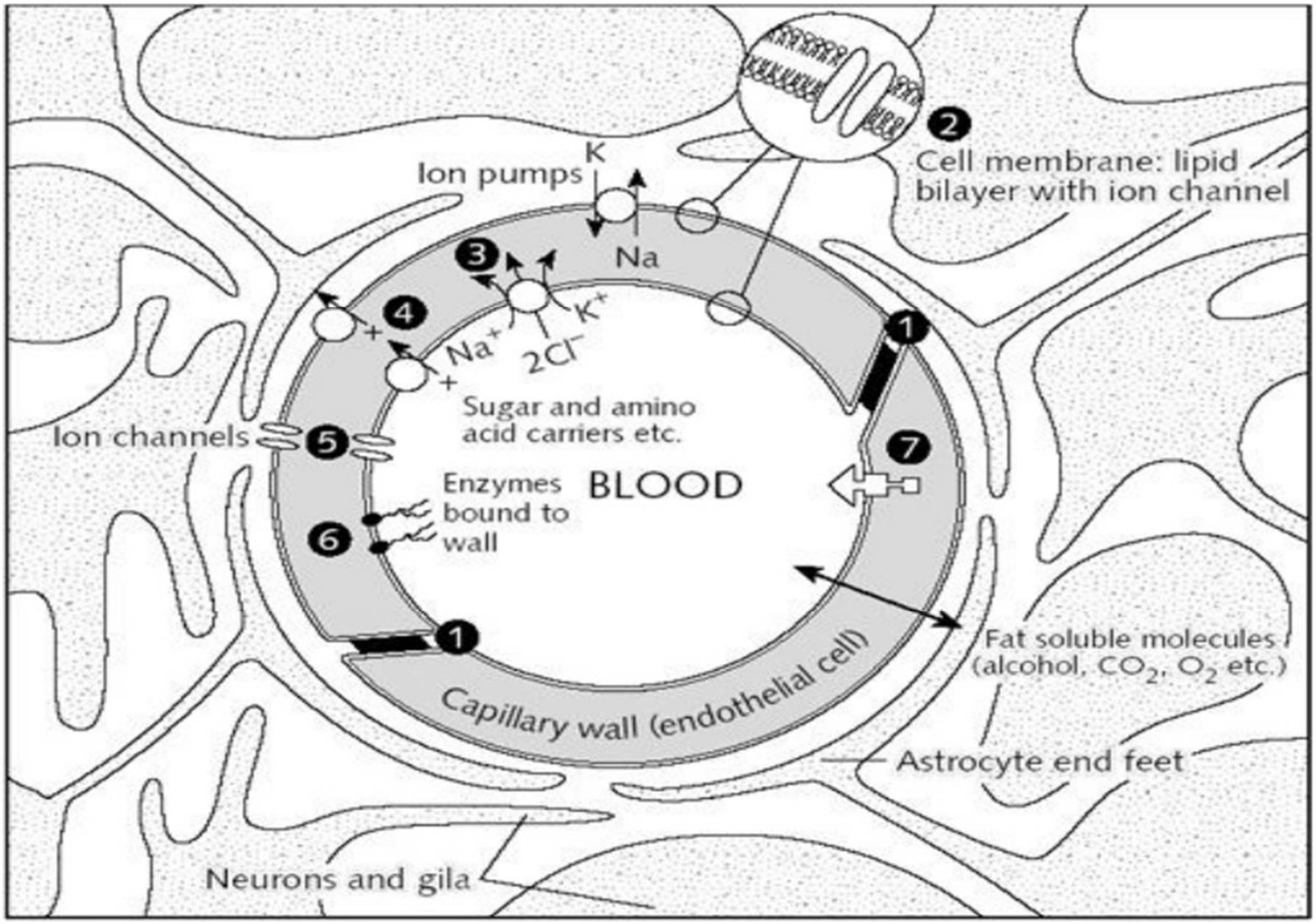
CHALLENGES TO TREATMENT

- Biologically aggressive
  - Most brain cancer are unresponsive to chemotherapy
- Drug delivery
  - Blood brain barrier
- Toxicity to normal brain
- Infiltration of malignant cells into brain parenchyma

Blood Tumor Barrier



The blood–brain barrier (BBB)



Characteristics of the BBB are indicated: (1) tight junctions that seal the pathway between the capillary (endothelial) cells; (2) the lipid nature of the cell membranes of the capillary wall which makes it a barrier to water-soluble molecules; (3), (4), and (5) represent some of the carriers and ion channels; (6) the 'enzymatic barrier 'that removes molecules from the blood; (7) the efflux pumps which extrude fat-soluble molecules that have crossed into the cells

The factors affecting particular substance to cross BBB

Drug related factors at the BBB

- Concentration at the BBB and the size,
- Flexibility,
- Conformation,
- Ionization (nonionized form penetrates BBB)
- Lipophilicity of the drug molecule,
- Cellular enzyme stability and cellular sequestration,
- Affinity for efflux mechanisms (i.e. P-glycoprotein),
- Hydrogen bonding potential (i.e. charge),
- Affinity for carrier mechanisms, and
- Effect on all of the above by the existing pathological conditions

How to overcome BBB ???

Newer delivery methods include:

Interstitial chemotherapy uses disc-shaped polymer wafers (known as Gliadel wafers) soaked with carmustine, the standard chemotherapeutic drug for brain cancer.

Intrathecal chemotherapy delivers chemotherapeutic drugs directly into the spinal fluid.

Intra-arterial chemotherapy delivers high-dose chemotherapy into arteries in the brain using tiny catheters.

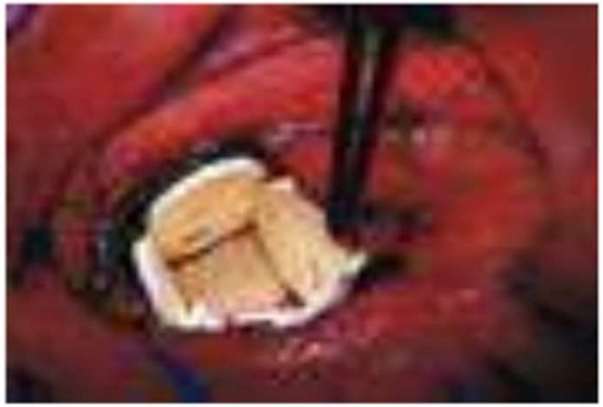
Convection-enhanced delivery (CED) involves placing catheters into the brain tumor or nearby brain tissue to deliver slowly and continuously a cancer drug over several days

http://www.umm.edu/patiented/articles/how_radiotherapy_used_treating_brain_tumors_000089_10.htm#ixzz256vtlVtR

GLIADEL WAFERS

- Gliadel wafers at time of surgery (carmustine soaked) in completely resected high grade glioma (3 or 4)
- The surgeon implants the wafer directly into the surgical cavity after a tumor is removed.

Tumor < 4 cm in recurrent gliomas ; cavity filled with I-125 liquid.



Standard ones include:

Temozolomide (Temodar)

-Taken oral

-First approved in 1999 for adult patients with anaplastic astrocytoma that did not respond to other treatments.

-In 2005, it was approved for use during and after radiation therapy for patients newly diagnosed with glioblastoma multiforme.

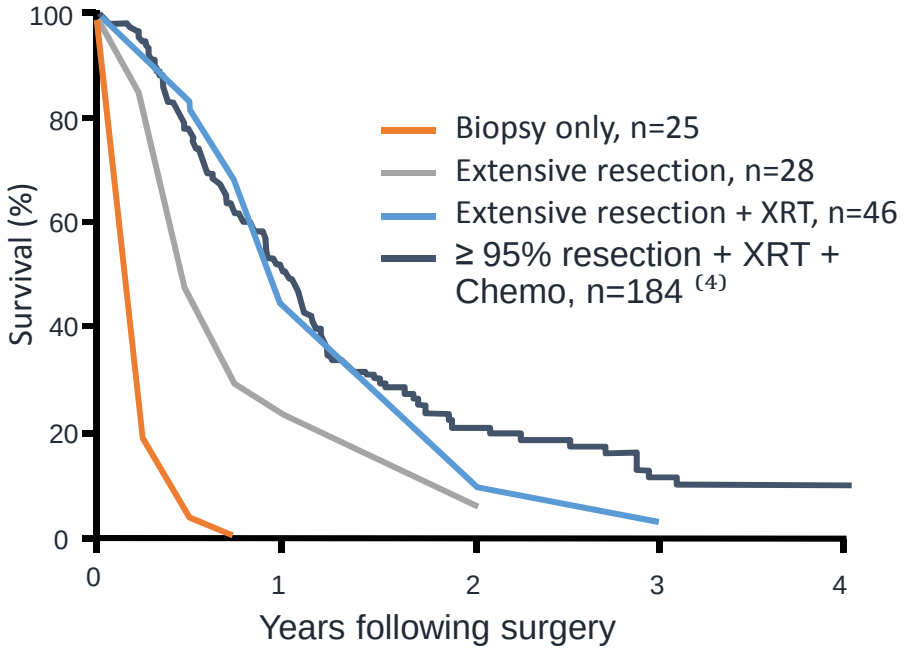
-Adverse effects: Relatively minor, but may include constipation, nausea and vomiting, fatigue, and headache.

GBM : Background

- Grade 4 astrocytoma [1]
- Represents 2/3 of primary brain tumor diagnoses [2]
  - Highly invasive, virtually incurable, rapidly fatal
  - Highly anaplastic, poorly differentiated, malignant neoplasms
  - Challenging to treat due to unpredictable chemosensitivity

High unmet need

- mOS of 10-12 months
- Recurrence occurs in 80% of patients [2]
- Causes substantial morbidity with poor prognosis [3]
  - 2-year OS: 26%
  - 4-year OS: 12%



1. Louis DN, et al. Acta Neuropathol. 2007;114:97-109. & National Comprehensive Cancer Network. Available at: www.nccn.org. 2. Central Brain Tumor Registry of the United States. http://www.cbtrus.org. 3. Stupp R, et al. N Engl J Med. 2005;352:987-996.4. Holland EC. Proc Natl Acad Sci U S A. 2000;97:6242-6244.

The NEW ENGLAND JOURNAL of MEDICINE

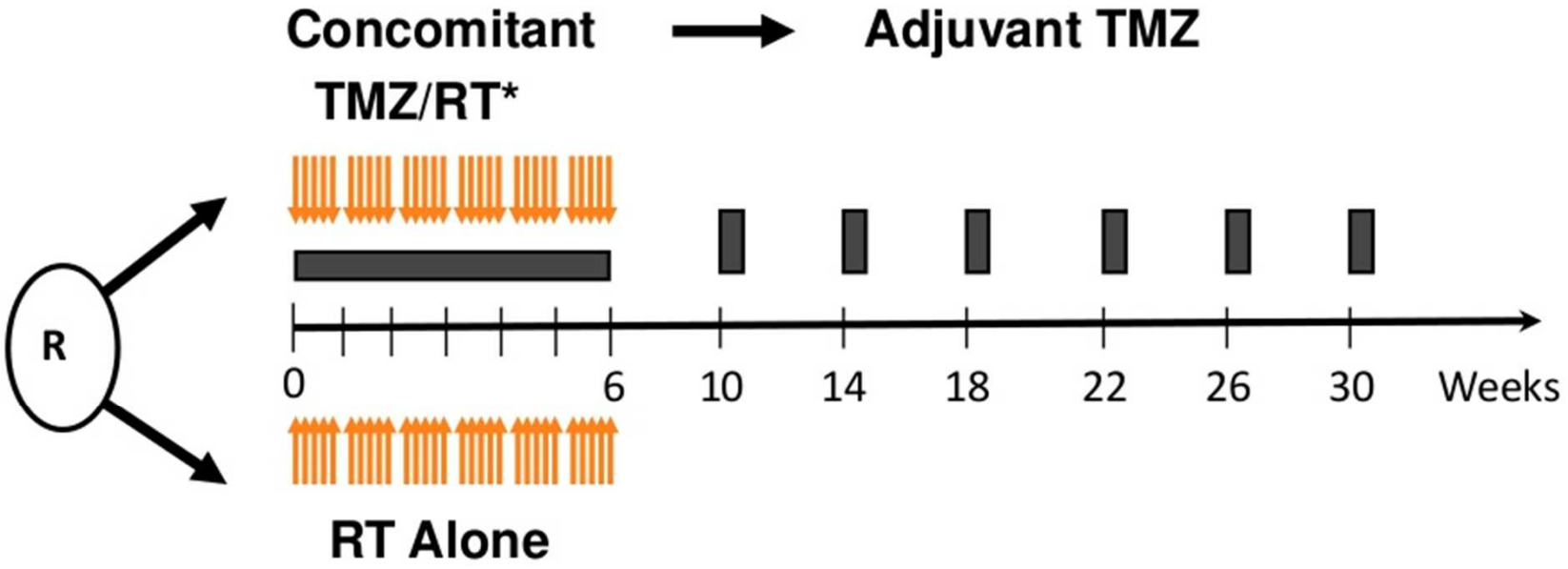
ORIGINAL ARTICLE

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*

NEJM 2005

STUPP TREATMENT SCHEMA

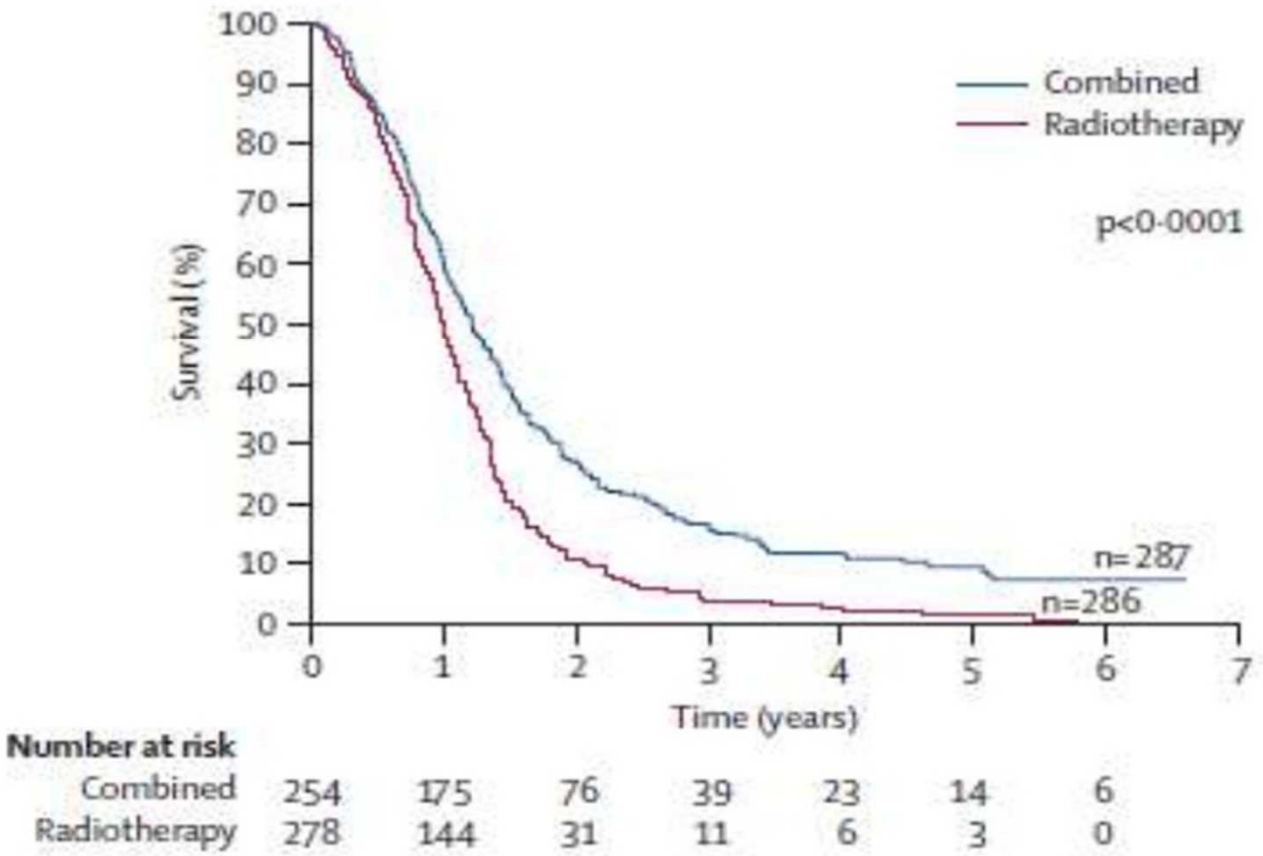


Temozolomide 75 mg/m^2 po qd for 6 weeks,
then 150–200 mg/m^2 po qd d1–5 every 28 days for 6 cycles

Focal RT daily — 30 x 200 cGy
Total dose 60 Gy

*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.

