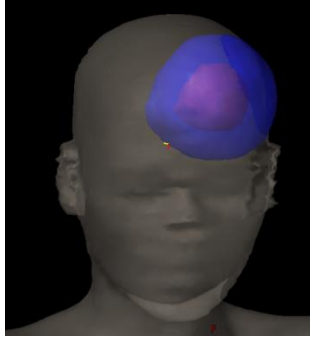


High Grade Gliomas: Advances & evidence based practise

Dr Jayant S Goda MD, DNB, MRes

Clinician Scientist & Professor

Member CNS and hematolymphoid Malignancies DMG

In-Charge Clinical Biology Lab, ACTREC

Tata Memorial Center

Mumbai

AROI-ICRO COURSE

9.7.2021

Email:godajayantsastri@gmail.com

High Grade Gliomas: Trivia

- **High-grade Gliomas**
  - Glioblastoma (GBM),& Gliosarcoma
  - Anaplastic astrocytoma (AA)
  - Anaplastic oligodendroglioma (AO)

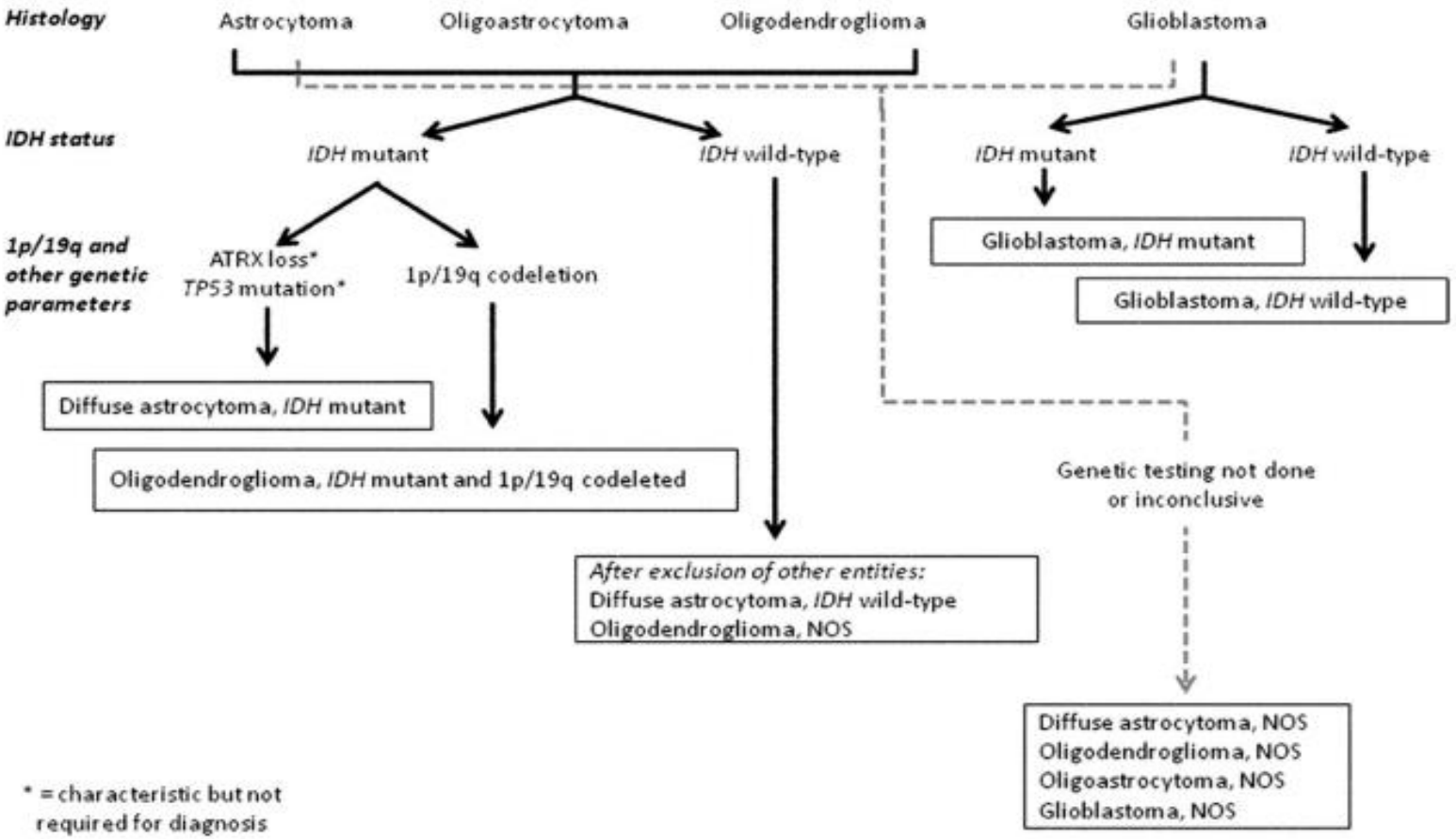
- Histologically :Originate from the supporting neuroglial cells of the CNS.

- GBM, the most common and most aggressive of the primary brain tumors, typically presents in late adulthood.

- AA and AO affect a younger age group and generally have a more protracted clinical course.

HGG: Molecular classification WHO

The classification of malignant gliomas is moving from a morphology-based guide to a system built on molecular criteria.



