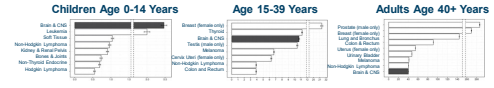
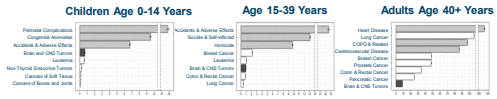
Brain and Central Nervous System Tumor Incidence and mortality



Age-Adjusted Incidence Rates of All Primary Brain and Other CNS Tumors Compared to Other Common Cancers



Annual Age-Adjusted Mortality Rates of All Primary Brain and Other CNS Tumors Compared to Other Common Cancers and Top Three Non-Cancer Causes of Death

361,802 primary brain and CNS tumors diagnosed in 2009-2013 in the US

CBTRUS Statistical Report. *Neuro Oncol.* 2016;18(suppl_5):1-75

Staging & Classification of Gliomas

- TNM classification not relevant
- Histology and grade determined by cellular characteristics and molecular testing
- Primary gliomas rarely spread outside of the central nervous system

WHO Classification	Histologic Subtype	
Grade I	Pilocytic astrocytoma	
Grade II	Astrocytoma Oligodendroglioma	No more oligoastrocytoma
Grade III	Anaplastic astro Anaplastic oligo	
Grade IV	Glioblastoma IDH mut astrocytoma	Important distinction between these grade 4 tumors

Gliomas: Median Survival historical Importance of Histologic Grading

Tumor Type	MS (mos)
Low-grade oligodendroglioma	~120
Low-grade astrocytoma	~60
Anaplastic oligodendroglioma	~60
Anaplastic astrocytoma	~36
Glioblastoma	12 - 15

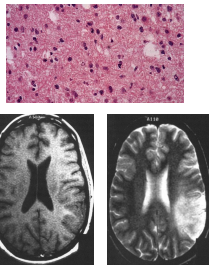
Astrocytoma Key Features

Histology:
- Increased astrocytic cellularity

WHO Grade 2

Median Survival:
- 5 - 7 years

Notes:
- Often present with seizures
- Often undergo malignant transformation



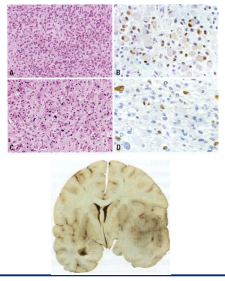
Anaplastic Astrocytoma Key Features

Histology:
- Increased astrocytic cellularity
- Cellular atypia and mitosis, no necrosis

WHO Grade 3

Median Survival:
- 3-4 years

Notes:
- Tissue sampling a major issue
- Progression to glioblastoma in some



Glioblastoma Key Features

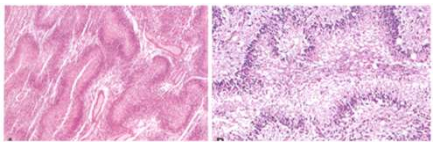
Histology

- Necrosis, mitosis, neovascularization and pseudopallisading

WHO Grade 4

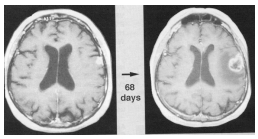
Median Survival

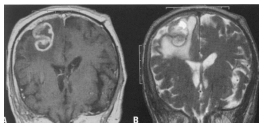
- 12-15 months



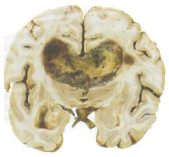
Glioblastoma

- Rapid progression
- Enhancing tumor
- Surrounding edema contains tumor





T1 post-contrast T2

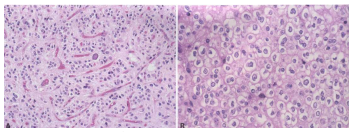


Histone mutated glioma

- Mutations in H3 K27 first noted in pediatric diffuse intrinsic pontine glioma (DIPG)
- Midline tumors in adults have also been found to harbor H3K27 mutations (H 3.3 or 3.1)
- Hemispheric tumors in adult can harbor G34 histone mutation
- Significance
  - All histone mutated gliomas are WHO Grade 4
  - Molecular profile distinct from GBM or IDH mutated tumors
  - Role of chemoradiation unclear (no benefit in pediatric DIPG)

Oligodendroglioma

- Histology reveals characteristic "fried egg" appearance
- Often microscopic and macroscopic calcification
- Classified as low-grade or anaplastic (WHO Grade 2 or 3)
- Very responsive to treatment: chemotherapy and radiation
- Definitive classification by 1p19q allelic chromosomal deletion

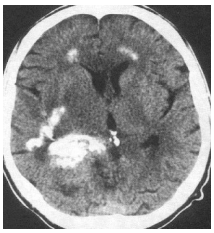


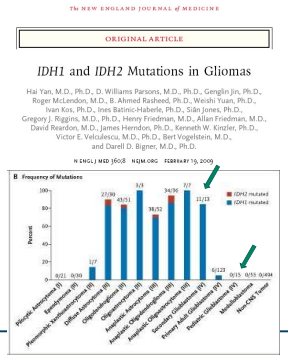
Dense network of branching capillaries

Clear cytoplasm and well-defined plasma membrane

Oligodendroglioma

- Noncontrast CT shows macroscopic calcification
- MRI not very good at evaluating calcification





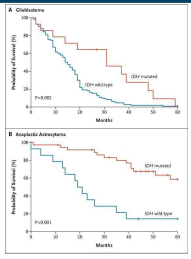
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

IDH1 and *IDH2* Mutations in Gliomas

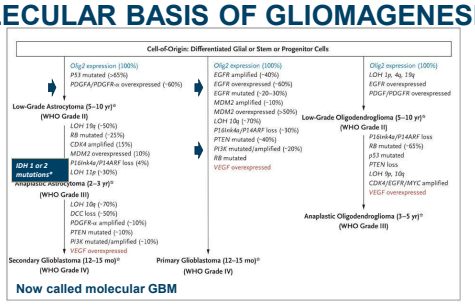
Hai Yan, M.D., Ph.D., D. Williams Parsons, M.D., Ph.D., Genglin Jin, Ph.D., Roger McLendon, M.D., B. Ahmed Rasheed, Ph.D., Weishi Yuan, Ph.D., Ivan Kos, Ph.D., Ines Batinic-Haberle, Ph.D., Siân Jones, Ph.D., Gregory J. Riggins, M.D., Ph.D., Henry Friedman, M.D., Allan Friedman, M.D., David Reardon, M.D., James Herndon, Ph.D., Kenneth W. Kinzler, Ph.D., Victor E. Velculescu, M.D., Ph.D., Bert Vogelstein, M.D., and Darell D. Bigner, M.D., Ph.D.

N ENGL J MED 360;8 NEJM.ORG FEBRUARY 19, 2009



- Immunohistochemical staining detects only canonical IDH R132H (90%)
- So 10% will only be found by sequencing

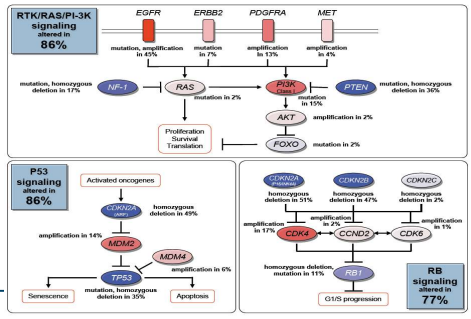
MOLECULAR BASIS OF GLIOMAGENESIS

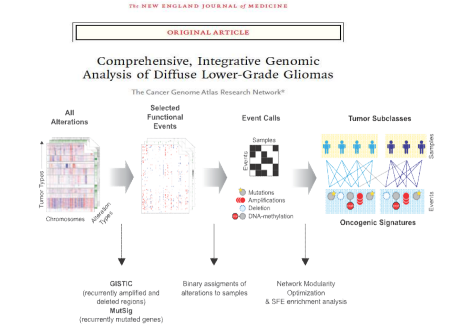


Now called molecular GBM

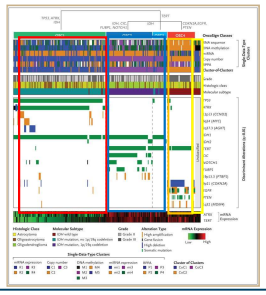
*Yan H. et al. *NEJM* 360:765, 2009

GENETIC ABERRATIONS INTEGRATE INTO PATHWAYS
PATHWAYNESS CRITICAL (TCGA GLIOMA)