SIGNIFICANT IMPROVEMENT IN SURVIVAL

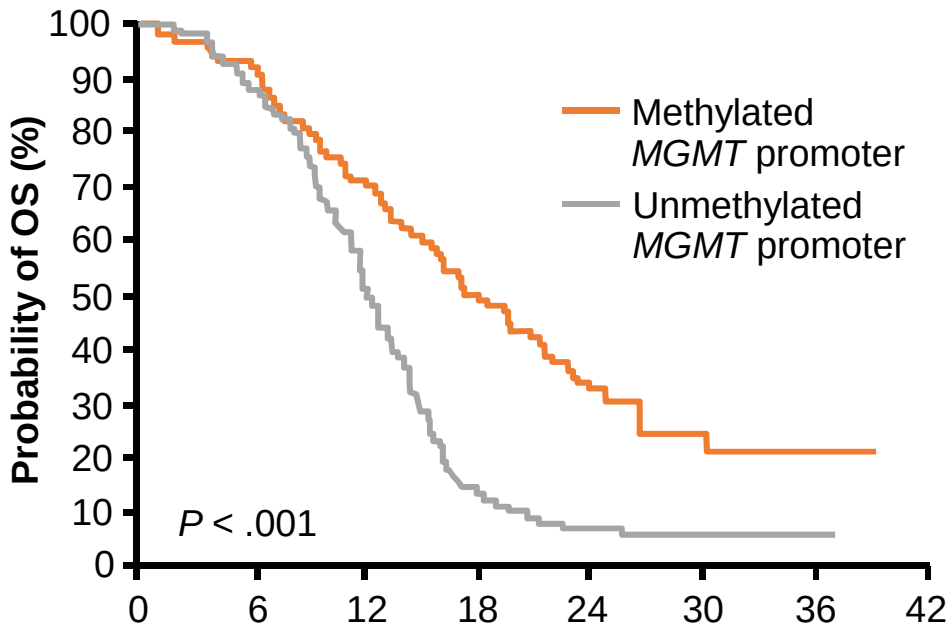


Survival	RT	RT + TMZ
Median, mos	**12.1**	**14.6**
2 yr, %	10.9	27.2
3 yr, %	**4.4**	**16.0**
4 yr, %	3.0	12.1%
5 yr, %	**1.9**	**9.8**

Stupp et al. Lancet Oncology 2009

MGMT Methylation and OS in GBM

- Methylation of *MGMT* promoter improves survival following adjuvant radiotherapy plus temozolomide
  - *MGMT* methylation occurs in approximately 1/3 of patients[1]
- Median survival[2]
  - Methylation: 22 mo
  - No methylation: 15 mo
- 2-year survival[2]
  - Methylation: 46%
  - No methylation: 25%



No. at Risk							
Unmethylated	114	100	59	16	7	4	1
Methylated	92	84	64	46	24	7	1

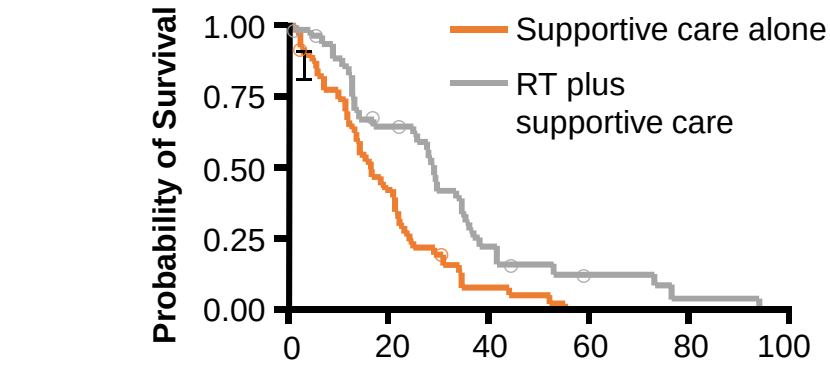
1. Rosell R, et al. Future Oncol. 2008;4:219-228. 2. Hegi M, et al. N Engl J Med. 2005;352:997-1003.

Adjuvant RT in GBM

- Fractionated external beam RT an important component in postsurgical standard of care for GBM

- Median survival in phase III studies of adjuvant RT
  - 118 patients with grade 3/4 supratentorial astrocytoma: 10.8 vs 5.2 months with best supportive care only[1]
  - 303 patients with anaplastic gliomas: 35 vs 14 weeks with best supportive care only[2]

- RT benefits older (> 70 years) patients with good PS[3]
  - Median OS: 29.1 vs 16.9 weeks with best supportive care only
  - QOL and cognition not affected by RT

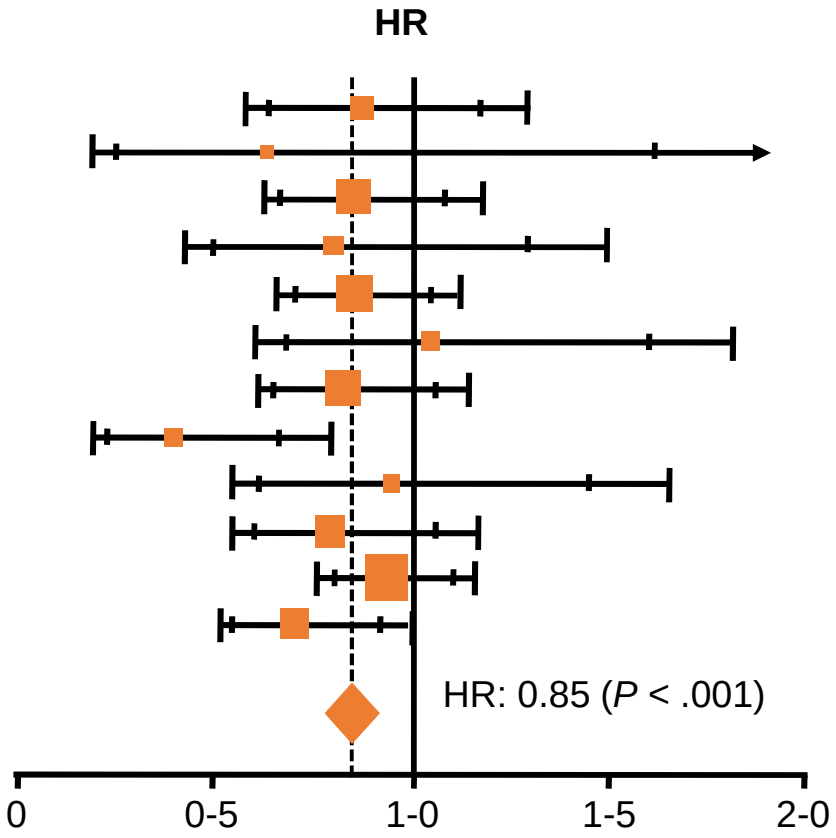


No. at Risk					
Supportive care alone	42	17	3	0	0
RT plus supportive care	39	24	8	3	1

1. Kristiansen K, et al. Cancer. 1981;47:649-652. 2. Walker MD, et al. J Neurosurg. 1978;49:333-343. 3. Keime-Guibert F, et al. N Engl J Med. 2007;356:1527-1535.

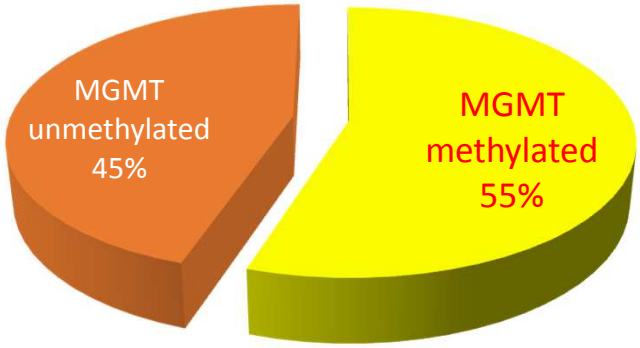
RT Plus Chemotherapy Improves Survival

- Meta-analysis of 12 randomized clinical trials of patients with high-grade gliomas (N = 3004)
- Adding chemotherapy to RT conferred a 15% reduction in risk of death
  - Year 1: 6% improvement
  - Year 2: 5% improvement
  - Benefit becomes apparent around Month 6
  - Effect independent of age, histology, PS, extent of resection

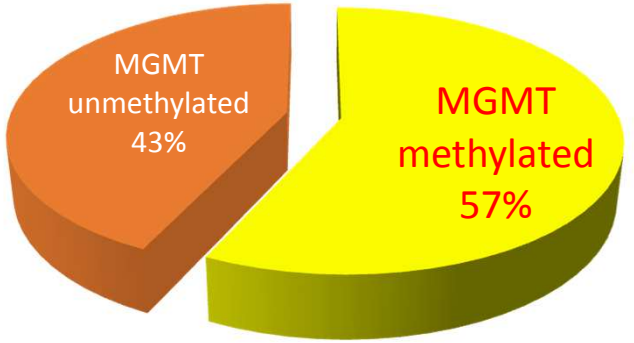


AIIMS data

Adult



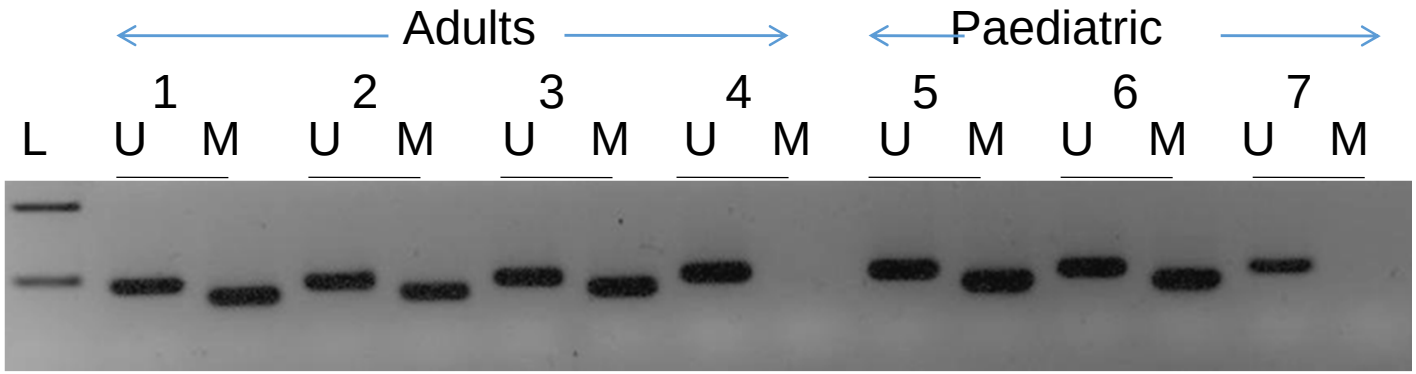
Paediatric



Great Variation in MGMT methylation status: tecnique dependent

Pyrrosequencing: RT-PCR TMH: routine

Representative gel showing MSP result:



Arti S, Sarkar C. *et al* Child Nerv Sys 2010
Jha P, Sarkar C. *et al*. Neurosurgery 2011

Carmustine (BCNU, BiCNU)

-Carmustine is used to treat many types of brain tumors, including glioblastoma, medulloblastoma, and astrocytoma.

-Administered IV or delivered through a wafer implant (Gliadel), which is surgically placed into the brain cavity after tumor removal.

-Adverse effects

-Intravenously: Nausea and vomiting, fatigue, respiratory problems and pulmonary fibrosis, bone marrow impairment.

-Delivered through a wafer: Seizures and cerebral infection

PCV Drug Regimen

-PCV is an abbreviation for a chemotherapy regimen that combines procarbazine (Matulane), lomustine (CCNU), and vincristine (Oncovin).

-PCV is commonly used to treat oligodendrogliomas and mixed oligoastrocytomas.

-Procarbazine and lomustine are taken by mouth. Vincristine is given by either injection or IV.

-Adverse effects:

Drop in blood cell counts, nausea and vomiting, constipation, fatigue, and mouth sores.

Procarbazine can cause high blood pressure when taken with foods high in tyramine. Patients should avoid foods such as beer, red wine, cheese, chocolate, processed meat, yogurt, and certain fruits and vegetables.

INVESTIGATIONAL DRUGS (TARGETED THERAPY)

-Targeted therapies work on a molecular level by blocking specific mechanisms associated with cancer cell growth and division.

-less severe side effects.

Promising targeted therapies for brain tumors include:

1. Tyrosine kinase inhibitors

-It block proteins involved in tumor cell growth and production.

-Drugs that specifically target epidermal growth factor receptors (EGFR) are a type of tyrosine kinase inhibitor of special interest in brain tumor research.

-These drugs include erlotinib (Tarceva), imatinib (Gleevac), and gefitinib (Iressa).