Glioblastoma : current evidence and Recent Advances

Stupp R: Landmark paper in NEJM 2005

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., et al., 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*

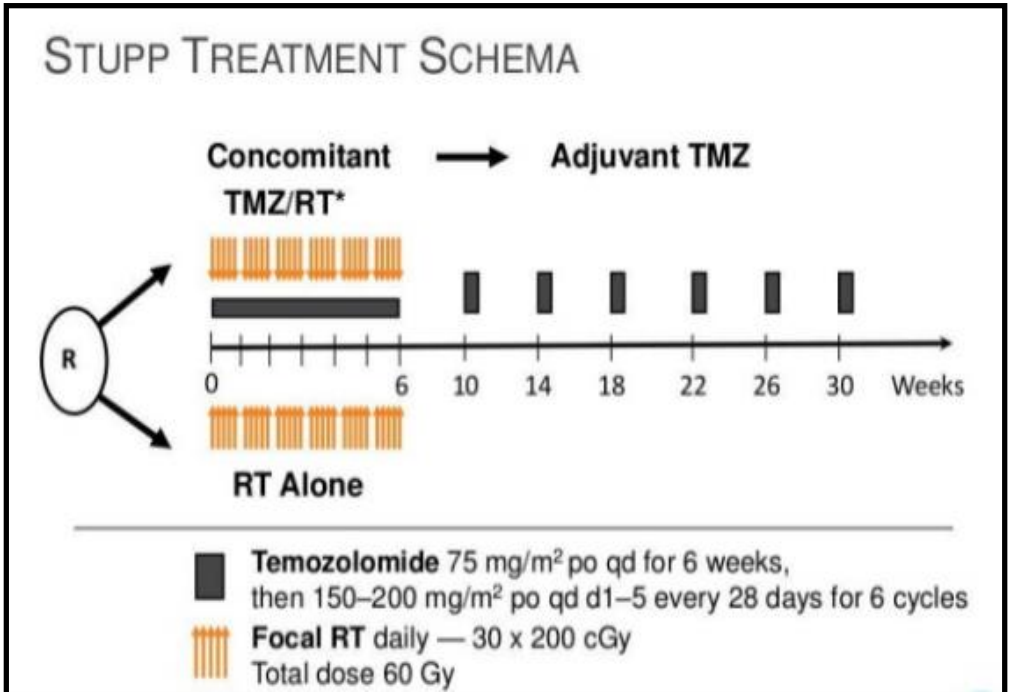
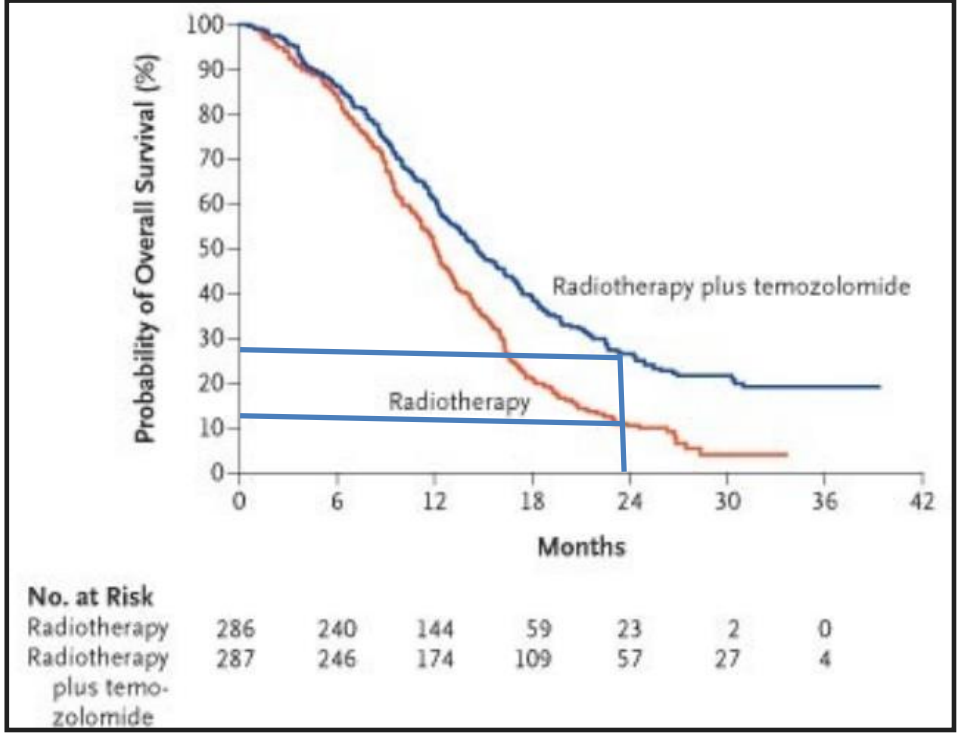