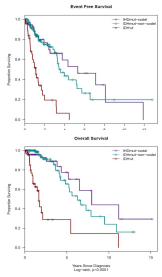




Multiplatform Analysis of Lower Grade Gliomas



- Astrocytoma
- Oligodendroglioma
- Pre-GBM (molecular GBM)
- ?Pilocytic Astrocytoma



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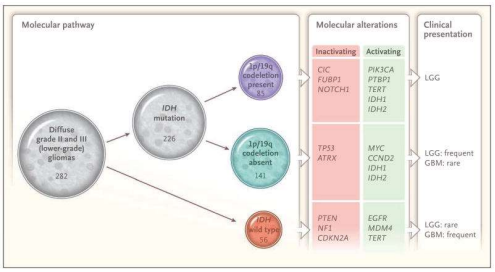
Summary of Molecular Classification of Gliomas



WHO 2021
LGG with
- chr 10 loss, 7 gain
- CDKN2A loss
- IDH wildtype
- = molec GBM

IDH mut Grade 4
- Grade 4 astrocytoma

IDH mut LGG
- CDKN2A loss = Grade 4

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Cancer Risk/Protective Factors

- Established risk factors
  - High-dose radiation
  - Hereditary syndromes
  - Male
  - Increasing age
  - Race (comparing white vs. African origin)

- Probable risk factors
  - Family history of primary brain tumors
  - Mutagen sensitivity (lab-based test)
  - Allergies and asthma (protective)
  - Chickenpox or anti-VZV (protective)

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Genetic Syndromes with High Risk of Brain Tumors

Genetic Syndrome	Associated Chromosome or gene
• Neurofibromatosis 1	• Chromosome 17q11
• Neurofibromatosis 2	• Chromosome 22q12
• Tuberous sclerosis 1	• Chromosome 9q34
• Tuberous sclerosis 2	• Chromosome 16p13
• Li-Fraumeni	• Chromosome 17p13
• Turcot Syndrome and Multiple hamartoma syndrome	• APC, hMLH1, hMSH2, PMS2, PTEN
• Lynch Syndrome	• Mismatch repair genes

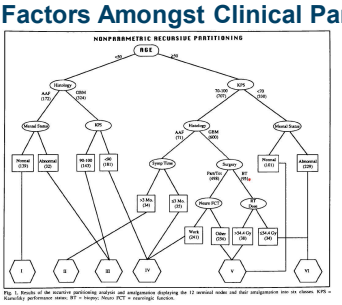
Clinical Prognostic Factors

- Tumor grade
- IDH mutational status

IDH Status dictates prognosis in grade 4 glioma

- Age
- Functional status (usually KPS)
- Extent of resection (somewhat controversial)
- Tumor location (may correlate with functional status)
- Radiation therapy

Prognostic Factors Amongst Clinical Parameters



Curran et al. JNCI 85: 704-710, 1993

Adapted from: Weller et al *JCO* epub Oct. 5, 2009

Treatment of Patients
Current Standards Of Care

Evidence-Based Review: Extent of Resection on Survival in Malignant Glioma

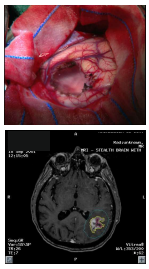
- Literature Review: text word astrocytoma 1966-2004; more than 12,000 references (T. Ryken)
- Review and selection of papers providing data on cytoreductive surgery in newly diagnosed malignant glioma

Results

- Randomized trials - 0
- Meta-analysis - 1
- Critical reviews - 2
- Prospective data collection - 8
- Matched pair analysis - 1
- Retrospective data collection - 19

5-ALA Trial (Stummer et al)

- Lancet Oncology 7:392-401, 2006
- Randomized trial
- White light vs 5-ALA
- Measured residual tumor
  - Compared none vs some residual
- Median survival 17.9 vs 12.9 months (p < 0.001)
- Factor significant in multivariate analysis
  - P = 0.006



External Beam Radiotherapy for Malignant Glioma

- Current standard is 60 Gy/2 Gy/fx to GTV + 2 - 3 cm margin
- 3D: conformal, multiple fields
- Pooling of 6 randomized trials (RT vs no RT) improved survival
  - Mean survival time 3 - 6 months without RT; 9 - 12 months with RT*

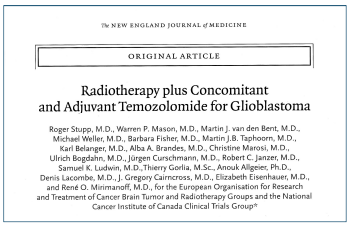
Author	N	Schema	Results
Andersen *Acta Radiol Oncol Radiat Phys Biol* 1978	108	RT vs best supportive care	Post-op RT significantly improves survival compared to best supportive care
Walker *J Neurosurg* 1978	303	BCNU vs RT vs BCNU +RT, vs best supportive care	Patients receiving RT had significantly longer MS than patients receiving BCNU or best supportive care
Walker *N Engl J Med* 1980	467	Semustine vs RT vs semustine + RT vs BCNU +RT	Patients receiving RT had significantly longer survival than patients receiving semustine alone
Kristiansen *Cancer* 1981	118	RT vs RT + bleomycin vs supportive care	MS with RT alone 10.2 months compared to 5.2 months with supportive care

*Walker MD, et al. *N Engl J Med.* 1980;303:1323-1329.

Limitations of Chemotherapy in Treating Brain Tumors

- Poor drug penetration into tumor (e.g., blood-brain barrier, hypoxia, intracranial pressure, etc.)
- Systemic toxicity
  - Serious myelosuppression
- Drug-drug interactions
  - Corticosteroids (phenytoin concentration)
  - Anticonvulsants (paclitaxel and CPT-11 clearance)
- Intrinsic resistance of brain tumors
  - MGMT overexpression, for example

Newly Diagnosed GBM: Changing the Standard of Care with Concomitant Radiation & Temozolomide



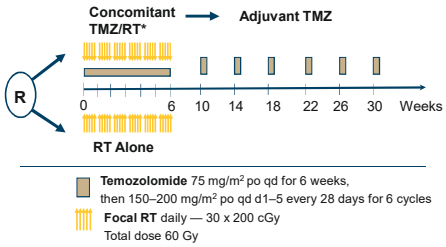
The NEW ENGLAND JOURNAL of MEDICINE

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*

Phase III Study: New GBM Radiation +/- Temozolomide



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

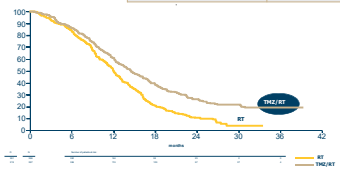
Focal RT daily — 30 x 200 cGy
Total dose 60 Gy

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

Phase III EORTC/NCIC Trial: Results

- 573 patients accrued
  - RT/TMZ = 287;RT alone = 286
  - Groups matched well for prognostic factors: age, PS, extent of tumor resection

	RT	RT/TMZ	p-value
Progression-free survival	5.0 months	7.2 months	P < 0.001
Median survival	12.1 months	14.6 months	P < 0.001
2-year survival	10%	26%	P < 0.001



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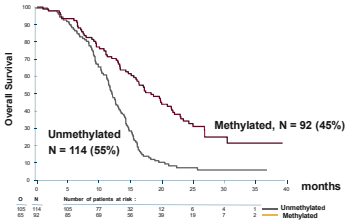
MGMT Promoter Methylation is a Positive Prognostic Factor for Outcome in Glioblastoma Patients of this Trial