Role of EGFR in GBM

- EGFR (Epidermal growth factor receptor)
  - is commonly over-expressed in malignant disease
  - regulates many vital cellular processes
  - seems to be a negative prognostic indicator

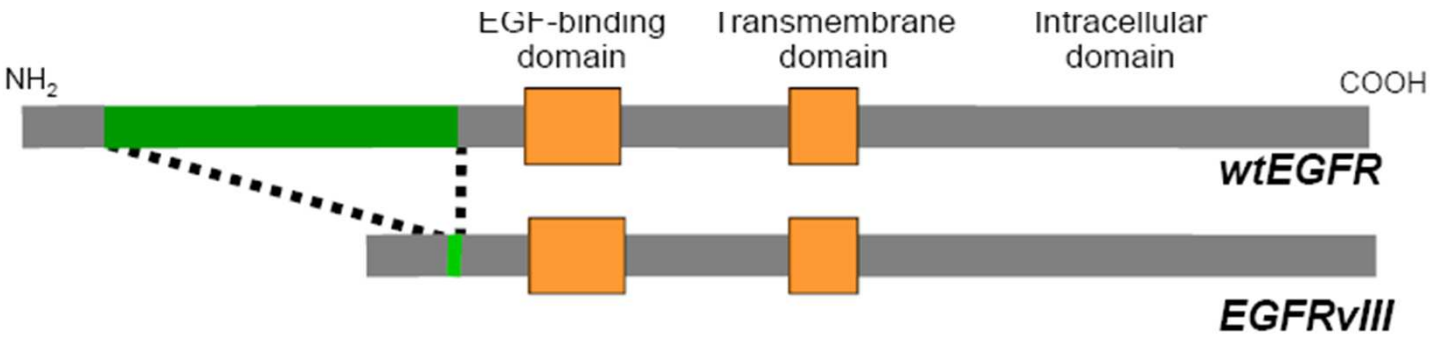
- EGFR frequently activated in GBM via overexpression or amplification
  - Amplification seen in > 40% and overexpression in > 60%
  - Focal amplifications with or without EGFR point mutations
  - EGFRvIII missing exons 2-7 most common EGFR mutant
  - Implicated in RT resistance

- EGFR inhibitors being studied for GBM treatment
  - Nimotuzumab
  - Cetuximab
  - Gefitinib
  - Lapatinib
  - Vandetanib
  - CDX-110 anti-*EGFRvIII* vaccine

1. Cancer Genome Atlas Research Network. Nature. 2008;455:1061-1068.

EGFR

over expressed/amplified in 50-90% of GBM



Anti-EGFR therapies:

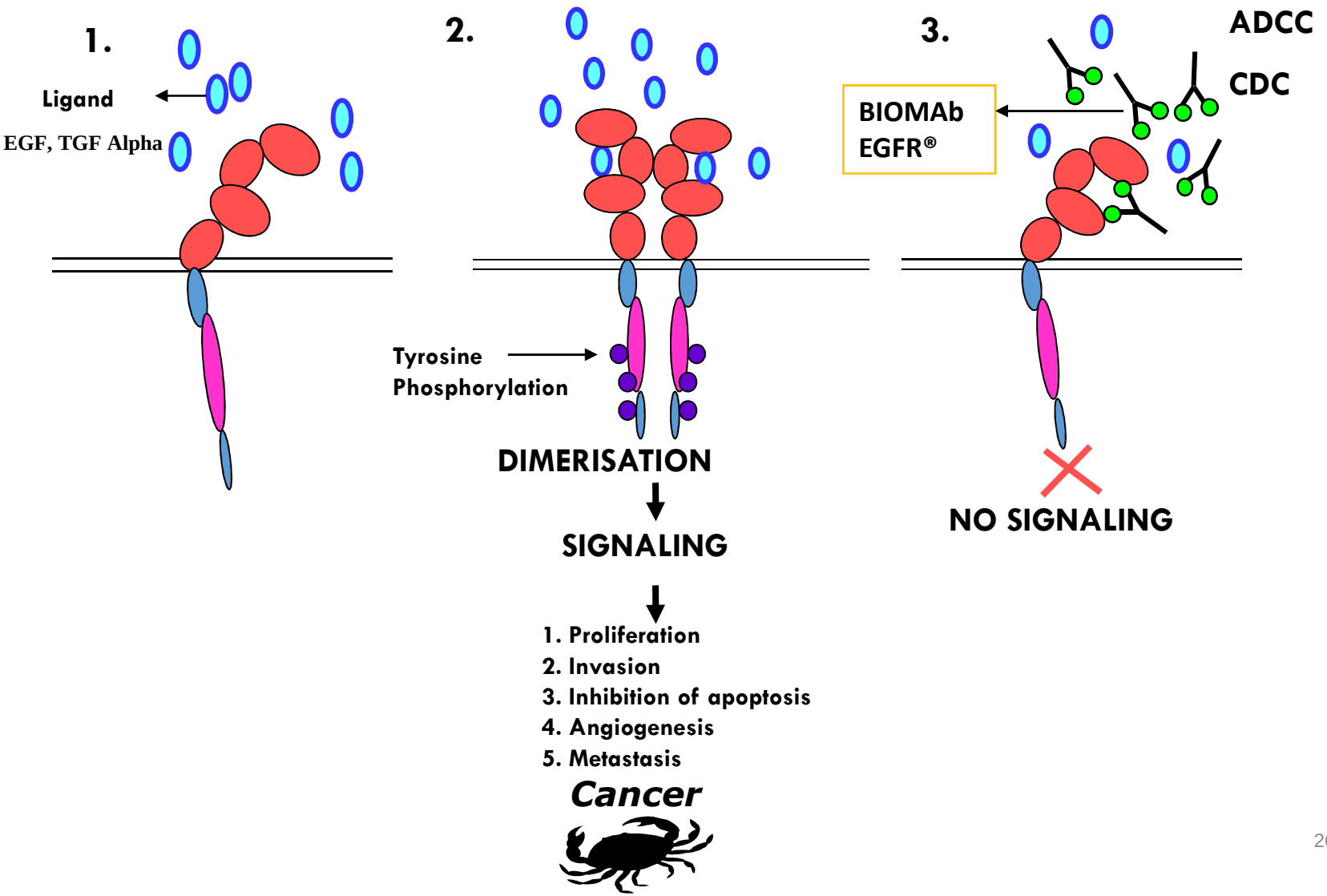
Erlonitib, Nimotuzumab, Cetuximab, Geftinib, Lapatanib

Anti EGFR therapies work especially in tumours with EGFR vIII mutations and intact p10 (NEJM 2005)

BIOMAb EGFR® (Nimotuzumab)

- Humanized IgG1 anti-EGFR monoclonal antibody with 95% human sequences
- Proven to be anti-proliferative, anti-angiogenic and pro-apoptotic
- Unique molecular profile leading to efficacy without associated toxicities in combination with chemo-radiotherapy/radiotherapy
- Approved in India for the treatment of locally advanced squamous cell carcinoma in head and neck (SCCHN)
- Approved globally for indications that include SCCHN, Glioma, Nasopharyngeal cancer & Esophageal cancer. It has received orphan drug designation for glioma in US and Europe

Mechanism of action



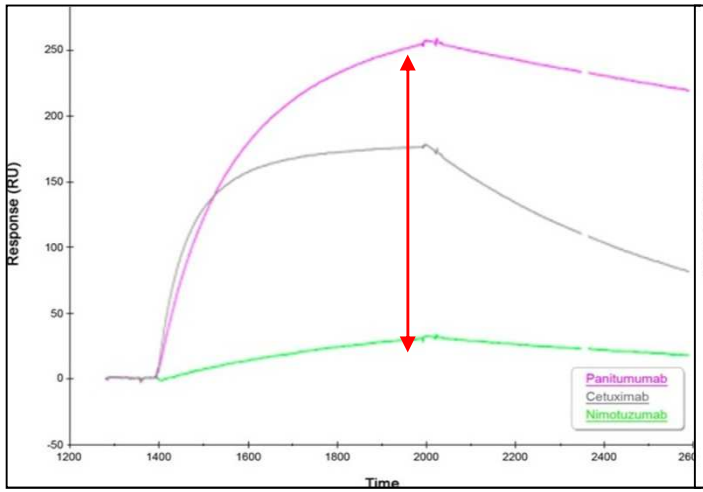
Comparative affinity & binding patterns

	Nimotuzumab	Cetuximab	Panitumumab
Affinity	1 X 10^{-9}	1 X 10^{-10}	5 X 10^{-11}
Toxicity (Rash)	< 10%	~90%	~100%

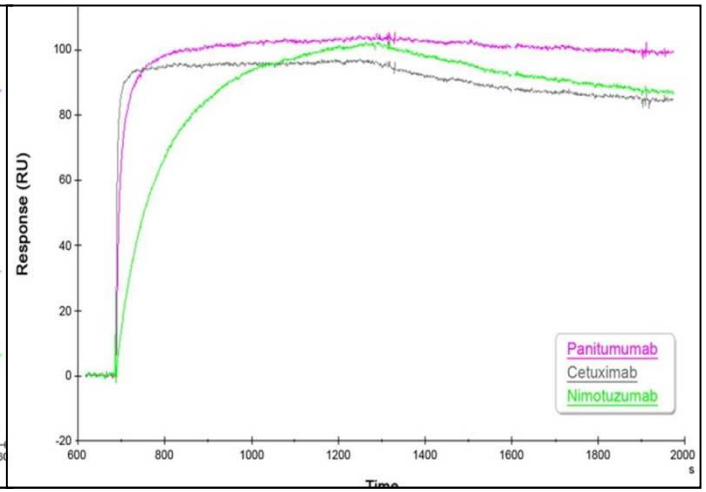
Decoupling rash & Efficacy

Optimal affinity & reliance on bivalent binding to form a strong stable bond lead to a better safety profile without compromising on efficacy

Low EGFR density



High EGFR density



BIOMAb EGFR as a therapy option for GBM

STUDY TITLE

An Open Label, Prospective, Multicentric Study to Evaluate the Safety and Efficacy of BIOMAb EGFR (Nimotuzumab) as Induction and Maintenance Therapy in Combination with Radiotherapy Plus Temozolomide (Concomitant & Adjuvant) in Indian Patients with Glioblastoma Multiforme

Objectives

To evaluate the safety and efficacy of BIOMAb EGFR (Nimotuzumab) in combination with Temozolomide and radiotherapy in the treatment of Glioblastoma multiforme

Primary objective	▪ **Overall Survival**
Secondary Objectives	▪ Progression free-survival ▪ Tumor Response ▪ Safety & Tolerability

Centre wise Subject Disposition

Centre no.	Centre Name	(N=56)
1	All Indian Institute Of Medical Sciences, New Delhi	7 (12.5%)
2	Dharamshila Cancer Hospital & Research Centre, New Delhi	6 (10.7%)
3	Rajiv Gandhi Cancer Institute And Research Centre, New Delhi	12 (21.4%)
4	Gujarat Cancer Research Institute, Ahmedabad	8 (14.3%)
5	Tata Memorial Hospital, Mumbai	5 (8.9%)
6	Curie Centre of Oncology, St. Johns Medical College & Hospital, Bangalore	7 (12.5%)
7	Christian Medical College, Vellore	6 (10.7%)
8	Regional Cancer Centre, Trivandrum	5 (8.9%)

Study Details

Phase	Phase II
Design	▪ Open Label ▪ Prospective ▪ Multicentric Study ▪ Single Arm
Number of subjects	56 patients
Total duration of study	▪ Five years from enrollment (which includes maximum two years of treatment stage and three years of follow-up stage)

Study Details

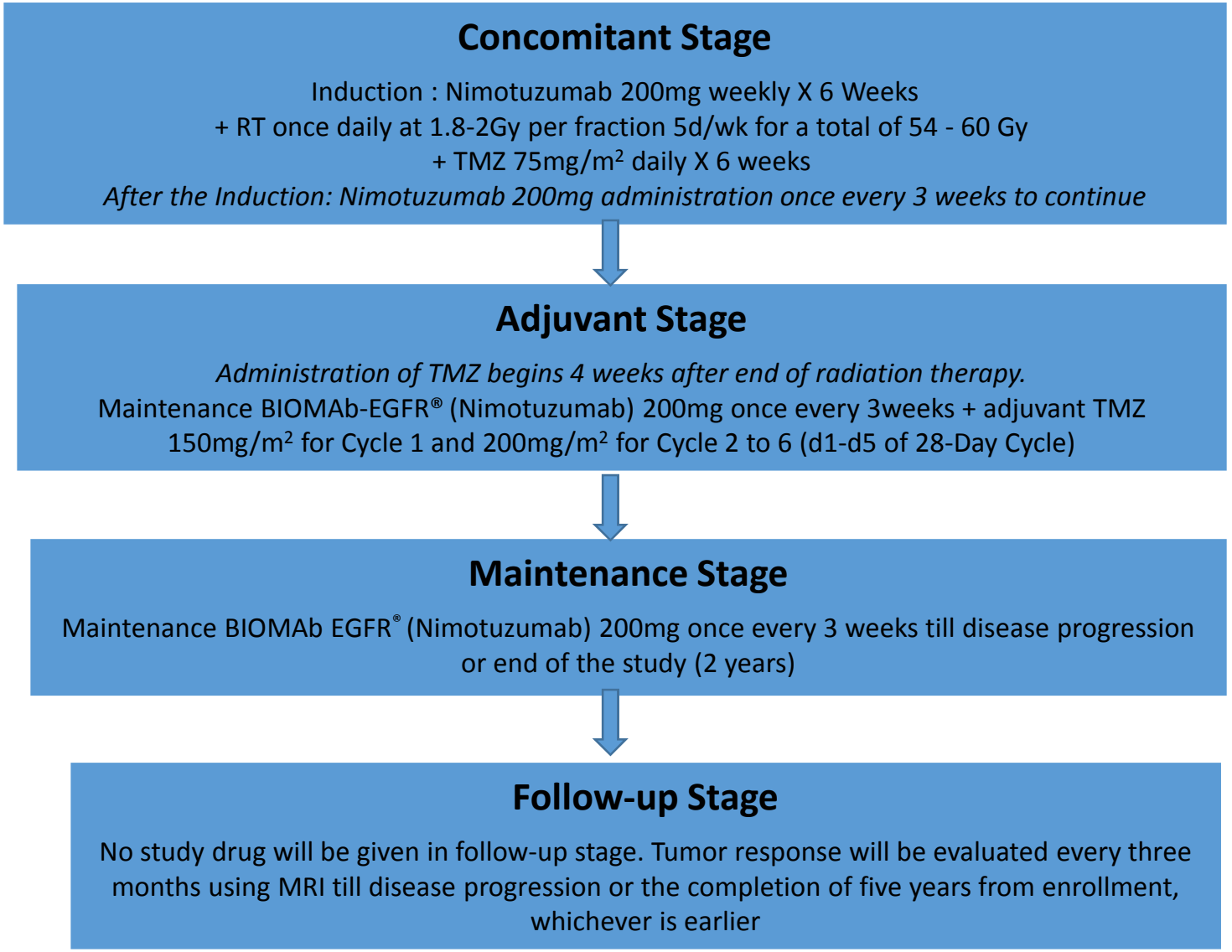
Inclusion Criteria

- Willingness to sign the informed consent.
- Newly diagnosed patients with GBM (Grade 4 Astrocytoma) confirmed by histopathology.
- Patients suitable for planned radiotherapy and chemotherapy with TMZ
- Patients who are chemotherapy naive
- Patients aged between 18-70 years (both inclusive).
- Karnofsky's Performance Status ≥ 60%.
- Adequate hematological, renal & hepatic function
- Patients who have undergone debulking surgery or tumor biopsy in the last 4 weeks are eligible for enrollment
- Patients should be willing to use effective methods of contraception during the study