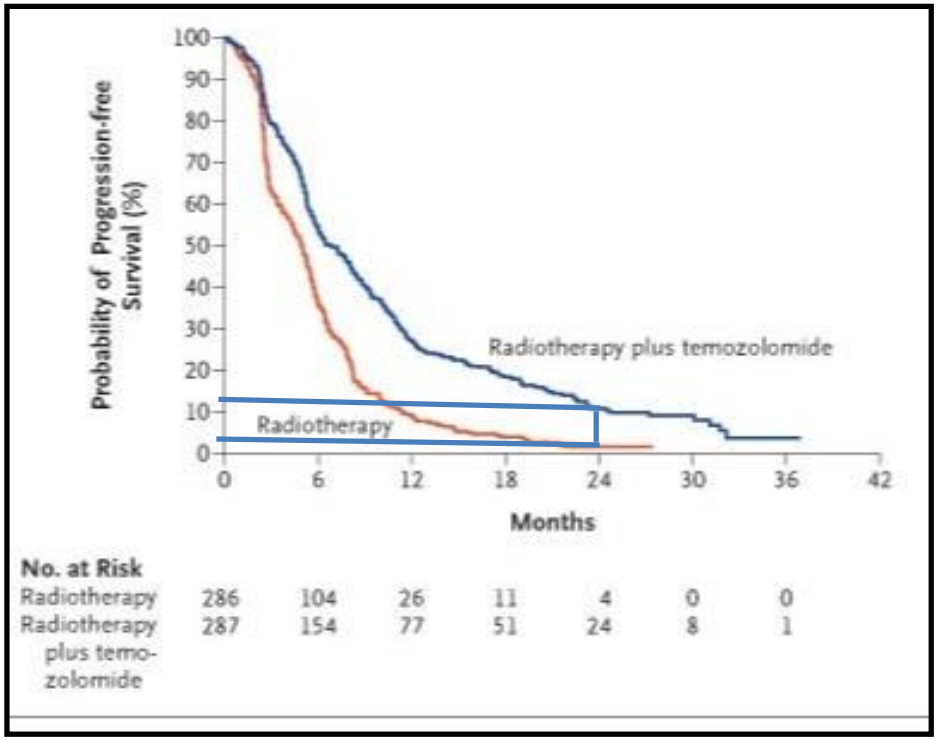
Table 3. Overall and Progression-free Survival According to Treatment Group.*

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	value (95% CI)	
Median overall survival (mo)	12.1 (11.2–13.0)	14.6 (13.2–16.8)
Overall survival (%)		
At 6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
At 12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
At 18 months	20.9 (16.2–26.6)	39.4 (33.8–45.1)
At 24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median progression-free survival (mo)	5.0 (4.2–5.5)	6.9 (5.8–8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
At 12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
At 18 months	3.9 (1.6–6.1)	18.4 (13.9–22.9)
At 24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)



Overall Survival

Progression Free Survival

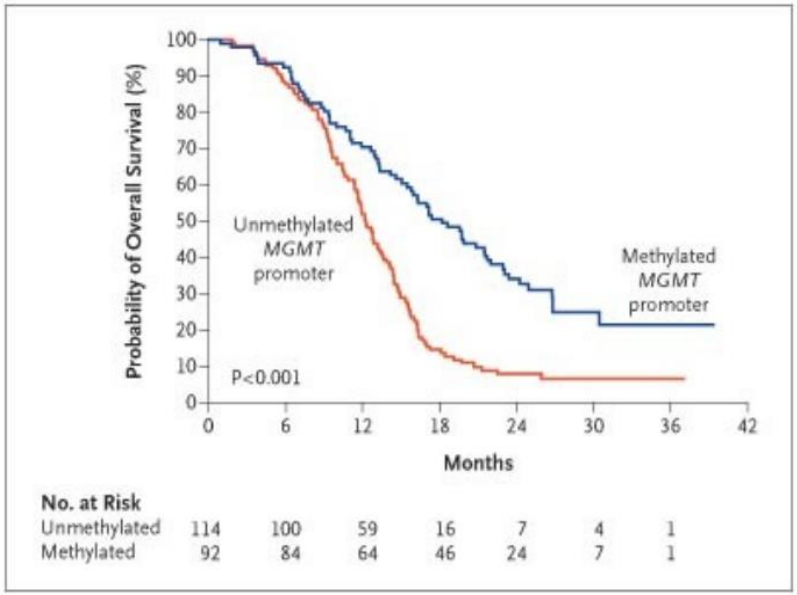


Glioblastoma : current evidence and Recent Advances

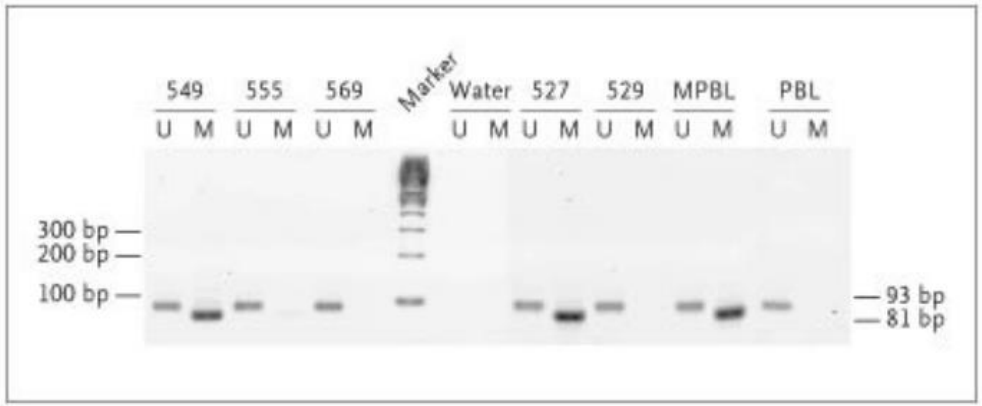
Monica Hegi: Landmark Paper demonstrating the prognostic impact of MGMT ; NEJM 2005