MGMT	Unmeth	Meth
Median OS, mo:	12.2	18.2
2-yr survival:	7.8%	34.1%
HR [95% CI]:	0.45 [0.32-0.61]	
Logrank test:	*p* <0.0001	
Risk of death reduced by 55%		

Total N=206

M. Hegi et al *N Engl J Med.* 2005, 352:997-1003

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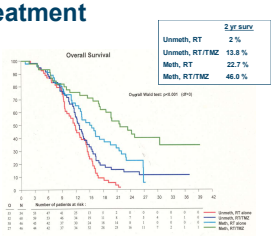
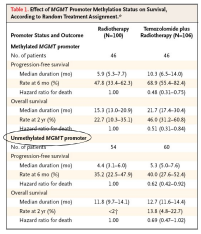
MGMT Promoter Methylation and Outcome Based on Treatment



	2 yr surv
Unmeth, RT	2 %
Unmeth, RT/TMZ	13.8 %
Meth, RT	22.7 %
Meth, RT/TMZ	46.0 %



- MGMT promoter methylation not a perfect predictor of durable response to TMZ
- Patients without MGMT promoter methylation also benefited from TMZ

Hegi et al., *NEJM*, 2005

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Five-year Follow Up Data

Treatment	RT-Unmeth	TMZ/RT-unmeth	RT meth	TMZ/RT - meth
Median(m)	11.8	12.7	15.3	23.4
2y OS(%)	1.9	14.8	23.9	46.9
5y OS(%)	0.0	8.3	5.2	13.8
Hazard Ratio	0.66 [0.45-0.97]		0.51 [0.33-0.81]	

From: Stupp et al *Lancet Oncol* 10:459-66, 2010

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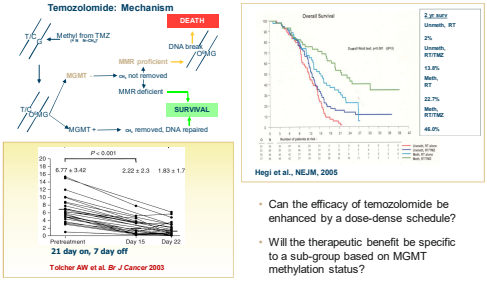
MGMT: A potential therapeutic target



- Can the efficacy of temozolomide be enhanced by a dose-dense schedule?
- Will the therapeutic benefit be specific to a sub-group based on MGMT methylation status?

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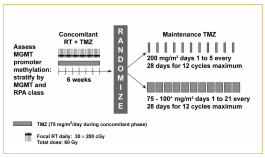
RTOG 0525/EORTC 26052-22053

- International randomized phase III clinical trial involving RTOG, EORTC and NCCTG
- Primary study objective: determine if dose-intensifying the adjuvant temozolomide improves OS
- Secondary objectives:
  - Impact of dose-dense on PFS
  - Impact of dose-dense on OS and PFS by MGMT methylation status
  - Toxicity profiles
  - Compare symptom burden, NCF and HRQOL between the two treatment arms



Treatment

Concomitant RT + TMZ

Focal (not IMRT) RT: 30 fx x 200 cGy

TMZ 75 mg/m^2 daily during RT

Arm 1: 150 - 200 mg/m^2 days 1-5 of 28 day cycle; 6 - 12 cycles

Arm 2: 75 - 100 mg/m^2 days 1-21 of 28 day cycle; 6 -12 cycles

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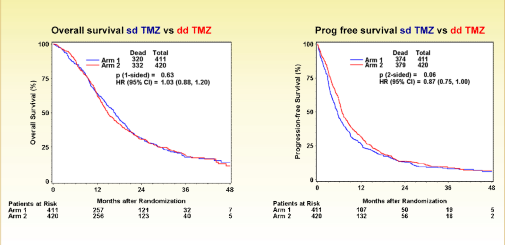
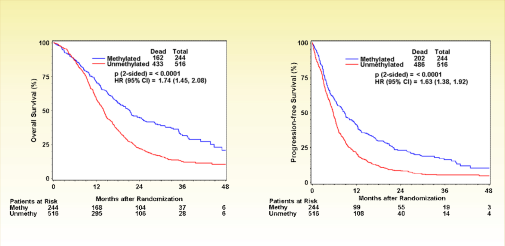
Primary Outcomes by Treatment

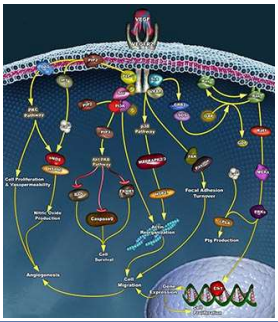


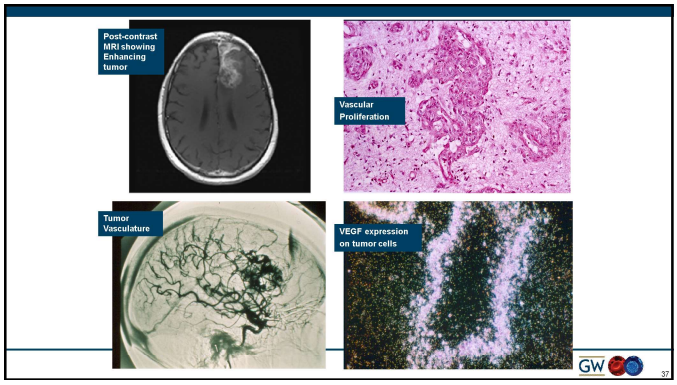
Outcomes by MGMT Status



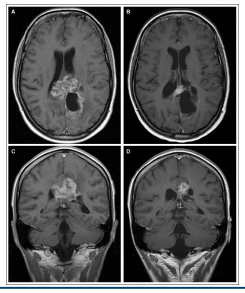
Angiogenesis Inhibitors

- Many of the early studies of angiogenesis used glioblastoma as the tumor model.
- Tumor cells make high levels of VEGF, particularly VEGF-A.
- VEGF production is very high in areas of necrosis, stimulating additional vascular proliferation.
- Newly formed blood vessels are often tortuous with blind loops and endothelial gaps
- Accounts for intravenous contrast leakage



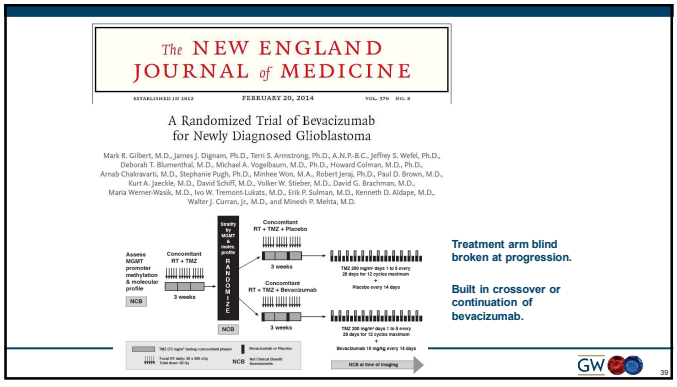


Example of Imaging Response

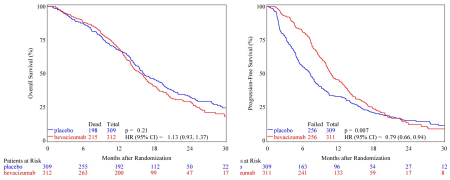


Vredenburgh, J. J. et al. *J Clin Oncol*; 25:4722-4729 2007

GW 38



Primary Outcomes by Treatment



Median overall survival
Placebo: 16.1 months
Bevacizumab: 15.7 months
HR (bev/placebo:1.13 (95%CI:0.93,1.37))

Median progression free survival
Placebo: 7.3 months
Bevacizumab: 10.7 months
HR (bev/placebo:0.79 (95%CI:0.66,0.94))