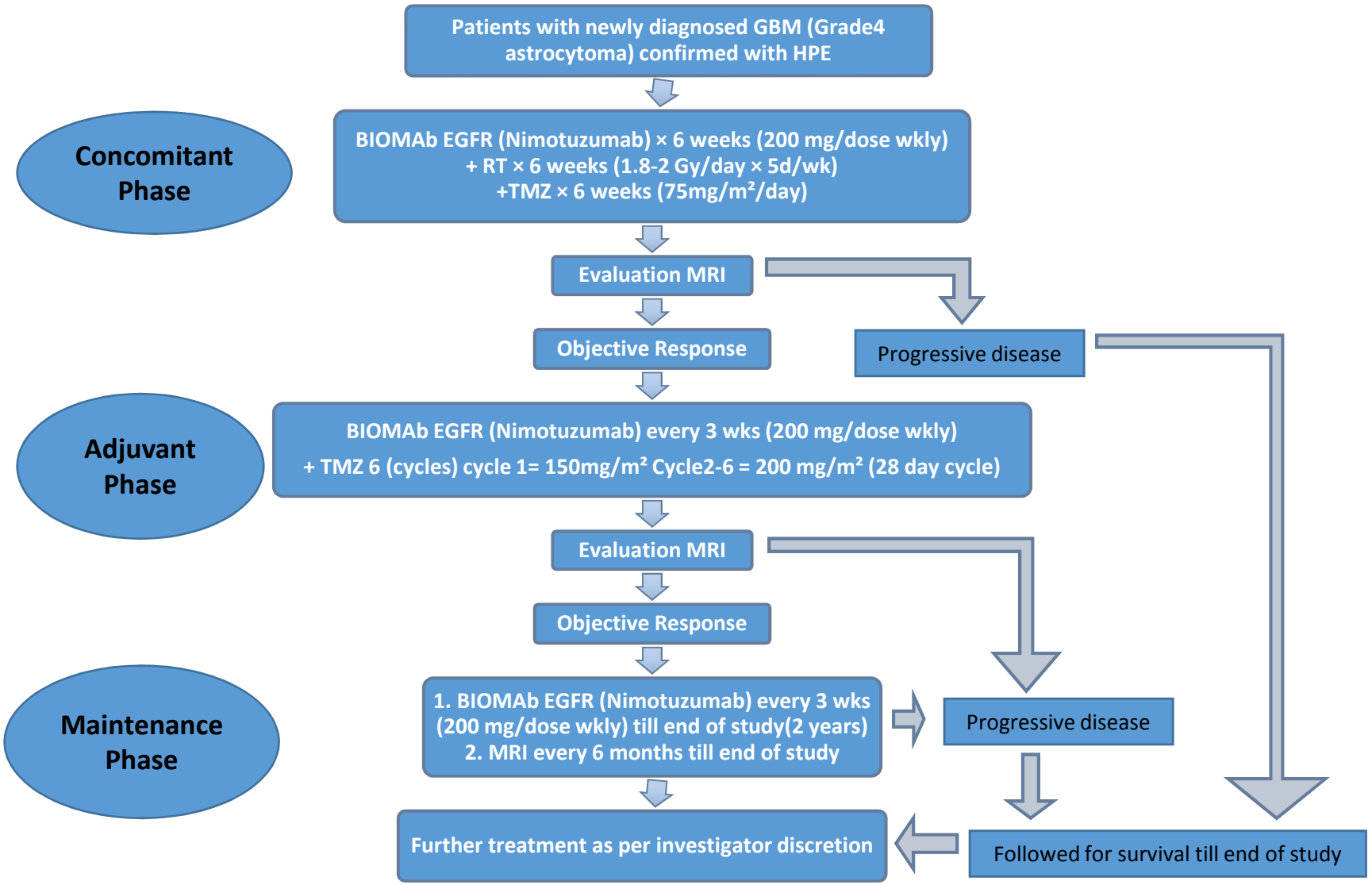
Exclusion Criteria

- Female patients who are pregnant or breast feeding.
- Patients with severe underlying disease/ not controlled by treatment in the opinion of the principal investigator.
- HIV, Chronic Hepatitis B or C if found to be positive
- Hypersensitivity to TMZ & BIOMAb-EGFR^{TM} (Nimotuzumab) or to any of its components.
- Previous or concurrent malignancies in other sites except surgically cured carcinoma-in-situ of cervix & non melanoma skin cancer

Study treatment plan



Schematic study flow



Tumor Response Evaluation

Macdonald Response Criteria

Complete Response (CR)	Disappearance of all enhancing tumor on consecutive CT or magnetic resonance imaging (MRI) scans at least 1 month apart, off steroids, and neurologically stable or improved
Partial Response (PR)	> 50% reduction in size of enhancing tumor on consecutive CT or MRI scans at least1 month apart, steroids stable or reduced, and neurologically stable or improved
Progressive Disease (PD)	> 25% increase in size of enhancing tumor or any new tumor on CT or MRI scans, or neurologically worse and steroids stable or increased.
Stable Disease (SD)	All other situations

Number of Subjects in Each Population Set

Population Set	Number of subjects in the set, N (%)
Safety Population	56 (100.0 %)
ITT Population	56 (100.0 %)
Efficacy Evaluable Population	51 (91.1%)

- Intention to treat - All subjects who were administered at least one dose of BIOMAb EGFR
- Efficacy evaluable Patients- Patients who received at least 6 or more doses of BIOMAb EGFR
- Safety analysis was performed for all subjects who were administered at least some amount of study drug

Demography at Enrolment

Variable	Statistics /Category	Value (N=56)
Gender	Male	41(73.2%)
	Female	15(26.8%)
Race	Asian	56 (100.0%)
Age (In Years)	N	56
	Mean ± SD	51.0 ± 10.76
	Median	52.0
	(Min,Max)	(22.0,70.00)
Age Group	Age < 50	22(39.3%)
	Age >= 50	34(60.7%)
Height(cm)	N	56
	Mean ± SD	163.4 ± 7.6
	Median	165.0
	(Min,Max)	(147.0,177.0)

Variable	Statistics /Category	Value(N=56)
BSA	N	56
	Mean ± SD	1.7 ± 0.2
	Median	1.7
	(Min,Max)	(1.3, 2.1)
Karnofsky's Performance Status	N	56
	Mean ± SD	81.1 ± 8.9
	Median	80.0
	(Min,Max)	(60.0, 90.0)
KPS Category	< 70	3(5.3%)
	70-89	31(55.4%)
	90-100	22(39.3%)
Time From Diagnosis (In Days)	N	56
	Mean ± SD	14.6 ± 9.2
	Median	13.5
	(Min,Max)	(1.0, 63.0)
Note: SD - Standard Deviation ; (Min,Max) - (Minimum,Maximum)		

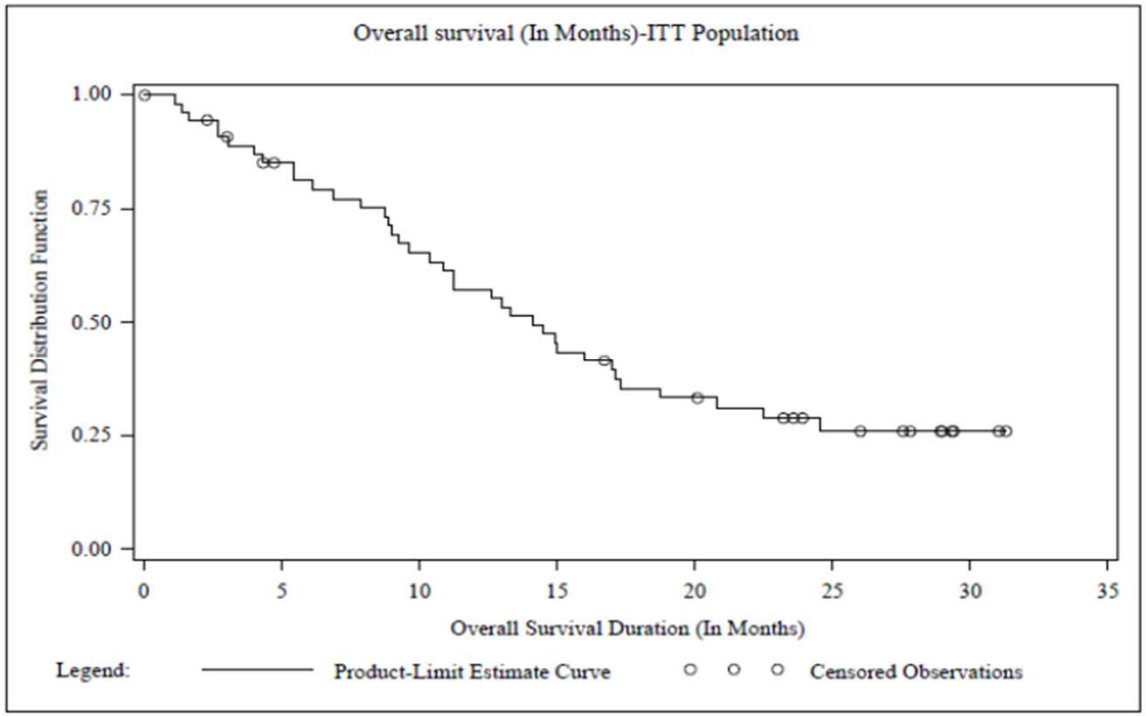
Surgical History and Residual Tumour Status at Enrolment

Variable	Category	Values
Evidence of Residual Tumor *	Yes	29 (78.4%)
	No	7 (18.9%)
	Missing	1 (2.7%)
*** Denominator will be the subjects who have undergone prior surgery**		

Safety and Efficacy of BIOMAb EGFR® in Indian Patients with Glioblastoma Multiforme

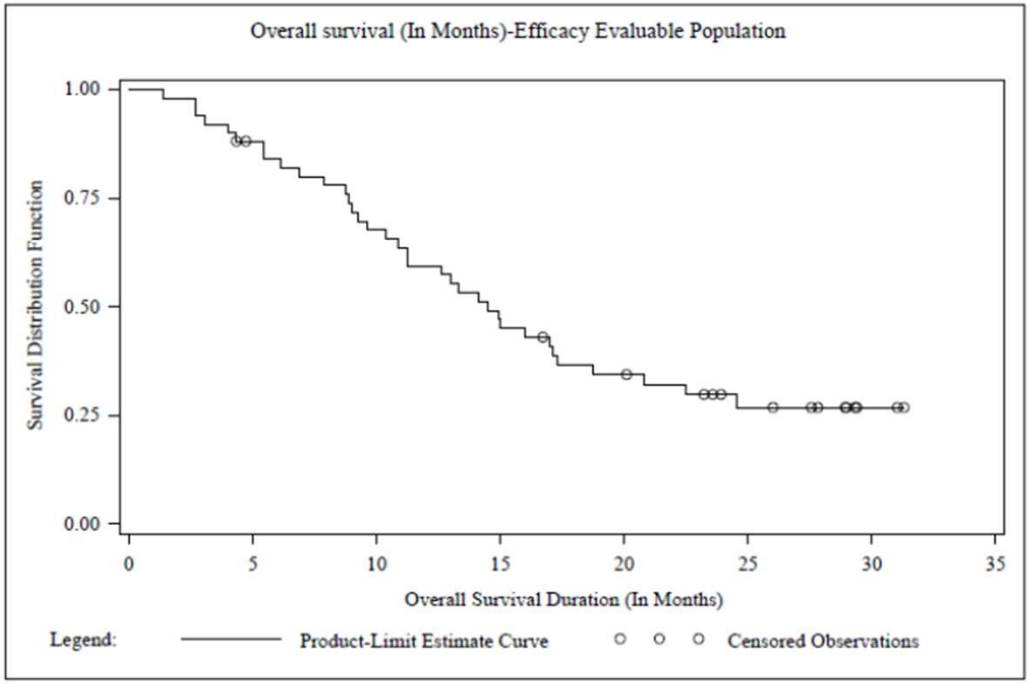
RESULTS

Overall Survival [ITT population]



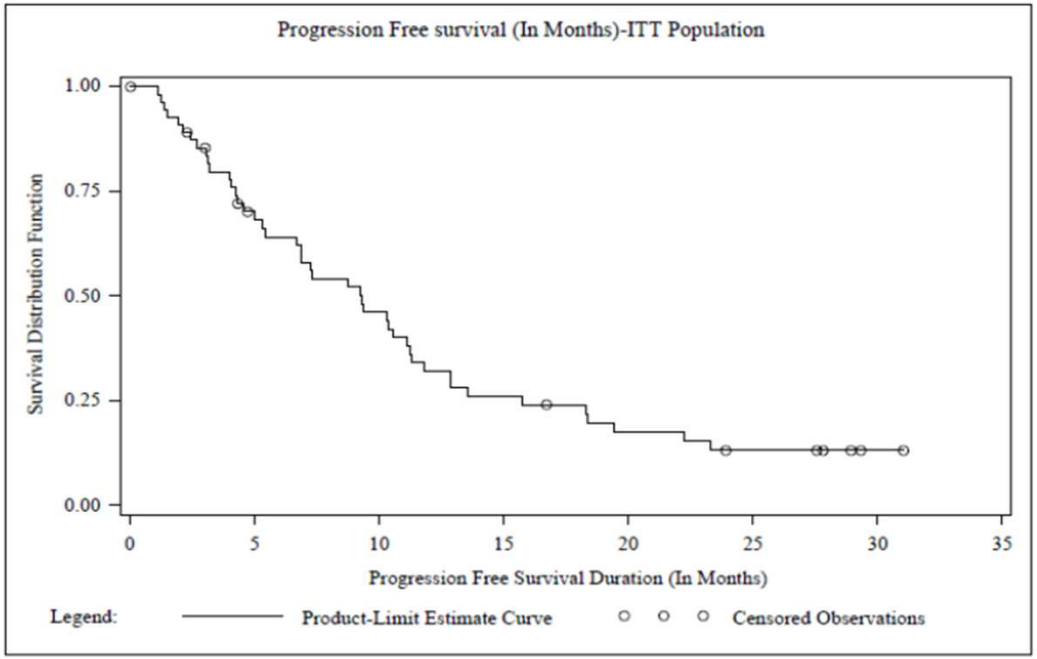
Statistics	Values
N	56
Mean (S.E)	14.5 (1.1)
Median (in months)	14.1
95% CI for Median	(10.9 , 17.3)

Overall Survival [EE population]