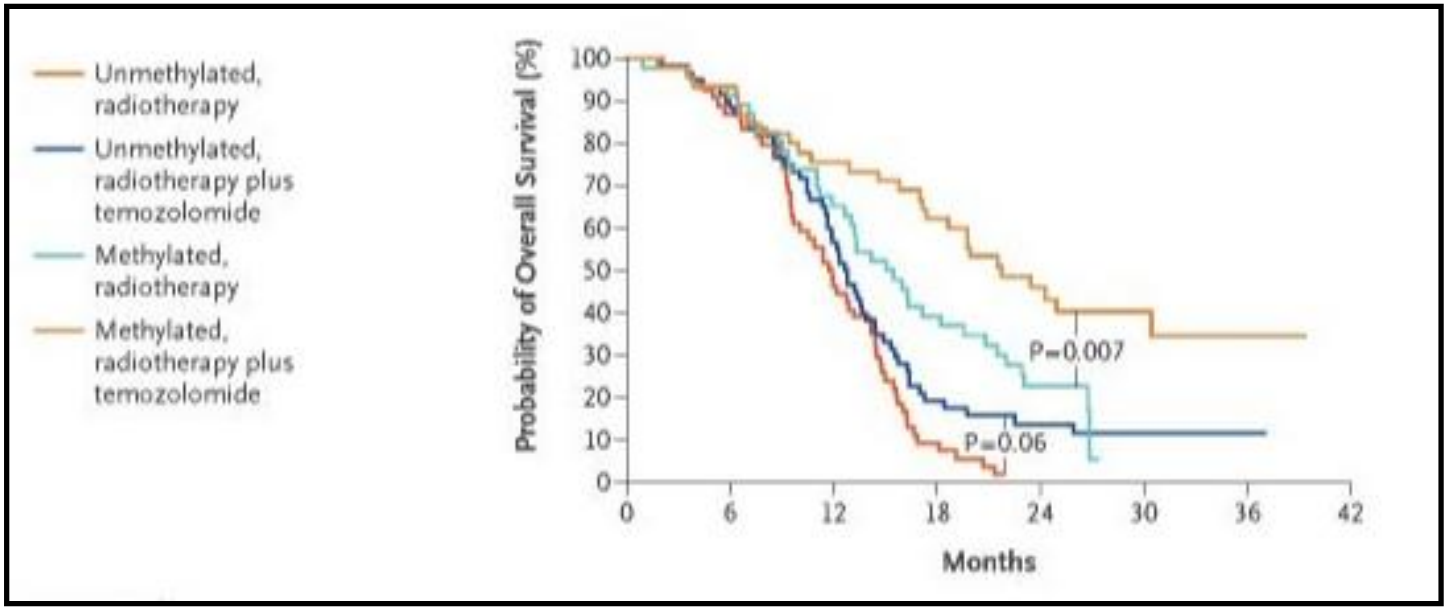
MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

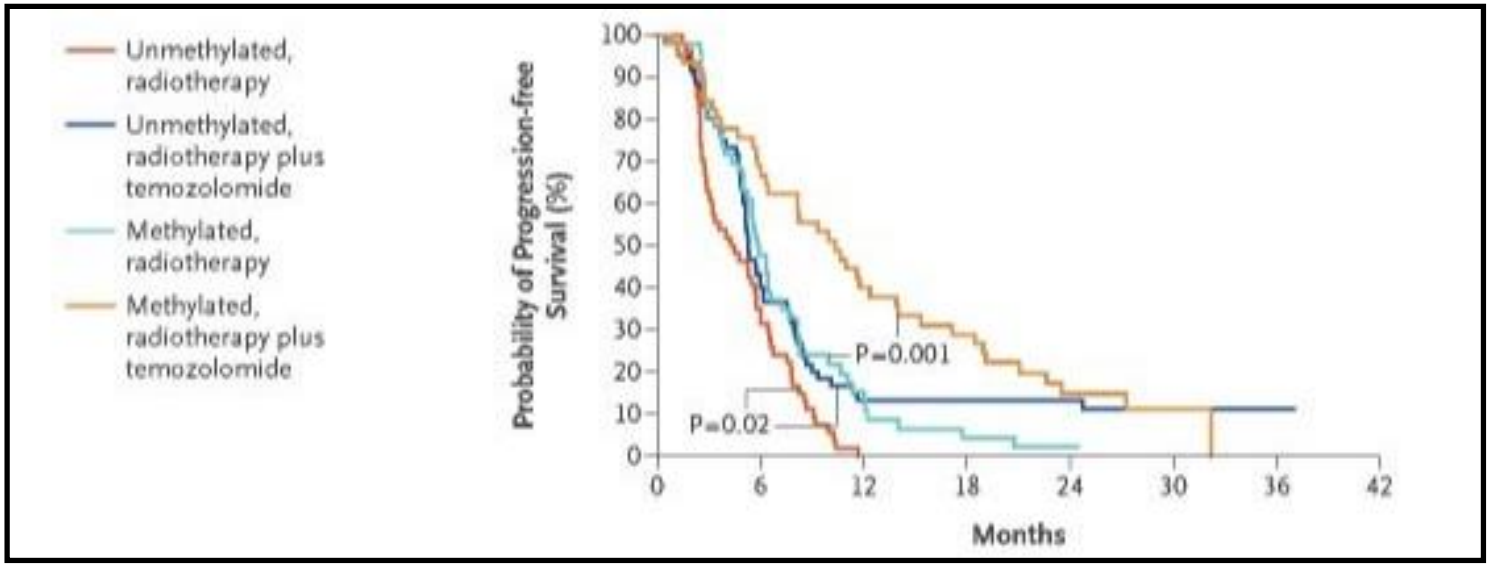
Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., et al.