Neither OS or PFS achieved pre-specified endpoints

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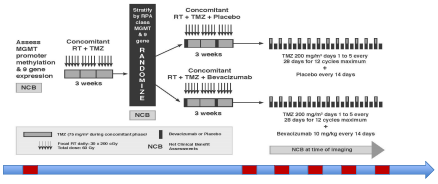
Net Clinical Benefits

Terri Armstrong, Jeffrey Wefel

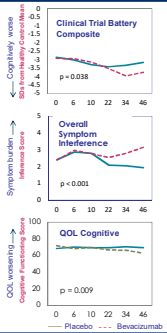
- Longitudinal measure of patient reported outcomes (PROs: MDASI-BT, EORTCQLQ30/BN20) and neurocognitive function (NCF)
- Inter-arm Analyses:
  - Discrete time points: differences in proportion with worsening/stable-improved
  - Longitudinal: changes in PROs and NCF over time



41

Net Clinical Benefits

- Longitudinal evaluation
  - General linear modeling with fixed effects; covariates: MGMT status and RPA class
  - Comparison between the 2 treatment arms in patients deemed progression free
  - P-value ≤0.05 was considered significant
- Results
  - Significant results found in both Objective (neurocognitive function) and Patient Reported (Symptom Burden and Quality of Life) Outcomes
  - Patients on Bevacizumab arm had significant worsening over time compared to Placebo arm



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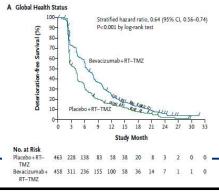
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma

Olivier L. Chinot, M.D., Wolfgang Wick, M.D., Warren Mason, M.D., Roger Henriksson, M.D., Frank Saran, M.D., Ryo Nishikawa, M.D., Antoine F. Carpentier, M.D., Ph.D., Khe Hoang-Xuan, M.D., Ph.D., Petr Kavan, M.D., Ph.D., Dana Cernea, Ph.D., Alba A. Brandes, M.D., Magalie Hilton, M.Sc., Lauren Abrey, M.D., and Timothy Cloughesy, M.D.

- Placebo-controlled, double-blinded, randomized phase III study
- 921 patients randomized
- Bevacizumab or placebo started with chemoradiation
- 6 cycles of maintenance temozolomide
- Co-primary endpoints
- QOL measures (EORTC)
- Bevacizumab or placebo continued until progression
- Blind broken only for medical reasons



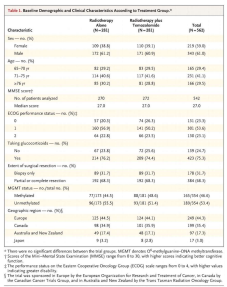
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

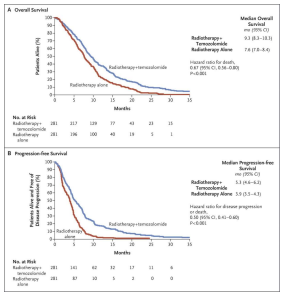
Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

James R. Perry, M.D., Normand Laperriere, M.D., Christopher J. O'Callaghan, D.V.M., Alba A. Brandes, M.D., Johan Menten, M.D., Claire Phillips, M.B., B.S., Michael Fay, M.B., Ch.B., Ryo Nishikawa, M.D., J. Gregory Cairncross, M.D., Wilson Roa, M.D., David Osoba, M.D., John P. Rossiter, M.B., B.Ch., Arjun Sahgal, M.D., Hal Hirte, M.D., Florence Laigle-Donadey, M.D., Enrico Franceschi, M.D., Olivier Chinot, M.D., Vassilis Golfinopoulos, M.D., Laura Fariselli, M.D., Antje Wick, M.D., Loic Feuvret, M.D., Michael Back, M.B., B.S., Michael Tills, M.B., B.S., Chad Winch, M.Sc., Brigitta G. Baumert, M.D., Wolfgang Wick, M.D., Keyue Ding, Ph.D., and Warren P. Mason, M.D., for the Trial Investigators*

Baseline Demographic and Clinical Characteristics According to Treatment Group.



Overall and Progression-free Survival Acct Primary Outcomes Results



Perry JR et al. *N Engl J Med* 2017;376:1027-1037.

Exploratory Analyses of Overall Survival Rate at 12, 18, and 24 Months According to Treatment Group and MGMT Status

Table 3. Exploratory Analyses of Overall Survival Rate at 12, 18, and 24 Months According to Treatment Group and MGMT Status.

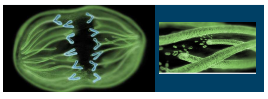
Population	At 12 Months	At 18 Months	At 24 Months
		percent (95% confidence interval)	
All patients			
Radiotherapy alone	22.2 (17.5–27.3)	10.8 (7.4–14.8)	2.8 (1.2–5.4)
Radiotherapy plus temozolomide	37.8 (32.1–43.6)	20.0 (15.5–24.9)	10.4 (7.1–14.5)
Patients with unmethylated MGMT			
Radiotherapy alone	21.3 (13.7–30.0)	12.7 (6.9–20.3)	3.8 (1.1–9.6)
Radiotherapy plus temozolomide	32.3 (23.0–42.0)	13.4 (7.3–21.2)	6.7 (2.7–13.1)
Patients with methylated MGMT			
Radiotherapy alone	29.9 (19.9–40.5)	13.6 (7.0–22.4)	4.1 (1.1–10.4)
Radiotherapy plus temozolomide	55.7 (44.7–65.3)	34.1 (24.4–44.0)	17.8 (10.5–26.7)

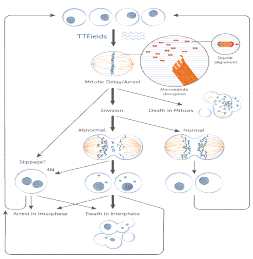
Perry JR et al. *N Engl J Med* 2017;376:1027-1037.

Prospective, Multi-center Phase III Trial of Tumor Treating Fields Together with Temozolomide compared to Temozolomide alone in Newly Diagnosed Glioblastoma

- Roger Stupp, Ahmed Idbaih, David M. Steinberg, William Read, Steven Toms, Gene Barnett, Garth Nicholas, Chae-Yong Kim, Karen Fink, Andrea Salmaggi, Frank Lieberman, Jay Zhu, Lynne Taylor, Giuseppe Stragliotto, Andreas F. Hottinger, Eilon D. Kirson, Uri Weinberg, Yoram Palti, Monika E. Hegi, and Zvi Ram on behalf of the EF-14 Trial investigators

Tumor Treating Fields - Mode of Action



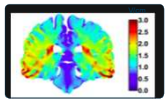


- Action on dividing cells
  - Effect on spindle apparatus
- Alternating fields effect on polar tubulin→
  - Disruption of microtubule assembly
  - Cell cycle arrest
    - → prolongation of mitosis
  - Aneuploidy

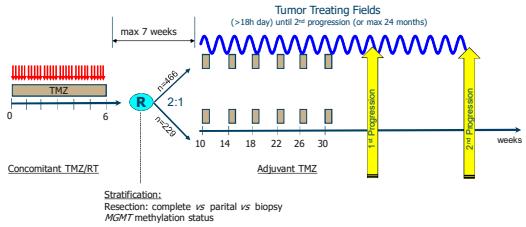
Giladi M et al., *Sci Rep.* 2015 Dec 11;5:18046

Delivery System and Field Distribution

- TTFields are delivered to the supratentorial brain using a portable medical device
- The device includes:
  - a field generator
  - batteries and power supply
  - four transducer arrays at a time
- Following EF-14 termination a second generation device is available
  - half size and weight of gen 1
  - device with battery weigh 2.7 lbs



EF14: Treatment Scheme & Study Design



Endpoints & Statistical Considerations

Primary:

- Progression-free survival
  - blinded central radiology review
  - 80% power; p=0.05; HR = 0.78

Secondary:

- Overall survival
  - Only if PFS positive
  - 80% power; p=0.05; HR=0.76
- **PFS6**
- Landmark survival rates every 12 months
- **Quality of life**