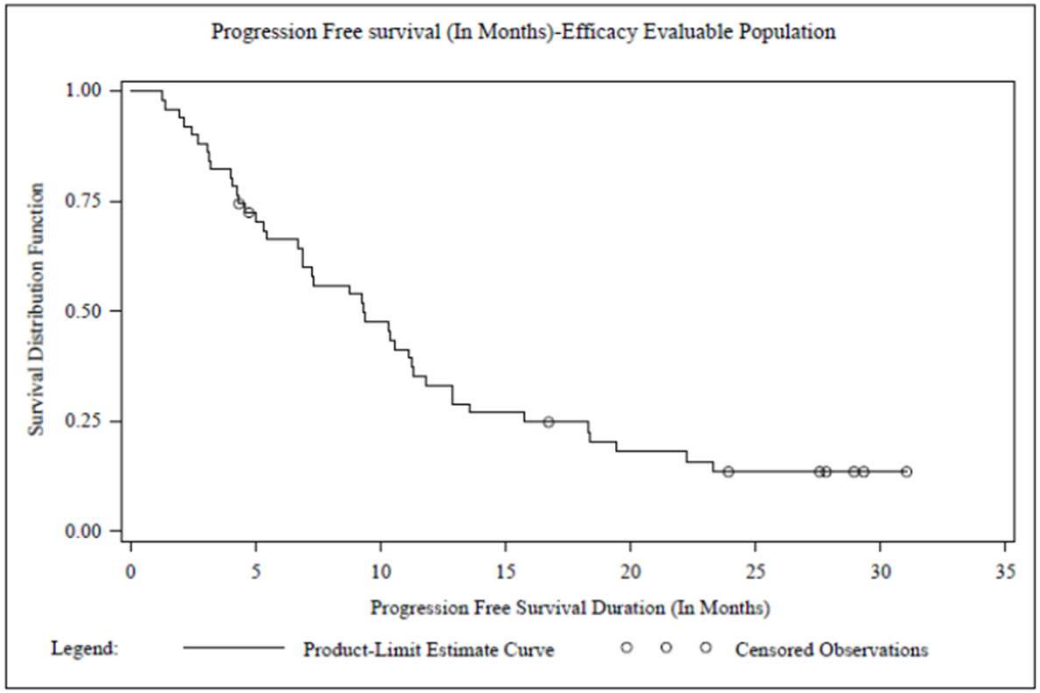
Statistics	Values
N	51
Mean (S.E)	15.0 (1.1)
Median (in months)	**14.5**
95% CI for Median	(11.2 , 18.8)

Progression Free Survival [ITT population]



Statistics	Values
N	56
Mean (S.E)	10.5 (1.0)
Median (in months)	**9.3**
95% CI for Median	(6.7 , 11.2)

Progression Free Survival [EE population]



Statistics	Values
N	51
Mean (S.E)	10.8 (1.1)
Median (in months)	**9.3**
95% CI for Median	(6.9 , 11.3)

RPA Analysis

A recursive partition analysis (RPA) model was defined post-hoc and the data was analyzed

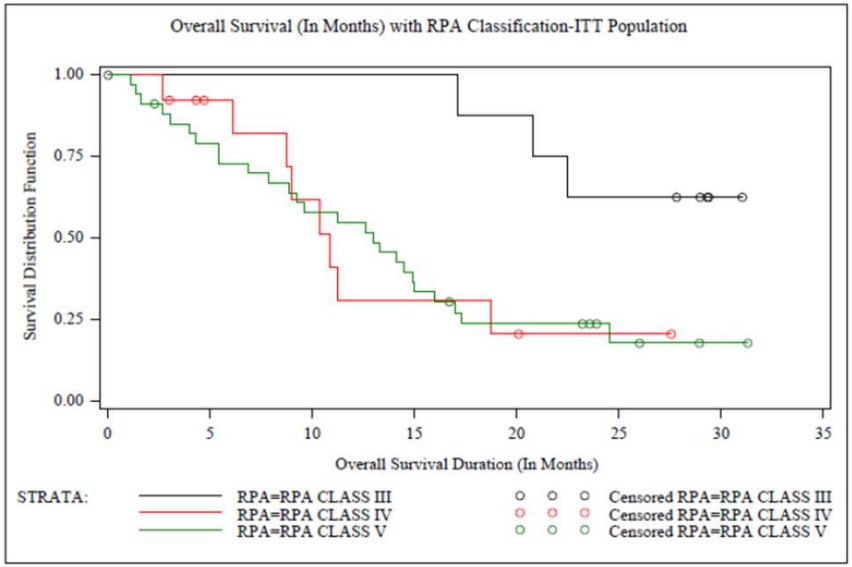
RPA Class	Definition Used
RPA III	Age<50 ;KPS 90-100 (both inclusive)
RPA IV	Age<50;KPS < 90
RPA V	Age≥50;KPS < 70 OR Age≥50;KPS 70-100

KPS :Karnofsky's Performance Status

Overall Survival Results
RPA Classification[ITT Population Set]

Statistics	RPA Class III	RPA Class IV	RPA Class V	p-value
N	9	13	34	0.0310
Mean (SE)	21.6 (0.8)	11.8 (1.7)	12.9 (1.4)	
Median	**NA**	**10.9**	**13.0**	
95% CI for Median	(20.8, NA)	(8.8, 18.8)	(8.9, 15.0)	

mOS not yet reached at 2-year follow-up in RPA Class III patient subset

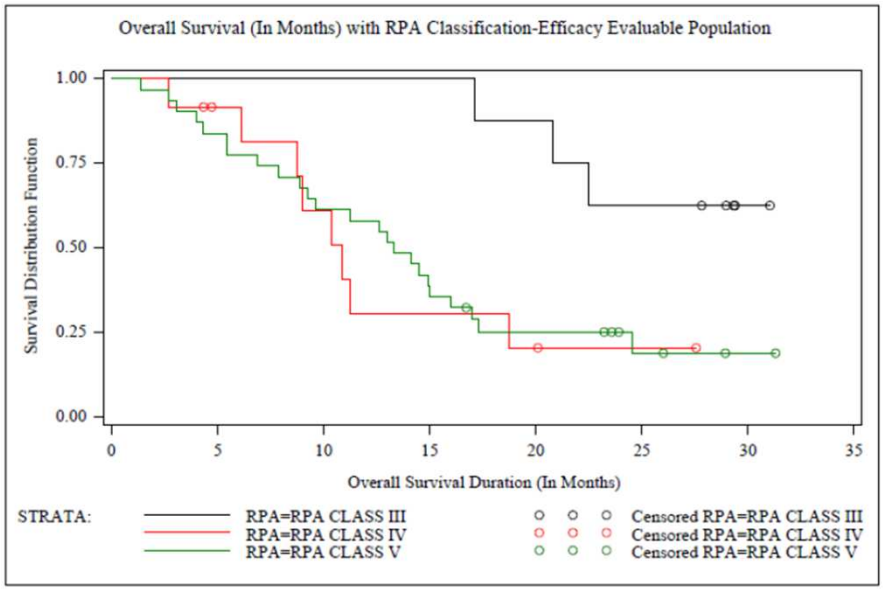


Median follow-up period of 27.1 months

Progression Free Survival
RPA Classification[ITT Population Set]

Statistics	RPA Class III	RPA Class IV	RPA Class V	p-value
N	8	12	31	0.0236
Mean (SE)	18.9 (1.9)	9.7 (2.0)	8.8 (1.2)	
Median	**20.8**	**8.8**	**6.9**	
95% CI for Median	(13.6, NA)	(5.0, 12.8)	(4.3, 10.3)	

Median PFS of 20.8 months observed in RPA class III.
mPFS between RPA classes was statistically significant



Prognostic Significance of Recursive Partitioning Analysis in GBM

- RPA classification developed to compare survival categories and determine homogenous patient subsets
  - Useful for refining stratification and phase III study design
  - Can determine which patient subsets will benefit from specific treatments (and which may be spared unnecessary treatment)

	Median Survival		2-Yr Survival	
RPA Class	Months	95% CI	%	95%CI
III*	17	15-21	32	21-42
IV	15	13-16	19	15-24
V	10	9-12	11	7-16

Mirimanoff R-O, et al. J Clin Oncol. 2006;24:2563-2569.

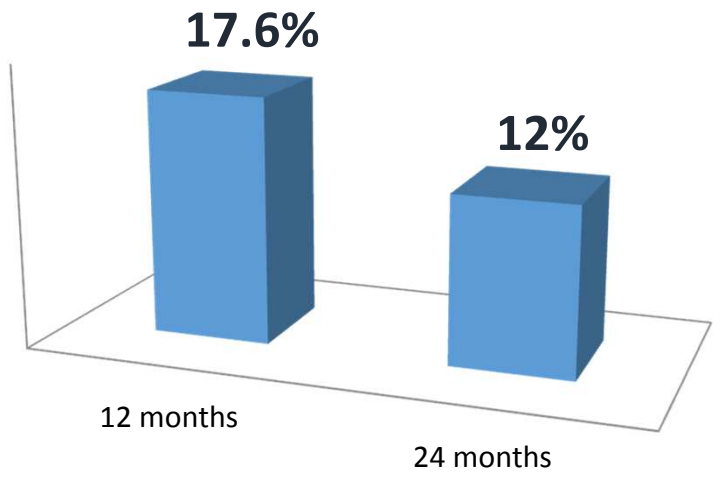
BIOMAb Study vs. Stupp's Study

Parameter	BIOMAb Study	Stupp's study
Overall Survival (median)	14.1 Mo	14.6 Mo
Progression Free Survival (median)	**9.3 Mo**	6.9 Mo
	RPA Class III	
Overall Survival	**Not Reached (>24mo)**	17 Mo
Progression Free Survival	20.8 Mo	Not Reported

Objective Response Rate[ITT Population set]

Statistics	At 6 months (N=51)	At 12 months (N=51)	At 18 months (N=50)	At 24 months (N=50)
CR	0	0	6	5
PR	9	9	3	1
ORR (%)	**9 (17.6%)**	**9 (17.6%)**	**9 (18.0%)**	**6 (12.0%)**
95% CI	(7.2, 28.1)	(7.2, 28.1)	(7.4, 28.6)	3.0% to 21.0%

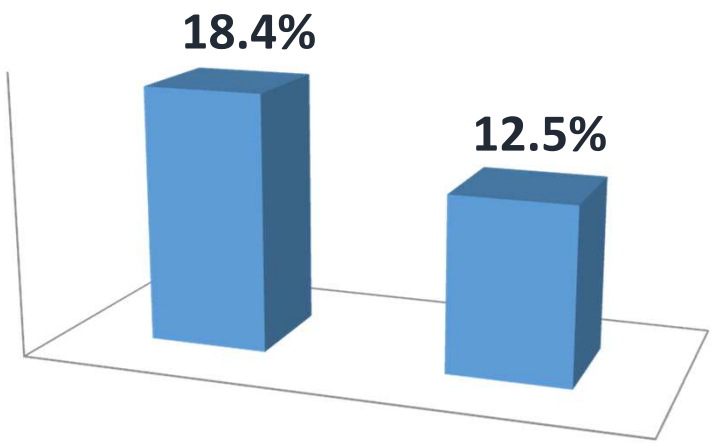
ORR of 17.6% observed after 1 year of treatment with BIOMAb EGFR in combination with chemotherapy (ITT population)



Objective Response Rate [EE Population set]

Statistics	At 6 months (N=49)	At 12 months (N=49)	At 18 months (N=48)	At 24 months (N=48)
CR	0	0	6	5
PR	9	9	3	1
ORR (%)	**9 (18.4%)**	**9 (18.4%)**	**9 (18.8%)**	**6 (12.5%)**
95% CI	(7.2, 29.2)	(7.5, 29.2)	(7.7, 29.8)	(3.1, 21.9)

ORR of 18.4% observed after 1 year of treatment with BIOMAb EGFR in combination with chemotherapy (EE population)



Extent of exposure

Cumulative Dose of BIOMAb EGFR® (Nimotuzumab)

Variable	Statistics	N = 56
Cumulative Dose (mg)	N	56
	Mean ± SD	3389.3 ± 2214.5
	Median	2800
	(Min, Max)	(200, 7600)

Duration of BIOMAb EGFR® (Nimotuzumab) Exposure

Variable	Statistics	N = 56
Days of Exposure (Days)	N	56
	Mean ± SD	272.3 ± 230.3
	Median	199
	(Min, Max)	(1, 715)

Conclusion

At median follow-up period of 27.1 months, Nimotuzumab in combination with TMZ and radiotherapy reported:

- mOS of 14.1 months
  - mOS observed in RPA class III and Class V were better than median OS observed in Stupp et al., (2009) study showing a possible median survival benefit in these two RPA sub-classes III and V by the addition of Nimotuzumab
- mPFS of 9.3 months, whereas it was 6.2 months in the Stupp et al., (2009) study on TMZ with radiotherapy
- Nimotuzumab in combination with standard of care was well tolerated with a good safety profile

Addition of BIOMAb EGFR (Nimotuzumab) to the temozolomide based chemoradiotherapy has an apparent progression free survival benefit and a possible overall survival benefit in RPA class III and V without major safety concerns

2. Farnesyl protein transferase inhibitors

Tipifarnib (Zarnestra) and lonafarnib (Sarasar)

-These drugs target a protein involved in the functioning of the cancer-causing Ras protein.

-Lonafarnib is being studied in combination with temozolomide, and tipifarnib in combination with radiation therapy.

3. MTOR inhibitors

-Everolimus (RAD-001) is being studied for glioblastoma multiforme and astrocytoma.

-Everolimus is related to rapamycin (Siroliumus) and tacrolimus (Prograf), which are also being investigated for brain tumor treatment.

-These drugs are commonly used to suppress the immune system to prevent rejection after organ transplantation.

4. Anti-angiogenesis drugs:

Bevacizumab (Avastin)

- It is being studied in combination with irinotecan for treatment of recurrent malignant gliomas.

Cediranib (Recentin, AZD2171)

- It is another VEGF inhibitor being investigated for glioblastoma treatment.