Methylation Status of the *MGMT* Promoter in Glioblastoma Biopsy Specimens, as Determined by a Nested Methylation-Specific PCR Assay.



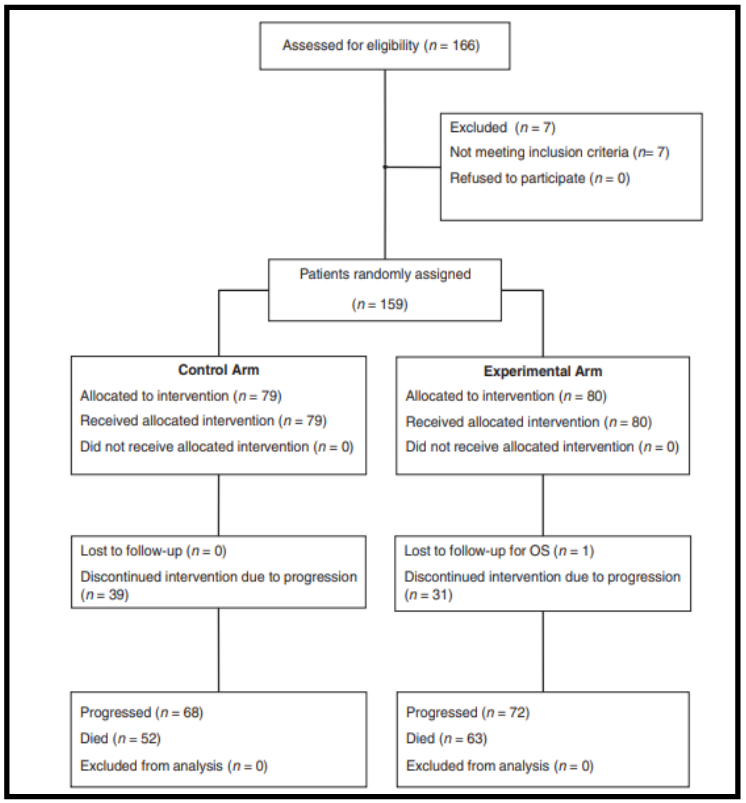

Unmethylated, radiotherapy
Unmethylated, radiotherapy plus temozolomide
Methylated, radiotherapy
Methylated, radiotherapy plus temozolomide
Probability of Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
Months
P=0.007
P=0.06


Unmethylated, radiotherapy
Unmethylated, radiotherapy plus temozolomide
Methylated, radiotherapy
Methylated, radiotherapy plus temozolomide
Probability of Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
Months
P=0.001
P=0.02

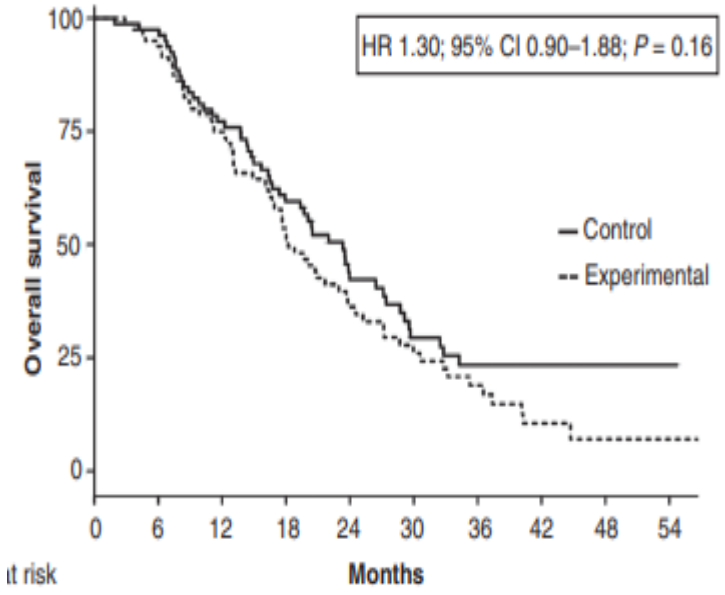
GBM: Adjuvant TMZ 6 vs 12 cycles

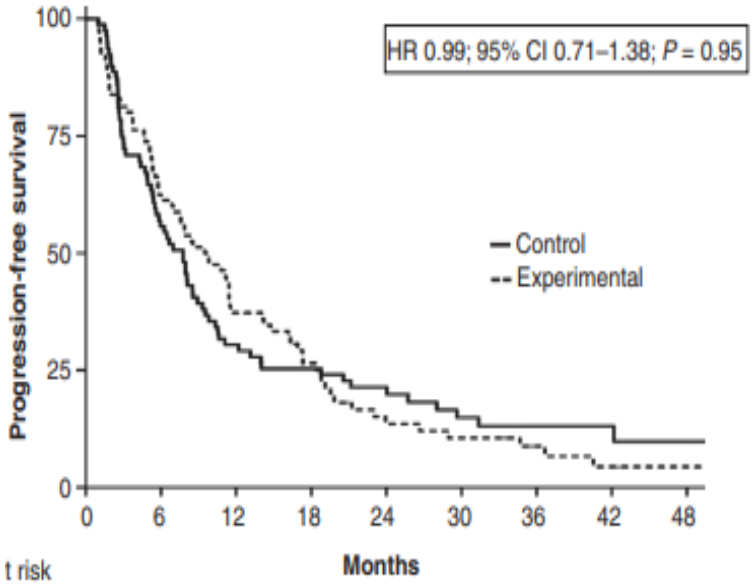
A phase II randomized, multicenter, open-label trial of continuing adjuvant temozolomide beyond 6 cycles in patients with glioblastoma (GEINO 14-01)