- Randomization 2 : 1
- 700 patients / 4 yrs
  - (630 pts + 10% for lost to follow-up)
- Planned interim analysis
  - *Stupp et al. JAMA Dec 2015*
- **Final analysis**
  - PFS - stratified Log Rank test
    - *P* <0.04574 (*at final analysis)
  - **OS – stratified log Rank test**
    - ***P* <0.0481 (*at final analysis)**
- **All results presented as**
  - **ITT** (intent-to-treat)

*Based on the Lan-DeMets – O'Brien-Fleming method

Safety (Grade 3-4 AEs) in ≥2% of Patients

	TTFields / TMZ (N=456)		TMZ Alone (N=216)	
System Organ Class \ Preferred Term	Grade 3	Grade 4	Grade 3	Grade 4
Number of Patients with >=1 AE	37%	14%	36%	12%
Blood and lymphatic system disorders	9%	4%	9%	2%
Leukopenia	2%	0	<1%	0
Lymphopenia	3%	1%	3%	0
Neutropenia	2%	1%	1%	<1%
Thrombocytopenia	6%	3%	4%	1%
Gastrointestinal disorders	5%	<1%	3%	<1%
General disorders + administration site conditions	9%	<1%	6%	0
Asthenia	3%	0	1%	0
Fatigue	4%	0	3%	0
Gait disturbance	2%	0	1%	0
Infections and infestations	7%	<1%	4%	1%
Injury, poisoning and procedural complications	5%	0	3%	0
Fall	2%	0	1%	0
Medical device site reaction	2%†	0	0	0

†: Grade 1+2 skin irritations in 52% of patients

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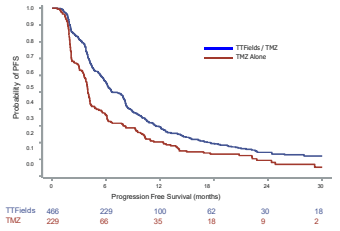
Progression Free Survival - ITT



Progr.-free	TTFields/TMZ	TMZ
Median	6.7 mo 6.1 – 8.1	4.0mo 3.8 – 4.4
Hazard ratio	0.63 (CI 0.52 – 0.76)	
P-value	0.00005	
PFS from diagnosis:		
Median	11.2 mo 10.0 – 11.8	7.8mo 7.3 – 8.2

(n = 695)

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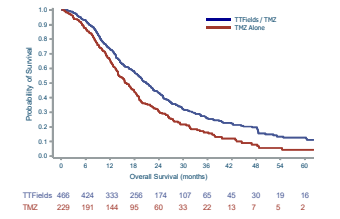
Overall Survival - ITT

(n = 695)



Survival (from random)	TTFields/TMZ	TMZ
Median 95% CI	20.9 mo 19.3 – 22.7	16.0 mo 14.0 – 18.4
2-year 95% CI	43.1 % (38.7 – 48.0)	30.7 % (25.1 – 37.5)
Hazard ratio	0.63 (CI 0.53 – 0.76)	
P-value	0.00006	
Survival from diagnosis (†):		
Median 95% CI	24.5 mo 22.8 – 26.3	19.8 mo 17.6 22.1

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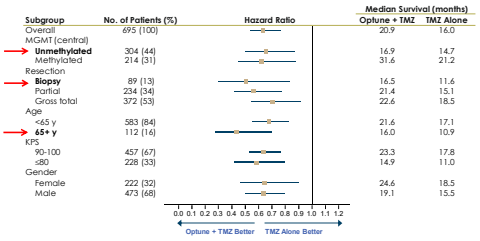
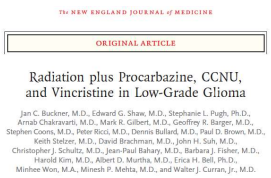
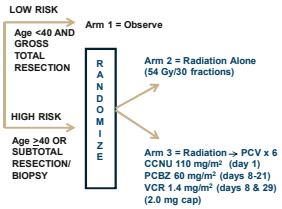
Subgroup Analysis for OS

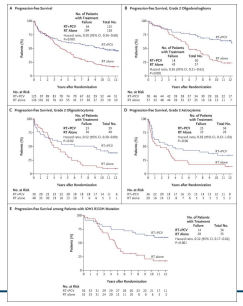


SCHEMA





Progression free survival on 98-02

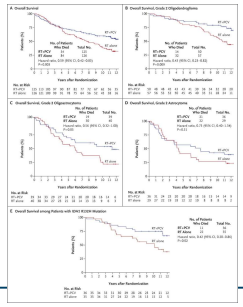


The addition of PCV to radiation treatment improved progression-free survival in all subtypes of grade II gliomas:

1. Oligodendrioglioma
2. Oligoastrocytoma (no longer a diagnosis)
3. Astrocytoma

IDH mutations also predicted for improved benefit with combination therapy

Overall Survival on 98-02



The addition of PCV to radiation treatment improved survival in all subtypes of grade II gliomas:
1. Oligodendrioglioma
2. Oligoastrocytoma
3. Astrocytoma

IDH mutations also predicted for improved benefit with combination therapy

- **The addition of PCV chemotherapy to radiation improves both progression-free and overall survival**
- **This impact was even more pronounced in tumors with mutation in the IDH-1 gene**
- **Although this study confirms the benefit of combined radiation and chemotherapy for low grade gliomas, it is not known if temozolomide will work as well as PCV**

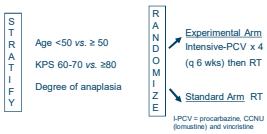
GW 58

Randomized Trials Evaluating Treatment for Newly Diagnosed Anaplastic Oligodendroglioma

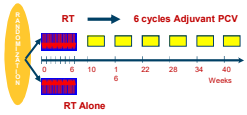
- Two randomized trials comparing radiation and chemotherapy with radiation alone in anaplastic oligodendroglial tumors
- Large, prospective trials:
  - RT vs PCV then RT (RTOG)
  - RT vs RT then PCV (EORTC)
- Diagnosis for inclusion based on histology

GW 59

Study Schemas



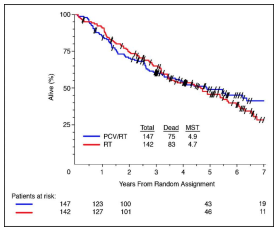
RTOG 9402



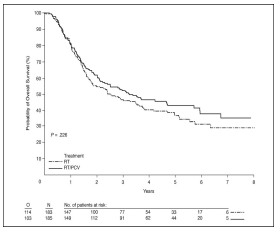
EORTC 26951

GW 60

Initial Results (2006) OS



RTOG 94-02



EORTC 26951

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Long-term Follow Up

- Maturation of outcome data
  - Median survival for 1p 19 q co-deleted cohorts not reached in initial reports (2006)
- Major effort to obtain missing tumor samples to improve statistical power for 1p 19q subgroups
  - RTOG (2006) 70% → 90%
  - EORTC overall 86%

Phase III Trial of Chemoradiotherapy for Anaplastic Oligodendroglioma: Long-Term Results of RTOG 9402

Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

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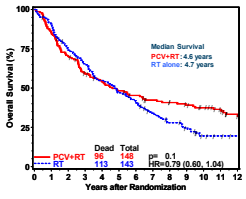
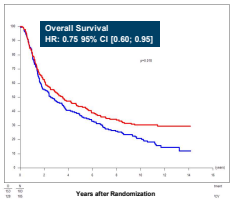
Current Results: All Patients





RTOG 94-02 EORTC 26951

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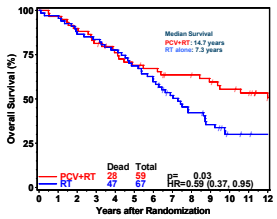
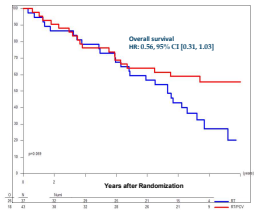
Current Results: 1p 19q co-Deleted