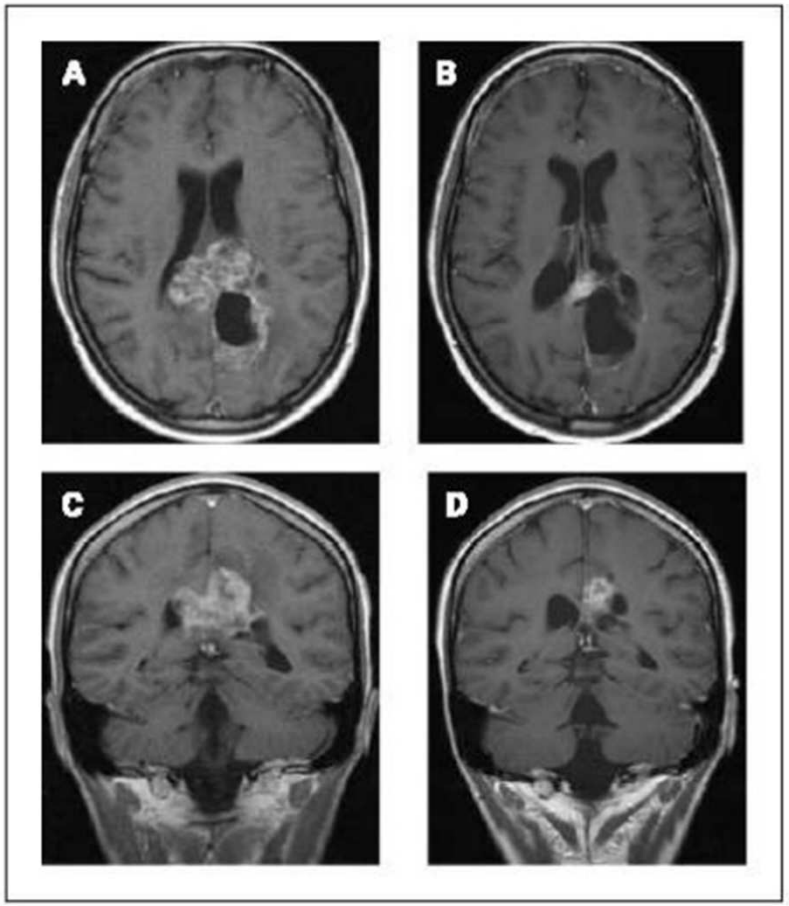
BEVACIZUMAB (AVASTIN)

- To date mainly investigated in Phase II trials
- Usually in combination with irinotecan chemotherapy
- No trials have demonstrated a survival benefit
- Side effects include
  - Hypertension (9%)
  - Delayed wound healing (2%)
  - Bowel perforation (2%)
  - Intracranial haemorrhage (2%)
  - Venous and arterial clots (4%)

BEVACIZUMAB IRINOTECAN IN RECURRENT GBM

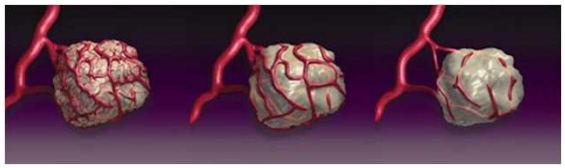
- Phase II study in 167 patients

	Bevacizumab (n = 85)	Bevacizumab + Irinotecan (n = 82)
Response %	28.2	37.8
6-mo PFS %	42.6	50.3
Survival (months)	9.2	8.7



Friedman HS, et al. JCO 2009

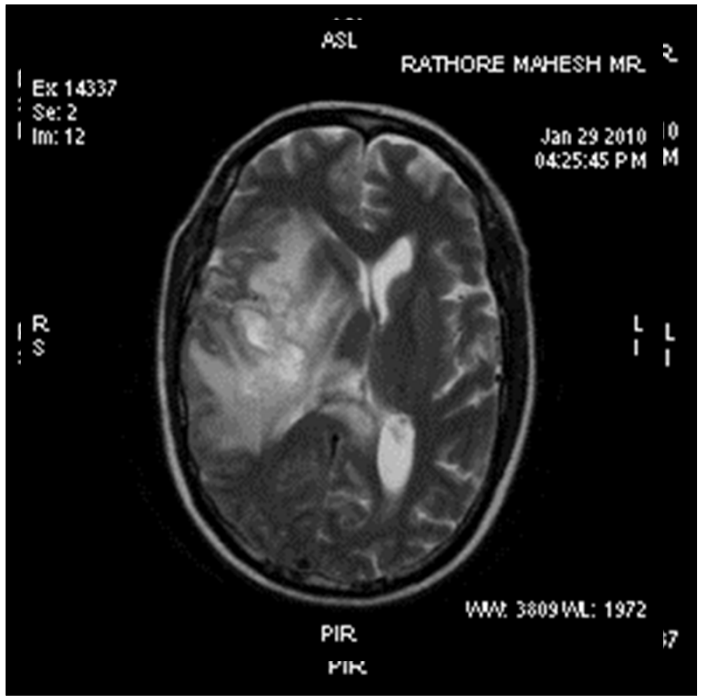
Bevacizumab (Anti-VEGF mAB)

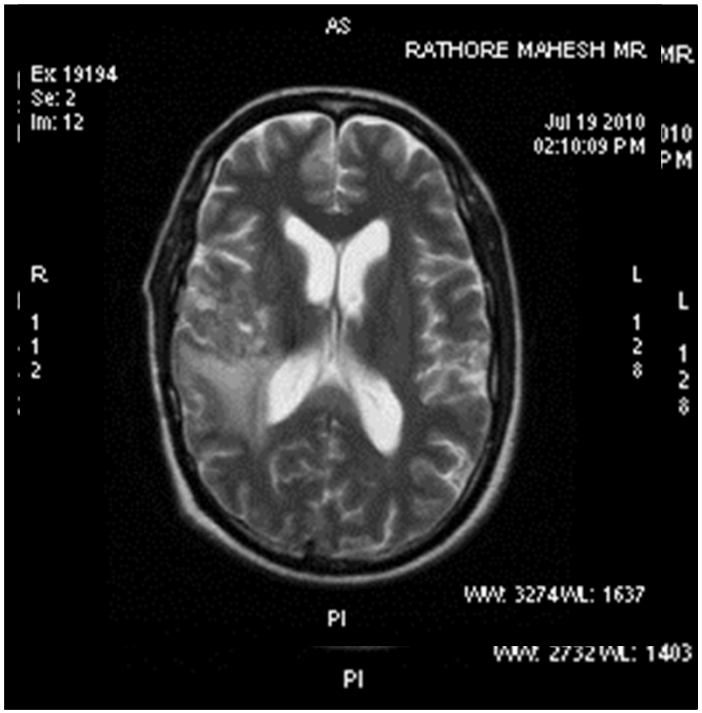


Before

6 cycles Bevacizumab

After



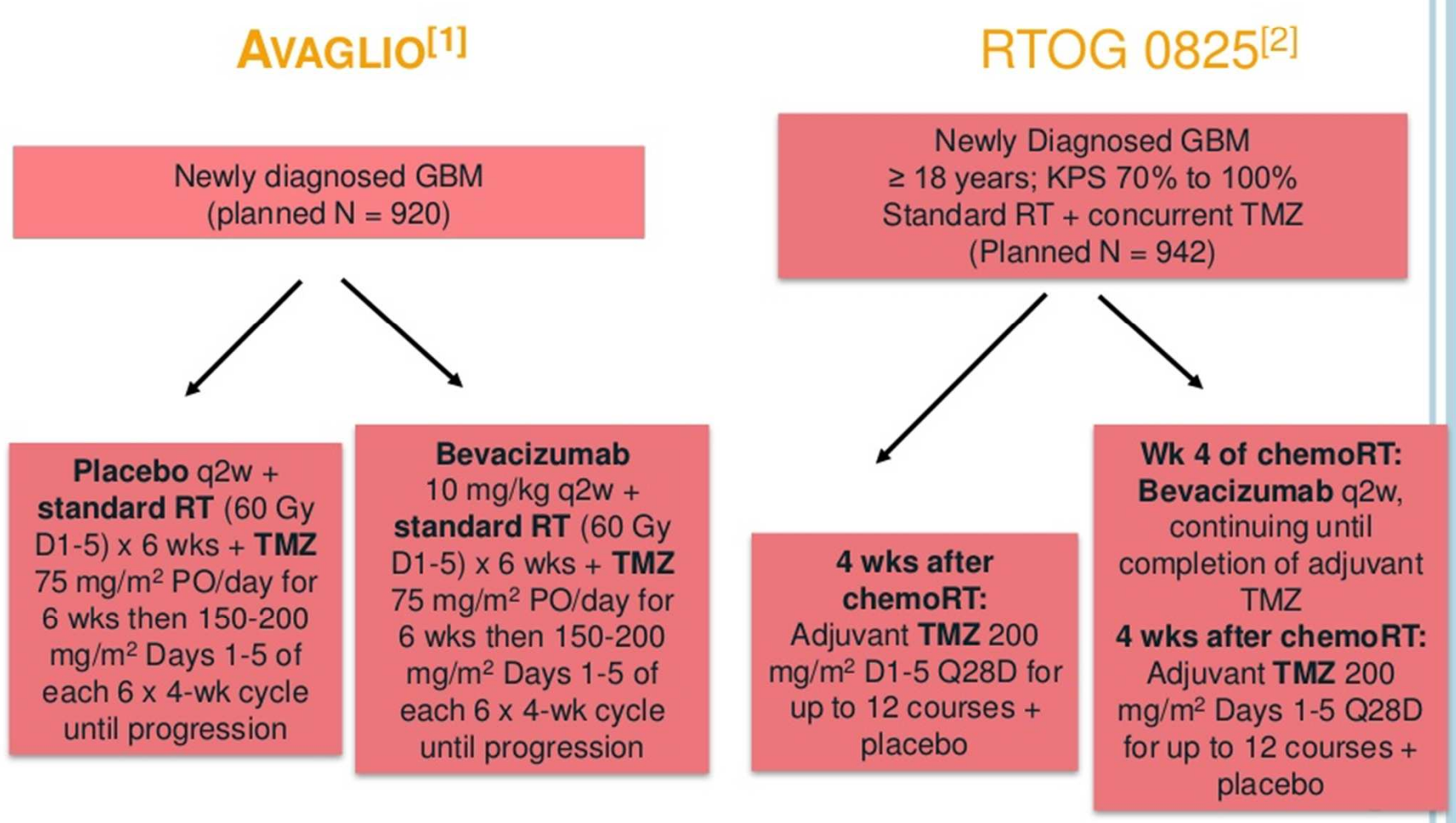


Experience with anti-angiogenic agents

Agent	Number patients	CR/PR (%)	PFS-6 (%)	OS, median (months)	Citation
Bevacizumab	85	28.2	42.6	9.2	Friedman 2009
Bevacizumab	48	35	29	7.8	Kreisl 2009
Bevacizumab	50	NR	25	6.4	Raizer 2010
Bevacizumab	82	37.8	50.	8.7	Friedman 2009
Bevacizumab	35	57	46	10.5	Vredenburgh, 2007
Bevacizumab	23	61	30	10.0	Vredenburgh, 2007
Bevacizumab	20	50	65	12.5	Gutin 2009
Bevacizumab	25	48	29.2	11.1	Sathornsumetee 2010
Bevacizumab	27	23	44.4	11.6	Reardon 2009
Bevacizumab	43	34	33	7.3	Hasselbalch 2010
Pazopanib	35	5.7	3	8.8	Iwamoto 2010
Sunitinib	21[a]	0	NR	3.8	Neyns 2010

Reardon Perry Brandes Jalali Wick *Expt Opin Drug Discovery 2011*

Phase III Trials of Bevacizumab in newly diagnosed GBM



1. ClinicalTrials.gov. NCT00943826. 2. ClinicalTrials.gov. NCT00884741.

Results

- The results of the phase III AVAglio trial were presented at the 49th (ASCO) in the Central Nervous System Tumours Session by Professor Wolfgang Wick, M.D., Professor of Neurology, Chairman of the Division of Neuro-oncology at the Neurology Centre.

- People who received Avastin plus radiotherapy and temozolomide chemotherapy did not have a statistically significant improvement in OS (the other co-primary endpoint), compared to those who received radiotherapy and temozolomide chemotherapy plus placebo (HR=0.88; [95% CI 0.76, 1.02], p=0.0987). Median survival was similar in both arms (16.8 months versus 16.7 months, respectively). No new safety findings were observed in the AVAglio study and adverse events were consistent with those seen in previous trials of Avastin across tumour types for approved indications.

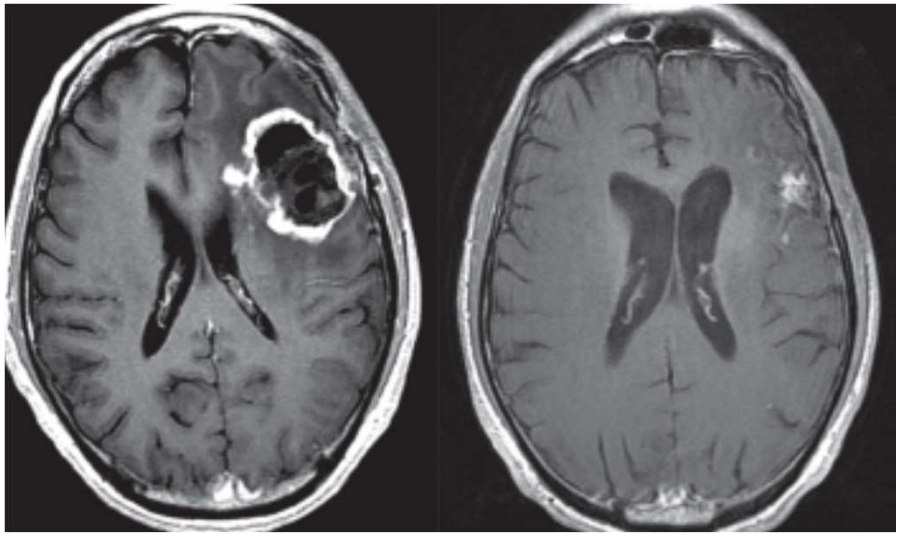
ANGIOGENESIS-TARGETING AGENTS FOR GLIOBLASTOMA

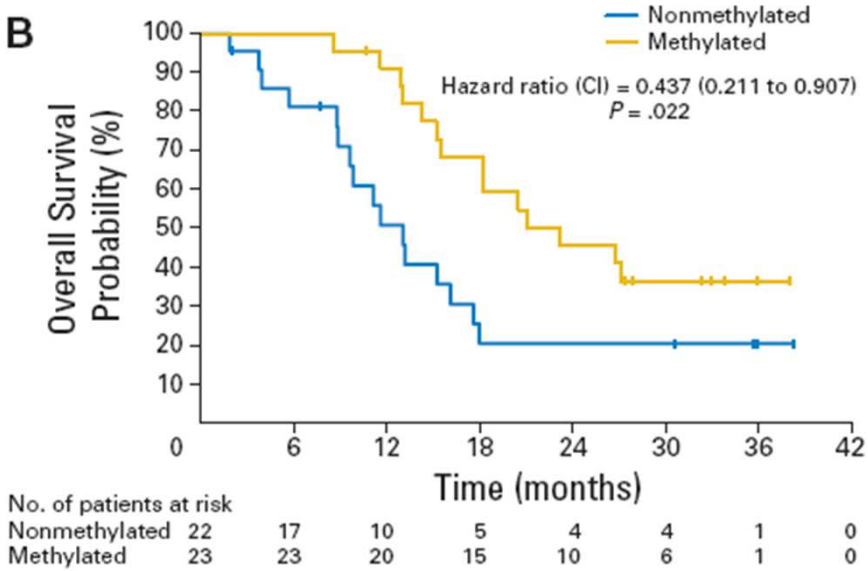
Target	Agent	Disease Setting	Study Phase
Integrins	**Cilengitide**	**nGBM** **rGBM**	**Phase III** **Phase I/II**
Angiopoietin/Tie 2	CVX-060	rGBM	Phase I/II
VEGF	**VEGF-trap (aflibercept)**	**rGBM** **nGBM**	**Phase II** **Phase I**
	VEGFR TKIs (cabozantinib, cediranib, axitinib, pazopanib)	**rGBM, nGBM**	**Phase I, II, III**
	Bevacizumab + strategies	**nGBM, rGBM**	**Phase I, II, III**
Endothelial cell proliferation	Metronomic temozolomide	nGBM, rGBM	Phase II, III