Neuro-Oncology, Volume 22, Issue 12, December 2020,

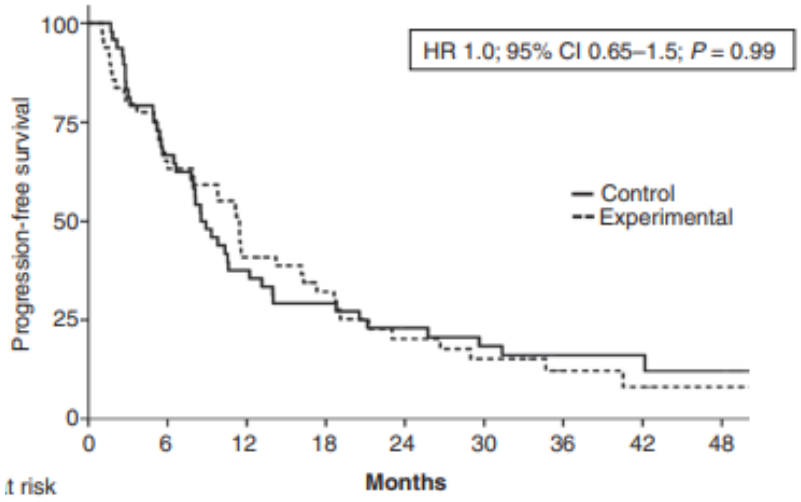


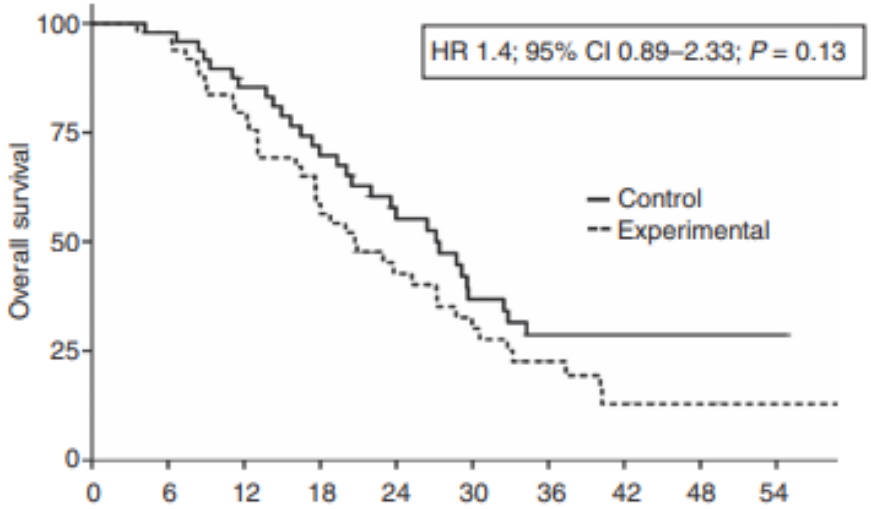
1. Extending adjuvant temozolomide to 12 cycles did not improve 6-month PFS.
2. Extending adjuvant temozolomide did not improve PFS or OS in any patient subset.
3. Extending adjuvant temozolomide was linked to increased toxicities.