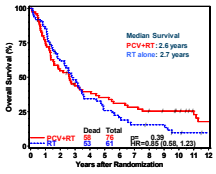


RTOG 94-02

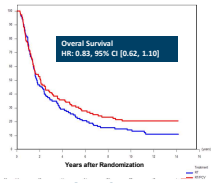


EORTC 26951

Current Results: 1p 19q not-codeleted



RTOG 94-02



EORTC 26951

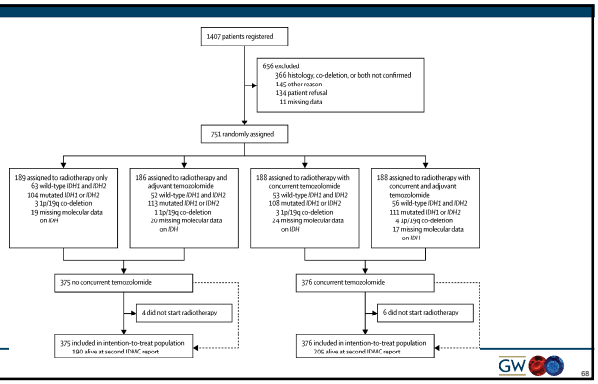
Conclusions

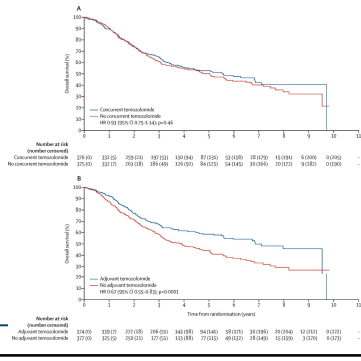
- Long term results of two cooperative group phase III trials determine radiation and chemotherapy as the new standard of care for newly diagnosed anaplastic oligodendroglioma with 1p 19q loss.
  - Perseverance in data and tumor collection
- Establishes 1p 19q loss as a predictive marker in addition to a prognostic marker
  - Underscores importance of prospective tumor collection and hypothesis-based clinical trials.

Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study

Martin J van den Bent, Brigitta Baumert, Sara C Erridge, Michael A Vogelbaum, Anna K Nowak, Marc Sanson, Alba Ariela Brandes, Paul M Clement, Jean Francois Baurain, Warren P Mason, Helen Wheeler, Olivier L Chinot, Sanjeev Gill, Matthew Griffin, David G Brachman, Walter Taal, Roberta Rudà, Michael Weller, Catherine McBain, Jaap Reijneveld, Rodilien H Enting, Damien C Weber, Thierry Lesimple, Susan Clenton, Anja Gijtenbeek, Sarah Pascoe, Ulrich Herrlinger, Peter Hau, Frederic Dhermain, Irene van Heuvel, Roger Stupp, Ken Aldape, Robert B Jenkins, Hendrikus Jan Dubbink, Winand N M Dinjens, Pieter Wesseling, Sarah Nuyens, Vassilis Golfinopoulos, Thierry Gorlia, Wolfgang Wick, Johan M Kros

For non-co-deleted grade 3 gliomas (anaplastic astrocytoma
Novel 2 X 2 design (double randomization)
Radiation vs Chemoradiation
Adjuvant chemotherapy vs observation





Primary Central Nervous System Lymphoma (PCNSL)

- Neurologic Involvement of the CNS in systemic NHL: 5-29%
- PCNSL accounts for 1-2% of NHL
- Large increase in incidence for both population at risk:
  - Immunocompetent
  - Immunocompromised
    - Aids
    - Organ allograft recipients
    - Congenital

- Focal Lesion most common presentation: others include diffuse, uveal, leptomeningeal, and intramedullary.
- Infiltrates normal brain diffusely.
- Spreads along CSF pathways.
- Rarely spreads outside the CNS.

Recognized subtypes:
Immunodeficiency-associated CNS lymphomas
AIDS-related diffuse large B-cell lymphoma
EBV-positive diffuse large B-cell lymphoma
Lymphomatoid granulomatosis
Primary CNS posttransplant lymphoproliferative disorder
Intravascular lymphoma
MALT lymphoma of the dura

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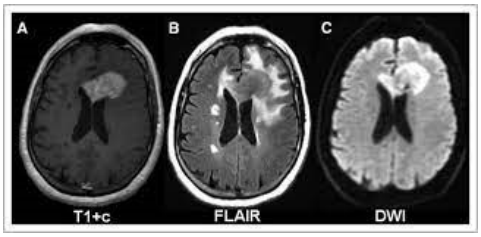
Characteristic imaging



From: https://www.drprempillay.org/brain/latest-updates-on-cns-lymphoma/

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PCNSL: Diagnosis/Staging

- Lumbar Puncture (if safe)
  - 80% of patients have a CSF pleocytosis
  - <10% have obvious lymphomatous involvement of CSF.
- Surgery: diagnosis, little data to support resection
- CNS Axis staging:
  - Spinal evaluation (MRI)
  - Ophthalamic Slit Lamp Examination
    - 10-20% of patients develop lymphomatous uveitis.
- Systemic staging
  - Physical exam, CxR, bloods
    - ? Utility of BM bx, body CT scans, gallium scans

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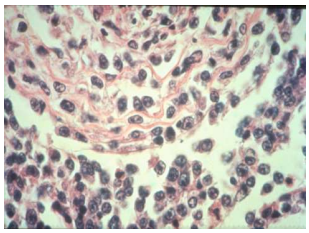
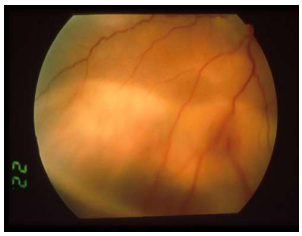
PCNSL: Histology

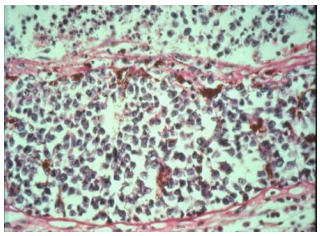
- Most are diffuse large B-cell lymphoma (>90%)
- Rarely Burkitt, low grade or T cell
- B cell with three molecular subgroups
  - B-cell like
  - Activated B-cell like
  - Type 3
- NfkappaB activation in B cell subtype



GW 73

Ocular involvement





GW 74

Primary CNS Lymphoma Treatment

Radiotherapy

- Historically standard Tx
- 80% radiographic CR
- Recurrence local +/- CSA
- 14-18 month median survival
- Associated with significant neurotoxicity in patients over 60

Chemotherapy

- Chemotherapy appears much more effective in non-irradiated tumors.
- Typical DNHL treatment regimens are not optimal
- BBB crossing agents (e.g. methotrexate, cytarabine, topotecan, temozolomide) seem to be best
- Rituxan also has activity.
- Glucocorticoids gives response rates up to 40%:
  - Direct lymphotoxic effect
  - Can obscure diagnosis (Ghost tumor)

GW 75

PCNSL: Pre-Radiation Chemotherapy

	# Pts	Age	Chemotherapy	Response	Radiation (cGy)	Survival (mo)
RMH:	10	53	MACOP-B	90% CR	4000-1500	14
MGH:	13	62	hdMTX	69% CR	3000	27+
OHSU:	39	56	CTX/MTX/PCB +BBBD	85% CR	0 or 5000	41
MSKCC:	31	58	Hd/tMTX/araC	77% PR	4000-1440	42.5
RTOG: (88-06)	51	60	CHOP		4140+1440	16.1
Blay:	25	51	COP/COPADEM	56% CR	2000+2000	70% 5yr