ClinicalTrials.gov

Cilengetide

Anti-integrin





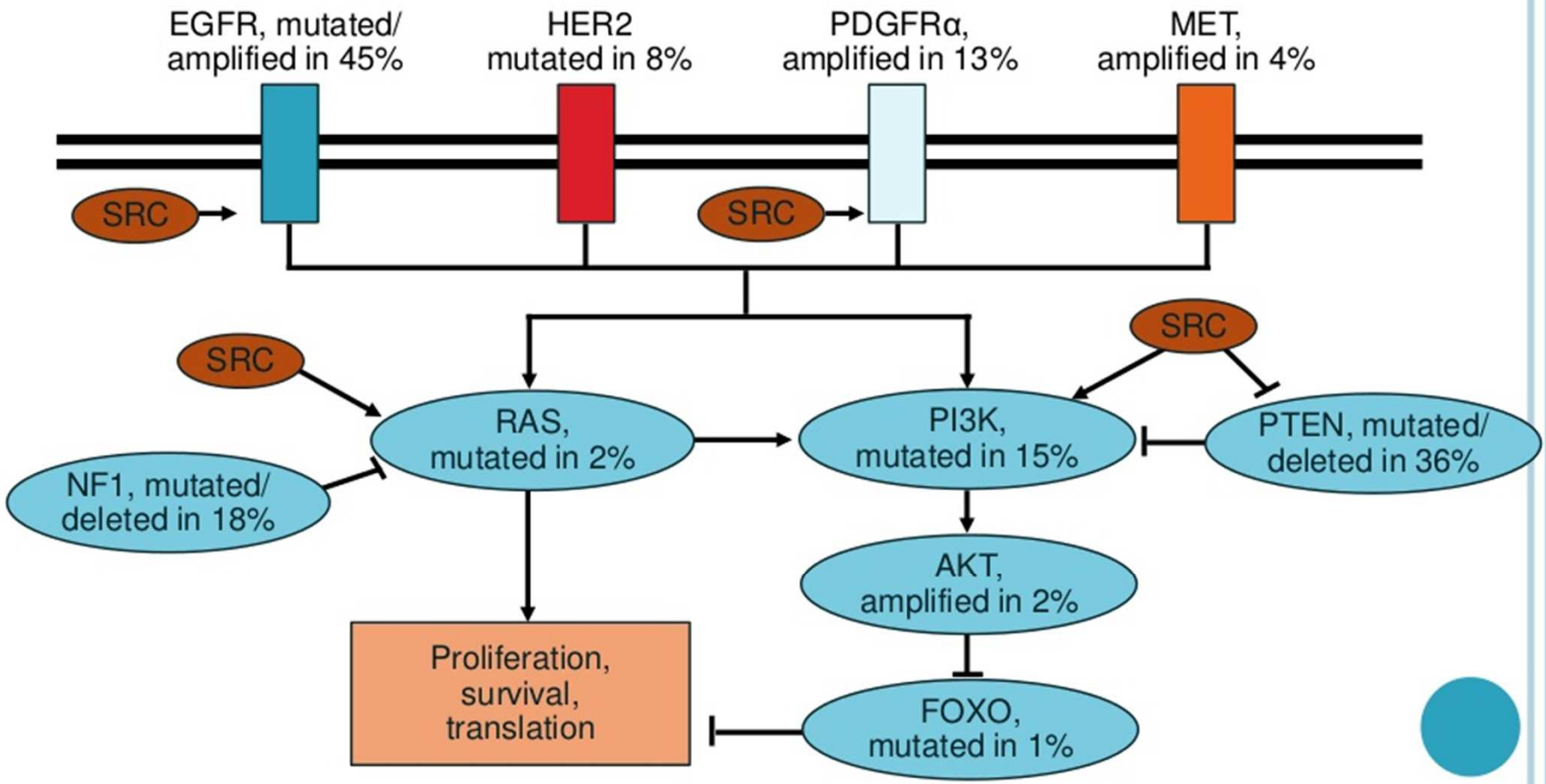
2 year OS: 35%

Stupp et al JCO 2010

Phase III Randomised Clinical trial of S+RT+TMZ Vs S+RT+TMZ+Cilengitide (EORTC); Global accrual completed including in India

'CENTRIC and CORE trials'

GENETIC TARGETS IN GLIOBLASTOMA

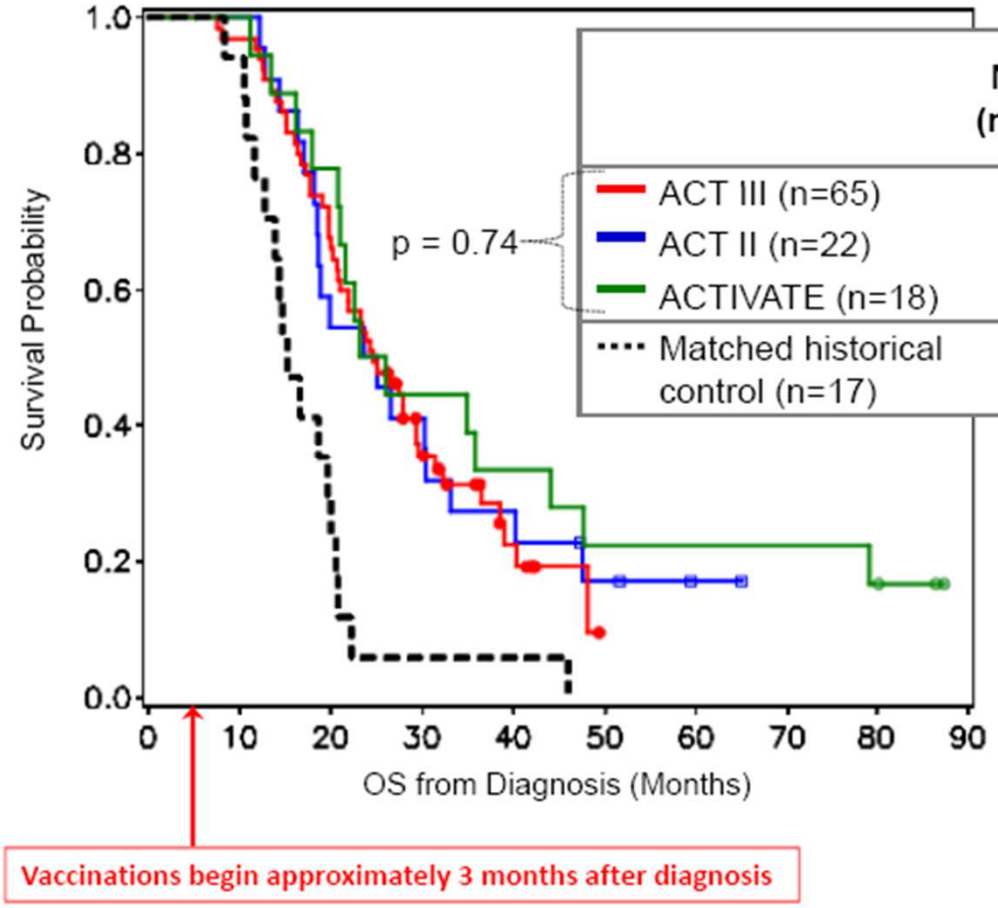


Wick W, et al Neuro-Oncol. 2011

Anti EGFR vIII vaccine in recurrent GBM

Impressive results

SNO 2011

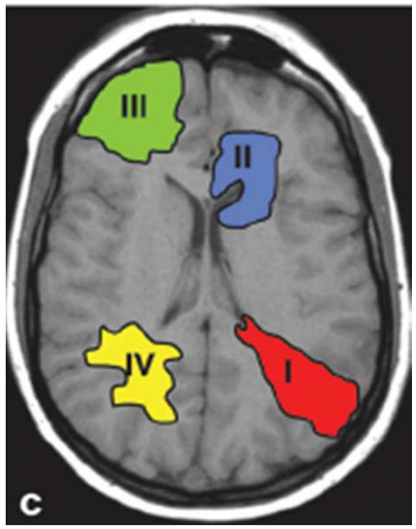


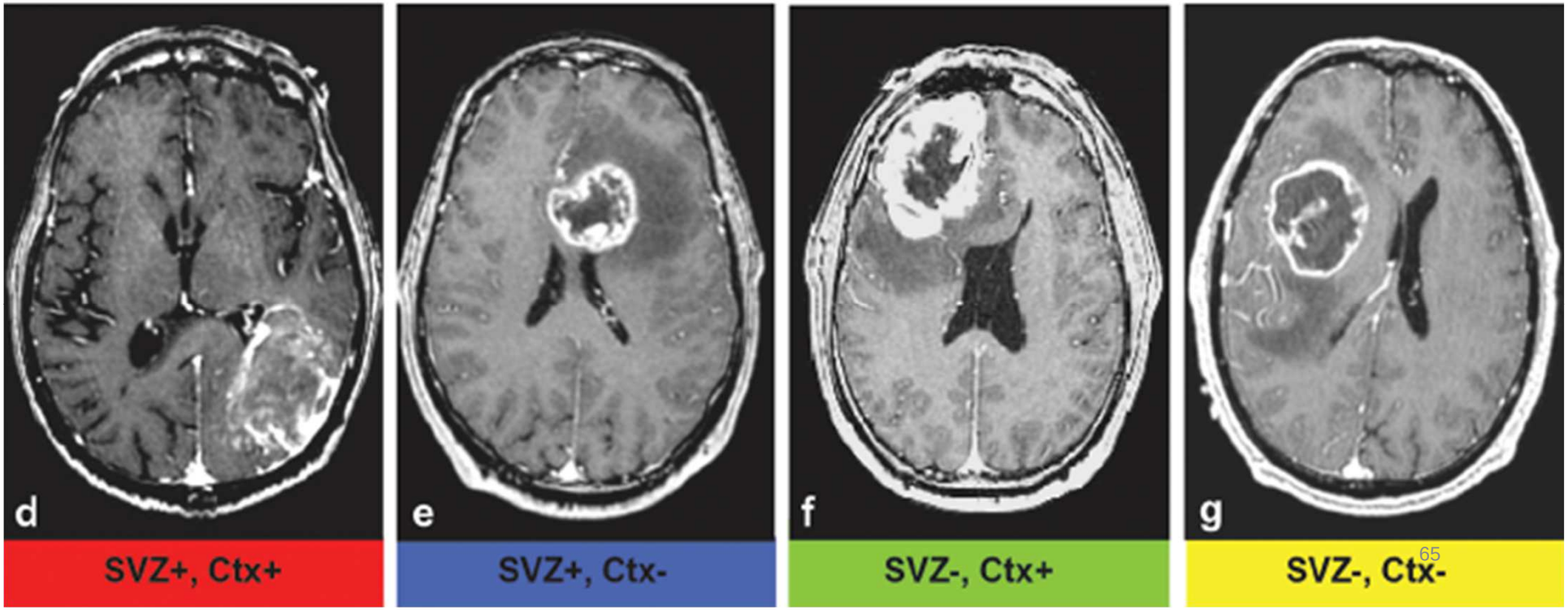
	Median (months)	OS at 24 Months	Comparison to Historical Control
ACT III (n=65)	24.6	52%	p = <0.0001
ACT II (n=22)	24.4	50%	p = 0.0023
ACTIVATE (n=18)	24.6	50%	p = 0.0003
Matched historical control (n=17)	15.2	6%	

Median duration of follow-up:
ACT III: 38.5 months
ACT II: 59.4 months
ACTIVATE: 86.5 months

Ongoing clinical 'vaccine' trials against EGFR vIII (CDX-110 Indian centres participating)

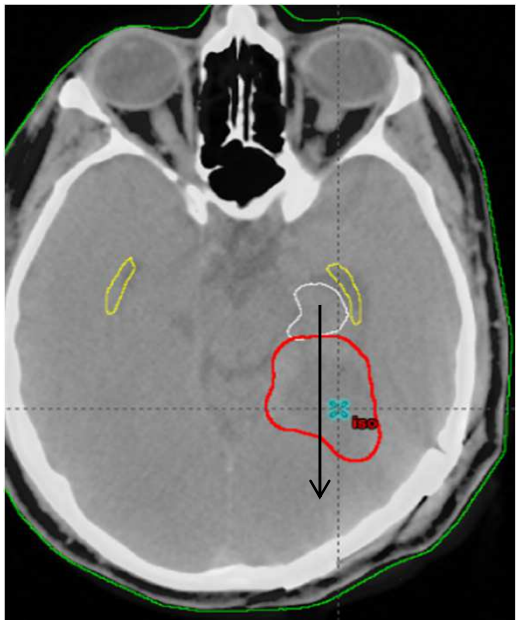
GBM in relation to stem cell niches – a novel approach



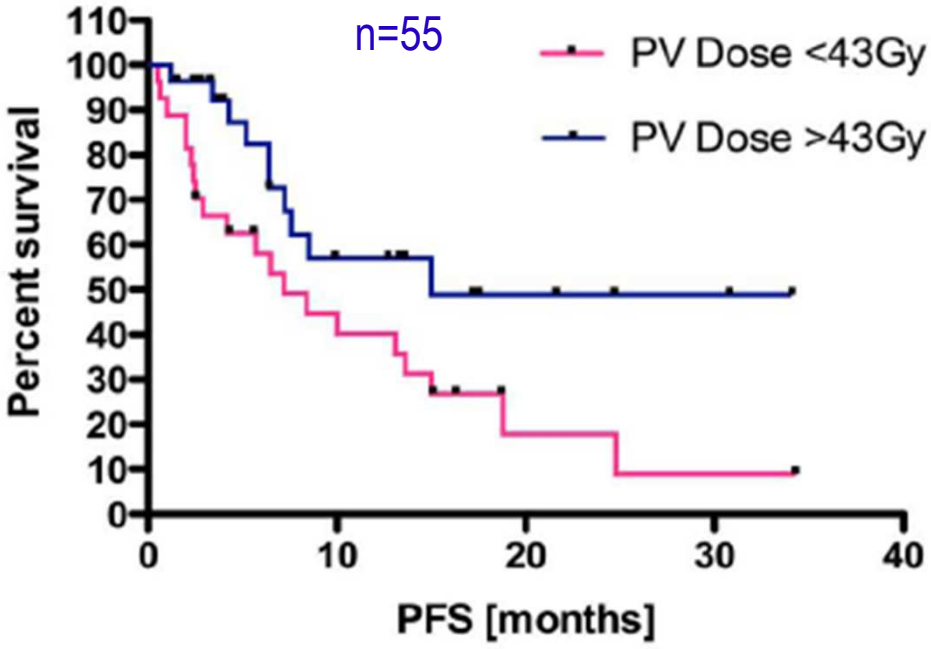


Irradiation of the potential cancer stem cell niches in the adult brain improves progression-free survival of patients with malignant glioma

Evers et al BMC Cancer 2010;10:384



Periventricular Zone (PV)



Possible Clinical Trial: Std Volume RT Vs RT Volumes encompassing stem cell niches

Alternating electron field therapy

- In 2011, the FDA approved a portable medical device that generates low intensity electric fields termed Tumor Treating Fields (TTF) for recurrent glioblastoma.
- Approval was based on results of a clinical trial that randomized 237 patients to TTF or chemotherapy.
- Similar survival was observed in both arms with TTF having lower toxicity and improved QOL.
- Due to lack of efficacy, not all panelists recommend treatment.