Unselected GBM



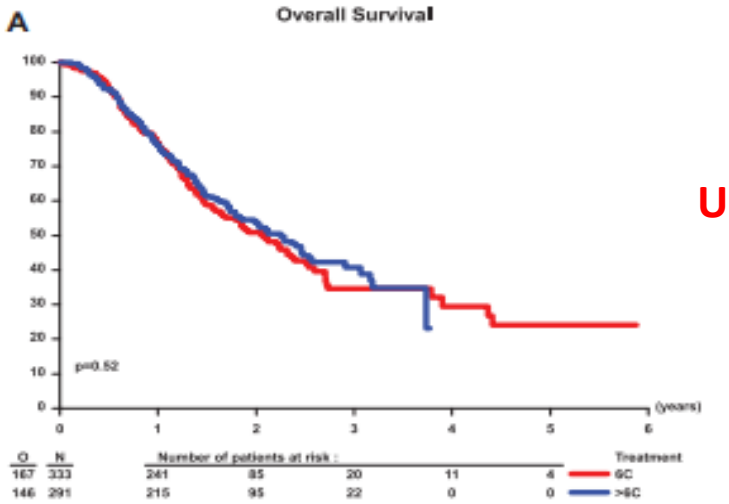


MGMT selected GBM

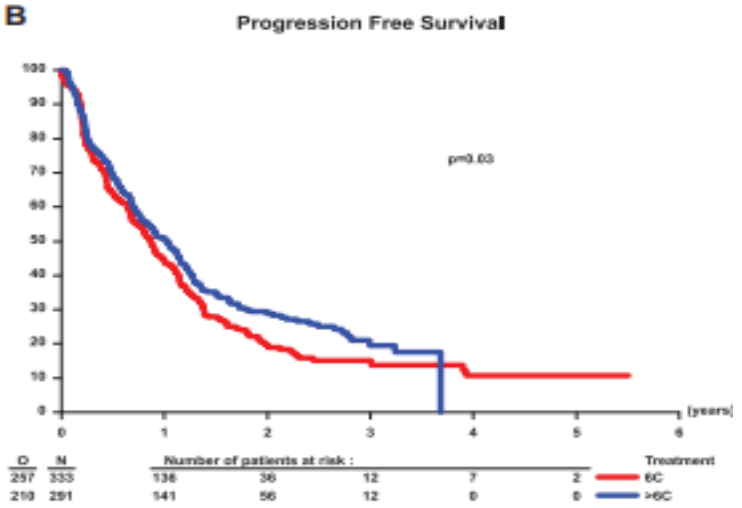
N=2214 from 4 trials
Analysed : 624
TMZ 6 cycles: 333
TMZ 12 cycles:291

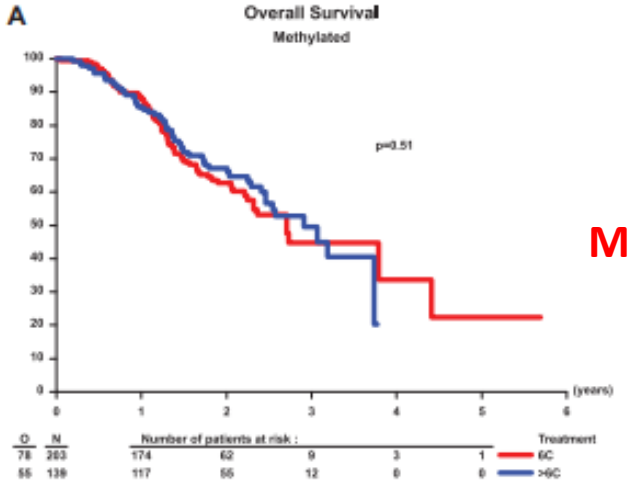
Neuro-Oncology
19(8), 1119–1126, 2017 | doi:10.1093/neuonc/nox025 | Advance Access date 24 March 2017

Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/RTOG

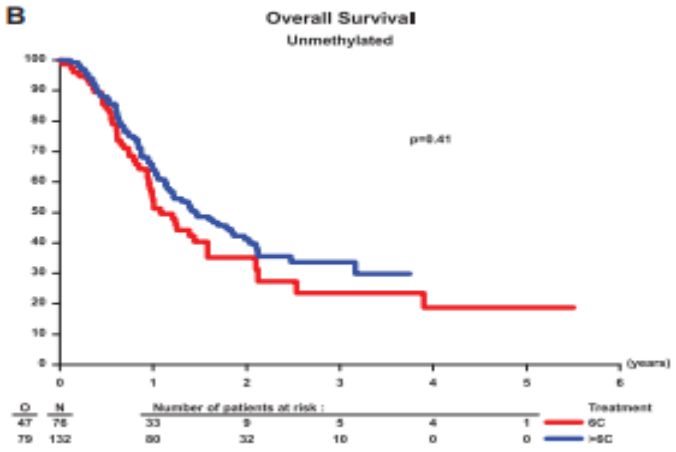


Unselected GBM





MGMT selected GBM



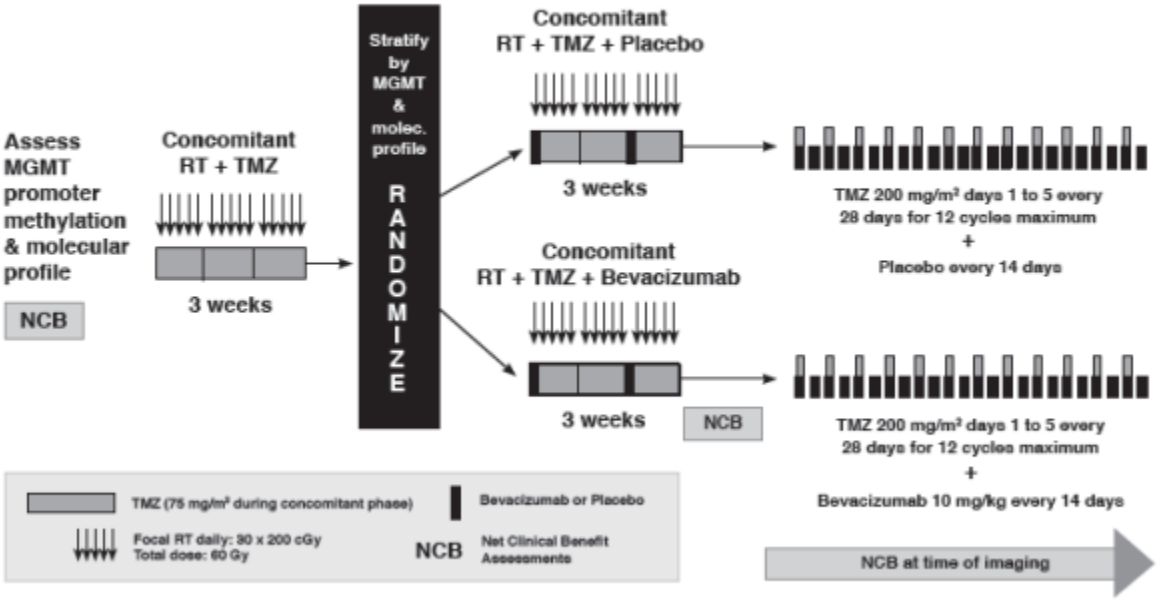
Role of Bevacizumab in newly diagnosed GBM