Traditonal NHL chemotherapy not very effective

Table 1. Prospective Upfront Treatment Trials in Primary CNS Lymphoma

First Author	Year	Agents	No. of Patients	Median Age (years)	ORR, PR+CR (%)	Median PFS (months)	Median OS (months)
Radiation only							
Nelson[23]	1992	RT(40+20 boost)	41	NR	21/26 (80)	NR	12.2
Chemoradiation							
DeAngelis[25]	1992	M(1)+RT(40+14 boost)+AraC(3)	31	58	27/31 (87)	41	42.5
Glass[26]	1994	M(3.5)+RT(30-40)	25	56	23/25 (90)	32	33
Schultz[27]	1996	CHOP+RT(41.4+18 boost)	52	NR	10/52 (19)	9.2	16.1
O'Neill[28]	1999	CHOP+RT(50.4) + AraC	55	60	32/53 (60)	6.7	9.7
Mead[29]	2000	RT(40+14 boost)±CHOP	53	57	NR	10 *v* 22	NR
O'Brien[30]	2000	M(1)+RT(45+5.4 boost)	46	58	44/46 (96)	NR	33
Abrey[31]	2000	M(3.5)+P(100)+V(1.4)+AraC(3)+IT M+IT A+RT(45)	52	65	49/52 (94)	NR	60
Ferreri[32]	2001	M(3)+P(100)+V(1.4)+AraC(3)+ RT(45)	13	54	12/13 (92)	18	≥ 25
DeAngelis[33]	2002	M(2.5)+V(1.4)+P(100)+AraC(3)+IT M+RT(45 Gy)	102 (98 treated)	56.5	47/50 (94)	24	37
Poortmans[34]	2003	M(3)+Ten(100)+B(100)+pred(60)+ IT M+IT A+RT(40)	52	51	42/52(81)	NR	46
Ferreri[35]	2009	M(3.5)+/−AraC(2)+RT(45)	79	59/58	27/39 (69) *v* 16/40 (40)	3 *v* 18	NR
Thiel[7]	2010	M(3;+ifos)±RT(45)	526 (all)/318 (PPP)	61	283/526 (53)	18.3 *v* 11.9	32.4 *v* 37.1
Morris[36]	2013	R(500)+M(3.5)+V(1.4)+P(100)+ RT(23.4)	52	60	41/52 (78)	92.4	Not reached
Glass[37]	2016	R(375)+M(3.5)+T(100)+RT(36)	66	57	30/35 (86)	63	90
Chemo only							
Herlinger[38]	2005	M(8)	37	60	13/37 (35)	10	25
Batchelor[5]	2003	M(8)	25	60	17/23 (74)	12.8	22.8+
Pels[39]	2003	M(5)+AraC(3)+V(2)+ifos(800)+ dex(10)+cyclo(200)+IT M+IT A+IT P	65	62	43/61 (71)	21	50
Rubinstein[40]	2013	R(375)+M(8)+T(150)+AraC(2) + eto(40)	44	61	34/47(72)	48	Not reached
Ferreri[41]	2016	M(3.5)+AraC(2)±R(375)±thio (30)	227	58/57/57	40/75 (53)/51/69 (73)/65/75 (86)	6/20/not reached	12/30/not reached
Omuro[61]	2015	M(3.5)+V(1.4)+P(100)+AraC(3) *v* M(3.5)+T(150)	95	72/73	37/45 (82) *v* 34/42 (74)	9.5 *v* 6.1	31 *v* 14
Chemo only with SCT							
Abrey[43]	2003	M(3.5)+AraC(3); BEAM	28 (14 transplanted)	53	induction: 16/24 (57), SCT 11/14 (77)	5.6	Not reached
Colombat[44]	2006	M(3)+B(100)+eto(100)+pred (60); BEAM+RT(30)	25 (17 transplanted)	52	induction: 21/25 (84), SCT 16/16 (100)	40	Not reached
Illerhaus[45]	2006	M(8)+AraC(3)+thio (40 mg/m2); B(400)+thio(5mg/kg)+RT(45)	30 (23 transplanted)	54	induction: 21/30 (70), SCT 21/21 (100)	NR	Not reached
Omuro[42]	2015	R(500)+M(3.5)+V(1.4)+P(100); thio(250)+cyclo(60)+bus(3.2)	32 (26 transplanted)	57	induction: 31/32 (97), SCT 24/26 (92)	Not reached	Not reached
Illerhaus[46]	2016	R(375)+M(8)+AraC(3)+thio(40); R(375)+B(400)+thio(5mg/kg)	79 (73 transplanted)	56	induction: 73/79 (92), SCT: 72/79 (91)	74	Not reached

Abbreviations: A, cytarabine; AraC, cytarabine (g/m^2); B, carmustine (mg/m^2); BEAM, carmustine, etoposide, cytarabine, melphalan; bus, busulfan (mg/kg); chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete remission; cyclo, cyclophosphamide (mg/m^2); dex, dexamethasone; eto, etoposide (mg/m^2); ifos, ifosfamide (mg/m^2); IT A, intrathecal cytarabine; IT M, intrathecal methotrexate; IT P, intrathecal prednisone; M, methotrexate (g/m^2); NR, not reported; ORR, overall response rate; OS, overall survival; P, procarbazine (mg/m^2/day); PFS, progression-free survival; PPP, per-protocol population; PR, partial remission; pred, methylprednisone (mg/m^2); R, rituximab (mg/m^2); RT, radiation therapy (dose used in Gy); SCT, stem cell transplant; T, temozolomide (mg/m^2); Ten, teniposide (mg/m^2); thio, thiotepa (mg/m^2); V, vincristine (mg/m^2).

Many single arm studies hard to compare as eligibility criteria vary

Table 2. Salvage Regimen in Primary CNS Lymphoma

First author	Year	Agents	No. of Patients	Median Age (years)	ORR, PR+CR (%)	Median PFS (months)	Median OS (months)
Retrospective							
Herrlinger[70]	2000	PCV	7	57	6/7 (86)	NR	39
Arellano-Rodrigo[71]	2003	Eto+ifos+AraC	16	54	6/16 (37)	4.5	6
Wong[72]	2004	Ritux+temozolomide	7	64	7/7 (100)	6	8
Enting[73]	2004	Ritux+temozolomide	15	69	8/15 (53)	2.2	13.6
Plotkin[74]	2004	HD-MTX	22	58	20/22 (91)	25.8	61.9
Nguyen[75]	2005	WBRT	27	66.8	20/27 (74)	9.7	10.9
Hottinger[76]	2007	WBRT	48	62	38/48 (79)	10	16
Makino[77]	2012	Temozolomide	17	68	8/17 (47)	1.9	6.7
Wong[78]	2012	Temozolomide	7	58	1/7 (14)	2	4
Zhang[79]	2013	Pemetrexed	30 (18 PCNSL)	67	18/30 (60)	4.1	22.6
Pentsova[80]	2014	HD-MTX	39	66	33/39 (85)	16	41
Chamberlain[81]	2014	Bendamustine	12	61.5	6/12 (50)	3.5	5
Houillier[82]	2015	Lenalidomide	6	73.5	3/6 (50)	1.5	2.5
Chamberlain[83]	2016	AraC	14	60	5/14 (36)	3	12
Prospective							
Fischer[84]	2006	Topotecan	27	51	9/27 (33)	2	8.4
Reni[85]	2007	Temozolomide	36	60	11/36 (31)	2.8	3.9
Soussain[86]	2008	CYVE+SCT	43	52	20/40 (50)	11.6	18.3
Batchelor[87]	2011	Ritux	12	64	5/12 (42)	1.9 (57 days)	20.9
Raizer[88]	2012	Pemetrexed	11	69.8	6/11 (55)	5.7	10.1
Rubenstein[59]	2013	IT Ritux+IT M	14 (6 PCNSL)	61	6/14 (43)	1.2	NR
Nayak[89]	2013	Ritux+temozolomide+pred	16	63	5/14 (36)	1.6 (7 weeks)	Not reached
Korfel[90]	2016	Temsirolimus	37	70	20/37 (54)	2.1	3.7

Abbreviations: AraC, cytarabine; CYVE, cytarabine plus etoposide; CR, complete response; eto, etoposide; HD-MTX, high-dose methotrexate; ifos, ifosfamide; IT M, intrathecal methotrexate; IT Ritux, intrathecal rituximab; NR, not reported; ORR, overall response rate; OS, overall survival; PCNSL, primary CNS lymphoma; PCV, procarbazine, CCNU (lomustine, bleomycin, vinblastine, dexamethasone), vincristine; PFS, progression-free survival; PR, partial response; pred, methylprednisone; Ritux, rituximab; SCT, stem cell transplant; WBRT, whole-brain radiation.