Table 2. Selected Investigational Treatments for Malignant Gliomas.*

Type of Treatment	Example
mTOR inhibitors	Everolimus, sirolimus, temsirolimus, deforolimus
PI3K inhibitors	BEZ235, XL765
PKCβ	Enzastaurin
PDGFR inhibitors	Dasatinib, imatinib, tandutinib
Proteasome	Bortezomib
Raf	Sorafenib
Src	Dasatinib
TGF-β	AP12009
Combination therapies	Erlotinib plus temsirolimus, gefitinib plus everolimus, gefitinib plus sirolimus, sorafenib plus temsirolimus erlotinib, or tipifarnib, pazopanib plus lapatinib
Immunotherapies	
Dendritic cell and EGFRvIII peptide vaccines	DCVax, CDX-110

Wen and Kesari NEJM 2008

Molecular targeting agents in pediatric patients

Table 1. Current Phase I or II trials of molecular targeting agents in pediatric patients with CNS tumors (from http://www.cancer.gov)

Agent	Phase	Tumor type	Study group	Study number
Tipifarnib	II	Recurrent or progressive HGG, MBL/PNET, BSG	COG	COG-ACNS0226
Erlotinib + TMZ	I	Recurrent/refractory solid tumors	COG	COG-ADVL0214
Imatinib	I/II	Newly diagnosed BSG, recurrent intracranial malignant gliomas	PBTC	PBTC-006
Iressa + XRT	I/II	Newly diagnosed BSG, incompletely resected supratentorial gliomas	PBTC	PBTC-007
Tipifarnib + XRT	I/II	Newly diagnosed BSG	PBTC	PBTC-014
Lapatinib	I	Recurrent/refractory MBL, malignant gliomas, EP	PBTC	PBTC-016

Ongoing trials of targeted therapy

Table 1. Ongoing trials of targeted therapy in patients with solid tumor brain metastases

Agent	Phase of trial	Target	Patient population	ClinicalTrials.gov identifier
Everolimus+trastuzumab+vinorelbine	II	mTOR	HER2+ breast cancer	NCT01305941
BKM120+trastuzumab	I	PI3K	HER2+ breast cancer	NCT01132664
Lapatinib+WBRT	II	HER2	HER2+ breast cancer	NCT01622868
Neratinib	II	HER2	HER2+ breast cancer	NCT01494662
Afatinib	II	HER2	HER2+ breast cancer	NCT01441596
ARRY-380+trastuzumab	I	HER2	HER2+ breast cancer	NCT01921335
WBRT +/- erlotinib	II	EGFR	NSCLC	NCT01518621
WBRT+bevacizumab	I	VEGF	Solid tumors	NCT01332929
Bevacizumab	II	VEGF	Solid tumors	NCT01898130
Sunitinib+SRS	I	VEGFR	Solid tumors	NCT00981890
Sorafenib+SRS	I	VEGFR	Solid tumors	NCT01276210
Dabrafenib+SRS	II	BRAF	Melanoma	NCT01721603
Vemurafenib	II	BRAF	Melanoma	NCT01781026
Ipilumumab+WBRT or SRS	I	CLTA-4	Melanoma	NCT01703507
Veliparib+WBRT	II	PARP	NSCLC	NCT01657799

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

Adult Low-Grade Infiltrative Supratentorial Astrocytoma/ Oligodendroglioma (excluding pilocytic astrocytoma)

- Adjuvant Treatment:
  - Temozolomide[1-3]
- Recurrence or Progressive, Low grade disease:
  - Temozolomide*,[2-4]
  - Lomustine or carmustine
  - Combination PCV (lomustine + procarbazine + vincristine)[5]
  - Platinum based regimens[6-8]

Anaplastic Gliomas

- Adjuvant Treatment:
  - Temozolomide or PCV with deferred RT[9-11]
  - Concurrent (with RT) temozolomide[12] 75 mg/m^2 daily
- Recurrence/Salvage therapy
  - Temozolomide[3,4,13,14]
  - Lomustine or carmustine[15]
  - Combination PCV
  - Bevacizumab†,[16-18]
  - Bevacizumab + chemotherapy†† (irinotecan,[19,20] carmustine/lomustine,[21] temozolomide, carboplatin [category 2B for carboplatin][22,23])
  - Irinotecan[24,25]
  - Cyclophosphamide (category 2B)[26,27]
  - Platinum-based regimens$^{\alpha}$
  - Etoposide[28]

Anaplastic Oligoastrocytoma
Anaplastic Oligodendroglioma

- Adjuvant Treatment
  - RT and PCV for 1p19q co-deleted (category 1)[29]

Glioblastoma

- Adjuvant Treatment:
  - Concurrent (with RT) temozolomide[12] 75 mg/m^2 daily
  - Post RT temozolomide[12] 150-200 mg/m^2 5/28 schedule
  - Temozolomide[12,30] 150-200 mg/m^2 5/28 schedule
- Recurrence/Salvage therapy
  - Bevacizumab†,[31-33]
  - Bevacizumab + chemotherapy†† (irinotecan,[32-34] carmustine/lomustine,[21] temozolomide, carboplatin [category 2B for carboplatin][22,23])
  - Temozolomide[4,12,35]
  - Lomustine or carmustine[15]
  - Combination PCV
  - Cyclophosphamide (category 2B)[26]
  - Platinum-based regimens$^{\alpha}$

Adult Intracranial and Spinal Ependymoma (excluding subependymoma)

- Recurrence
  - Platinum-based regimens:$^{\alpha}$ Single agent or combination[36]
  - Etoposide
  - Lomustine or carmustine[36]
  - Bevacizumab†
  - Temozolomide

*For patients not previously treated.
$^{\alpha}$Platinum-based regimens include cisplatin or carboplatin.
†Patients who have good performance status but evidence of radiographic progression may benefit from continuation of bevacizumab to prevent rapid neurologic deterioration.
††Bevacizumab + chemotherapy can be considered for patients who have failed monotherapy with bevacizumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

Adult Medulloblastoma and Supratentorial PNET

- Adjuvant Treatment
  - Weekly vincristine[φ] during craniospinal radiation therapy followed by either of the following regimens:
    - ◊ Cisplatin, cyclophosphamide, and vincristine[37,φ]
    - ◊ Cisplatin, lomustine, and vincristine[37,φ]
- Recurrence/Salvage therapy
  - No prior chemotherapy
    - ◊ High-dose cyclophosphamide ± etoposide
    - ◊ Carboplatin, etoposide, and cyclophosphamide
    - ◊ Cisplatin, etoposide, and cyclophosphamide
    - ◊ Consider high-dose chemotherapy with autologous stem cell reinfusion[38] in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection
  - Prior chemotherapy
    - ◊ High dose cyclophosphamide ± etoposide
    - ◊ Oral etoposide[39,40]
    - ◊ Temozolomide[3]
    - ◊ Consider high-dose chemotherapy with autologous stem cell reinfusion[38] in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection

Primary CNS Lymphoma

- Primary Treatment
  - High dose methotrexate 3.5 g/m^2 combined with the following plus RT[λ]:
    - ◊ Vincristine, procarbazine, cytarabine ± rituximab[41-43]
    - ◊ Cytarabine[44]
    - ◊ Ifosfamide ± RT[45]
  - High dose methotrexate 8 g/m^2 combined with the following plus deferred RT[46]
    - ◊ Rituximab[47,48]
    - ◊ Rituximab and temozolomide[49]
  - Consider urgent glucarpidase (carboxypeptidase G2) for prolonged methotrexate clearance due to methotrexate induced renal toxicity[50]
- Recurrence or Progressive Disease
  - Retreat with high-dose methotrexate[46]
  - Temozolomide
  - Rituximab ± temozolomide[51]
  - Topotecan
  - Consider high-dose chemotherapy with autologous stem cell reinfusion in patients who achieve a complete response with conventional doses of salvage chemotherapy
  - High-dose cytarabine[52]
  - Dexamethasone, high-dose cytarabine, cisplatin[53]
  - Pemetrexed[54]

Meningiomas

- Interferon alfa (category 2B)[55]
- Somatostatin analogue[56]

[φ]Omission of vincristine during radiotherapy phase of therapy or dose modification may be required for adults because they do not tolerate this regimen as well. Data supporting vincristine's use have been found in pediatric trials only. Patients should be closely monitored for neurologic toxicity with periodic exams.
[λ]Other combinations with methotrexate may be used.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Progress Against Brain Cancer

2000–Present

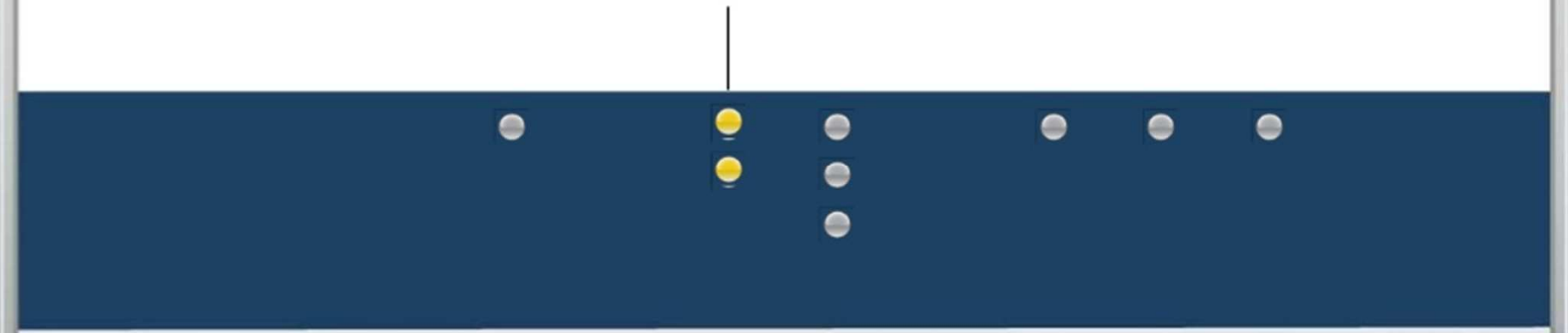
2003: Chemotherapy "wafer" active against malignant gliomas

Progress Against Brain Cancer

2000–Present

2005: MGMT gene alteration predicts response to chemotherapy

2005- 2008: Researchers begin mapping the genome of glioblastoma



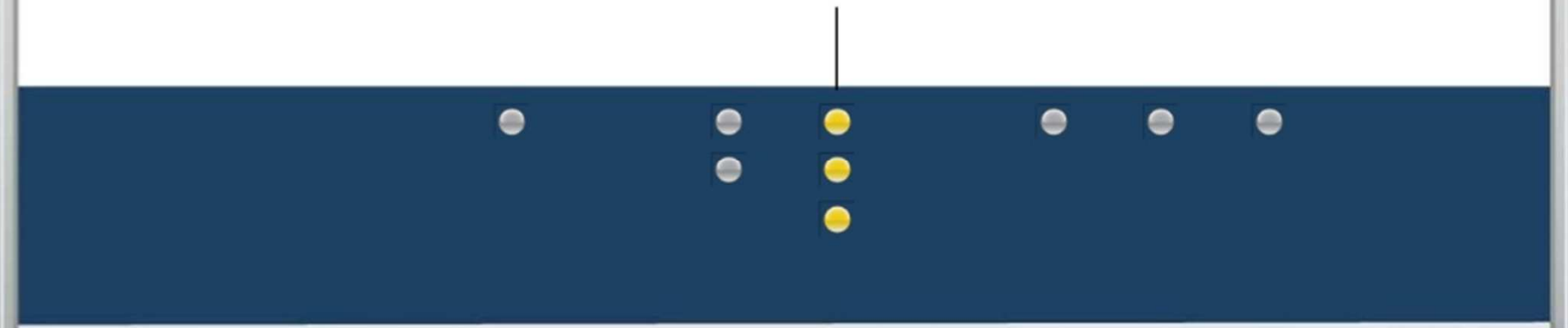
Progress Against Brain Cancer

2000–Present

2006: Genetic mutations affect survival for oligodendroglioma

2006: Chemically "illuminating" glioma tumors during surgery postpones recurrence

2006: Molecular sub-classification of high-grade gliomas predicts prognosis



Progress Against Brain Cancer

2000–Present

2008: Bevacizumab (Avastin) receives FDA approval for glioblastoma

Progress Against Brain Cancer

2000–Present

2009: Gene mutations linked to tumor aggressiveness

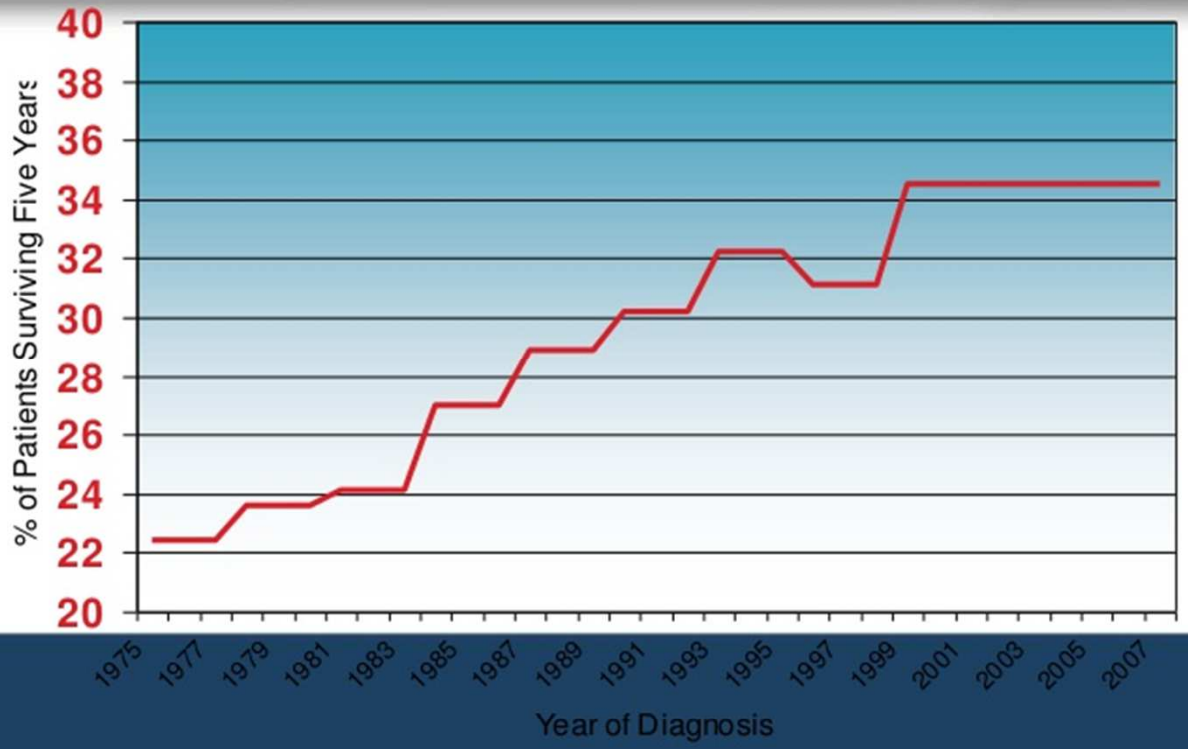
Progress Against Brain Cancer

2000–Present

2010: Nine-gene test can predict glioblastoma outcome

Progress Against Brain Cancer

Five-Year Survival



Source: National Cancer Institute


GO
GRAY
IN MAY
For Brain Tumors


Go Grey.
IN MAY


May
BRAIN
TUMOR
Awareness
Month
Support - Advocate - Cure

THANK YOU


understanding awareness talk future journey care
journey caring donors cure hope caregivers
research partnership future community support patients
support awareness survivors understanding research
learning
action brain tumour information
journey future
awareness month
family patients care hope learning
brain tumours future canadians
hope understand awareness
survivors journey
change canadian action
information care research community
braintumour
foundation
OF CANADA


Get Your
HEAD
In The
GAME!
A CURE CAN'T WAIT
National Brain Tumor Society