PCNSL: High-Dose Methotrexate

- Most active single agent.
- Anti-tumor activity related to concentration and exposure time of drug.
- Treating CNS disease with methotrexate gives large therapeutic window since the BBB is probably not permeable to reduced folates (leucovorin).
- Optimal dose and administration schedule for PCNSL not determined.
  - Currently bolus injection given over 2-3 hours is most commonly utilized.
  - Most commonly utilized doses are 3-8 gms/m2 every 2-3 wks
- Various studies report response rates for single agent MTX to be 52-88% with 2 year survivals of 58-72%.
- Various studies report response rates for methotrexate in combination with other agents of 70-94% with 2 year survivals of 43-73%.

GW 79

Two Active PCNSL Regimens Studied by NCI Cooperative Groups

RTOG 93-10

The "MSKCC Regimen"

- 5 cycles MTX (2.5 gms/m2)/vincristine procarbazine/intraventricular MTX followed by whole brain XRT
- 102 patients
- Following chemotherapy: 58% CR, 36% PR
- 24 month median PFS
- 36.8 month median survival
- Age a significant prognostic factor (survival 50.4 months pts <60 y.o.; 21.8 months pts >60 y.o.)
- Significant acute treatment-related toxicity (53% grade 3 or 4)
- Significant severe delayed neurotoxicity (15%)

NABTT 96-07

- hdMTX (8 gms/m^2) every 2 weeks until CR or a maximum of 8 cycles. XRT delayed
- 25 patients
- 53% CR; 22% PR
- Median # cycles to CR was 6
- 12.8 months median PFS.
- 22.8+(not yet reached) months median survival
- 4/5 CR for intra-ocular lymphomas
- 2/3 LMD (+ CSF cytology) progressed in brain during MTX tx
- Significant acute treatment-related toxicity (48% grade 3 or 4)
- No delayed severe neurotoxicity

GW 80

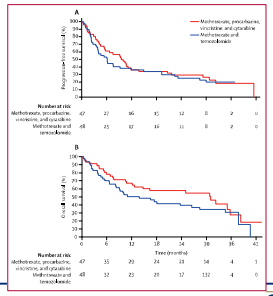
The R-MVP Regimen: The Current Standard

- Multicenter phase 2 trial
- Rituximab, MTX, PCB,VCR,WBRT(either 23.4 Gy or 45 Gy) followed by Hi-DAC.
- 52 pts; med. Age 60, KPS 70
- 60% CR with R-MVP
- PFS = 3.3 yrs; Overall Survival 6.6 yrs.
- Improved executive function and memory post R-MVP. Remained relatively stable long-term.

GW 81

MPV-A vs. MT in Elderly Patients with PCNSL

- >60 y.o.
- KPS >40
- Prophylactic G-CSF
- ORR: MPV-A (82% vs. 72%)
- PFS: MPV-A 9.5 vs 6.1 months
- OS: MVP-A (31 vs.14 months)



Omuro et al. *Lancet Oncology*, 2015.

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Consolidation Dose Intensive Chemotherapy and ASCT for PCNSL

Table 5. Trials or case series (20 or more patients) reporting outcomes in newly diagnosed PCNSL patients treated with consolidation HDC-ASCT after methotrexate-based initial treatment

Reference	N	Induction regimen	ORR to induction	HDC-ASCT regimen	Received consolidation HDC-ASCT	Received consolidation WBRT*	ORR to HDC-ASCT	Med F/u (mo)	ITT 3-y PFS	ITT 3-y OS
Regimens including WBRT to all patients										
29	30	MTX 8 g/m², Ara-C, thiotepa	80%	BCNU, thiotepa + WBRT	23 (77%)	21 (70%)	100%	63	ns	69%
33	25	MTX 3 g/m², BCNU, VP16, methylpred	84%	BEAM + WBRT	17 (68%)	24 (96%)	100%	34	58%	64%
Regimens with WBRT to patients achieving less than CR										
34	28	MTX 8 g/m²	61%	Busulfan, thiotepa + WBRT if no CR	16 (70%)	8 (29%)	69%	15	45%	48% (2 y)
Regimens without WBRT										
17	28	MTX 3.5 g/m², Ara-C	57%	BEAM	14 (50%)	0	77%	28	25%	60%
This study	32	MTX 3.5 g/m², rituximab, procarbazine, vincristine	97%	Thiotepa, busulfan, CTX	26 (81%)	0	92%	45	79%	81%

*Number of patients who received WBRT as part of initial treatment, in the absence of tumor progression.
Ara-C, cytarabine; CTX, cyclophosphamide; Med F/u, median follow-up; methylpred, methylprednisolone; MTX, methotrexate; na, not available; ORR, objective response rate; VP-16, etoposide.

High morbidity rate
May be best for younger pts
Good perf. status

Omuro et al. *Blood*, 2015.

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PCNSL: Unique features

Leptomeningeal Disease

- 5-30% have evidence of LMD at presentation.
- 40-50% of patients will have pathologic evidence of PCNSL invading the subarachnoid space.
- Majority of patients who relapse in the eptomeninges had evidence of LMD at presentation
- 90% of patients who relapse in the leptomeninges, also relapse in the brain parenchyma
  - Does treating LMD really change the overall prognosis of patients with PCNSL?

Ophthalmologic Involvement

- Untreated intraocular lymphoma will ultimately lead to CNS disease in the majority of patients.
- XRT associated with significant long-term morbidity
- Blood-eye barrier possibly more formidable than BBB.
- Systemic hdMTX can achieve lymphotoxic concentrations of MTX in the vitreous/aqueous humor
- Intra-ocular injection of MTX can temporarily eradicate disease and greatly improve vision.
  - ? No perspective study
  - No long-term follow-up

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Chemotherapy for PCNSL: What We Do Not Know

- The role of XRT in conjunction with chemotherapy
- Optimal dose and administration schedule for MTX
- Other agents add to the effectiveness of MTX
  - What agents
  - What dose and administration schedule
- Role of dose intense chemotherapy (ABMT)
- Is there a role for BBBD?
- Should the presence of overt leptomeningeal and/or intraocular disease change treatment approach.
- New agents undergoing evaluation:
  - Lenalidomide
  - Ibrutinib
  - Buparlisib
  - Nivolumab/pembrolizumab
  - Pemetrexed
  - Pomalidomide
  - Temsirolimus

PCNSL: Current Treatment Recommendations

- Most patients should receive pre-radiation chemotherapy with a regimen that at least contains high-dose methotrexate.
- Radiation therapy following chemotherapy may improve survival further; although at the risk of significant long term neurotoxicity particularly in elderly patients.
- Older (>70 y.o…?) patients should probably not receive combined modality treatment or at least not full dose WBRT.
  - Methotrexate-based regimen optimal if medically appropriate
  - Methotrexate alone if combination not tolerable.
  - XRT alone for poor KPS patients who could not tolerate chemotherapy.
- Strongly encourage enrollment on a clinical trial.

Conclusions and "Take Home" Messages

- Malignant gliomas are staged by tumor grade, not TNM
- Key molecular features such as 1p19q LOH, IDH mutational status and MGMT methylation status assist in diagnosis, prognosis and treatment
- More precise diagnoses have enabled development of standard therapies for glioblastoma and IDH mutated tumors
- Standard of care for glioblastoma remains chemoradiation with temozolomide, but ongoing trials with immunotherapies, viral therapies and novel targeted agents are underway
- Primary CNS lymphoma advances focus on combination chemotherapy regimens; ibrutinib and related agents may have a role; radiation should be delayed in older patients