The NEW ENGLAND JOURNAL of MEDICINE

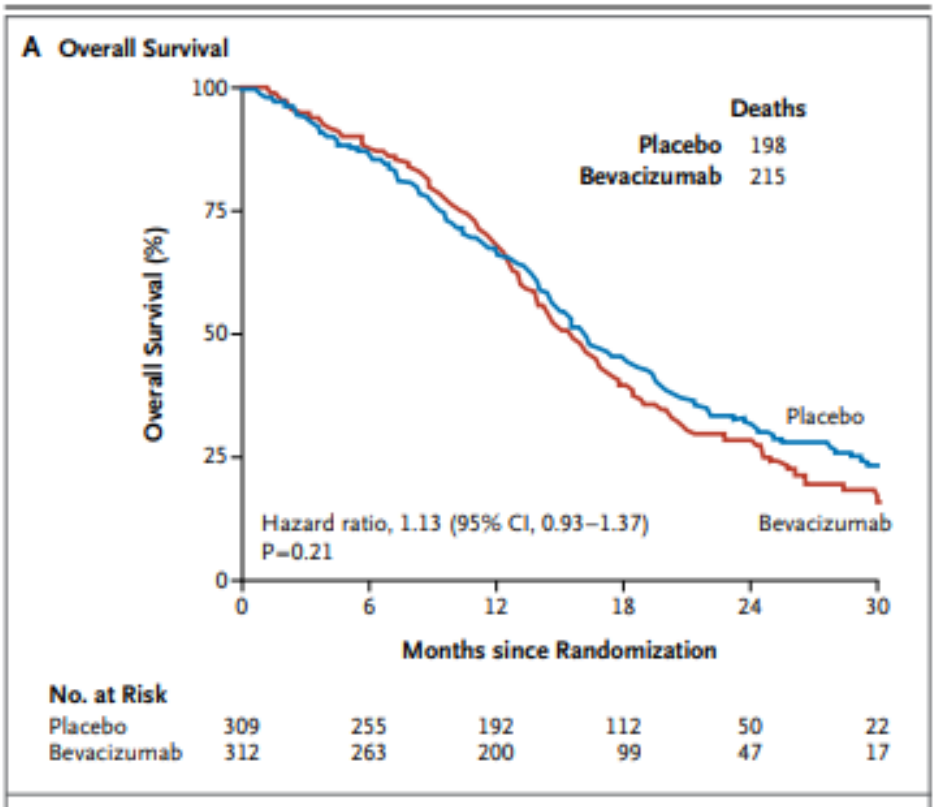
ESTABLISHED IN 1812 FEBRUARY 20, 2014 VOL. 370 NO. 8

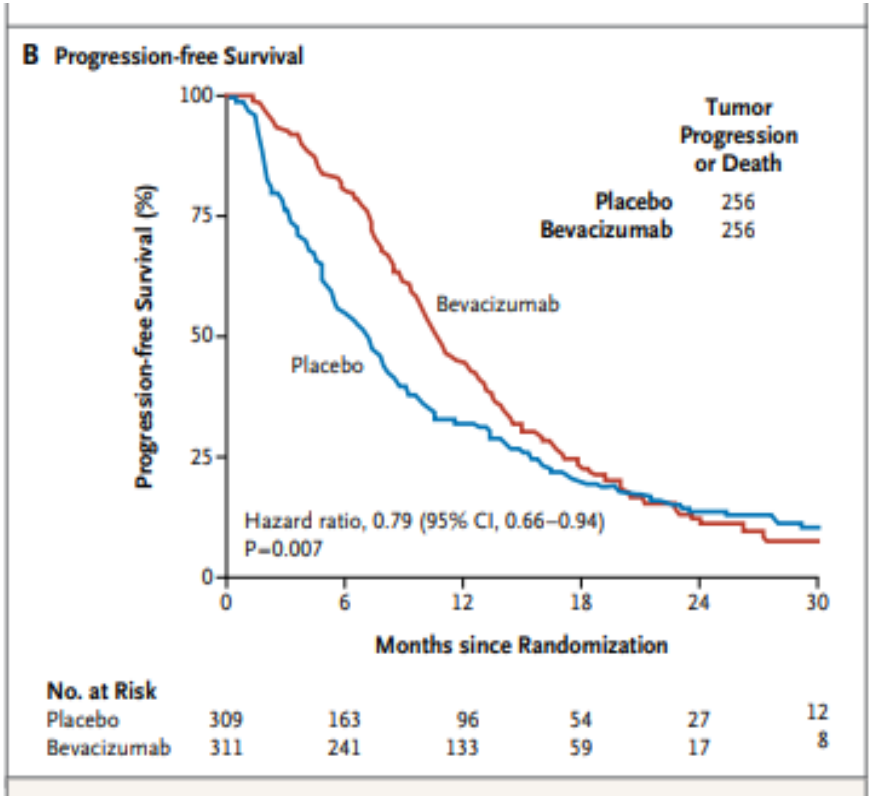
A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

RTOG 0825



Role of Bevacizumab in newly diagnosed GBM:RTOG0825





CONCLUSIONS

- First-line use of bevacizumab did not improve overall survival
- Progression-free survival was prolonged but did not reach the prespecified improvement target

The NEW ENGLAND JOURNAL of MEDICINE

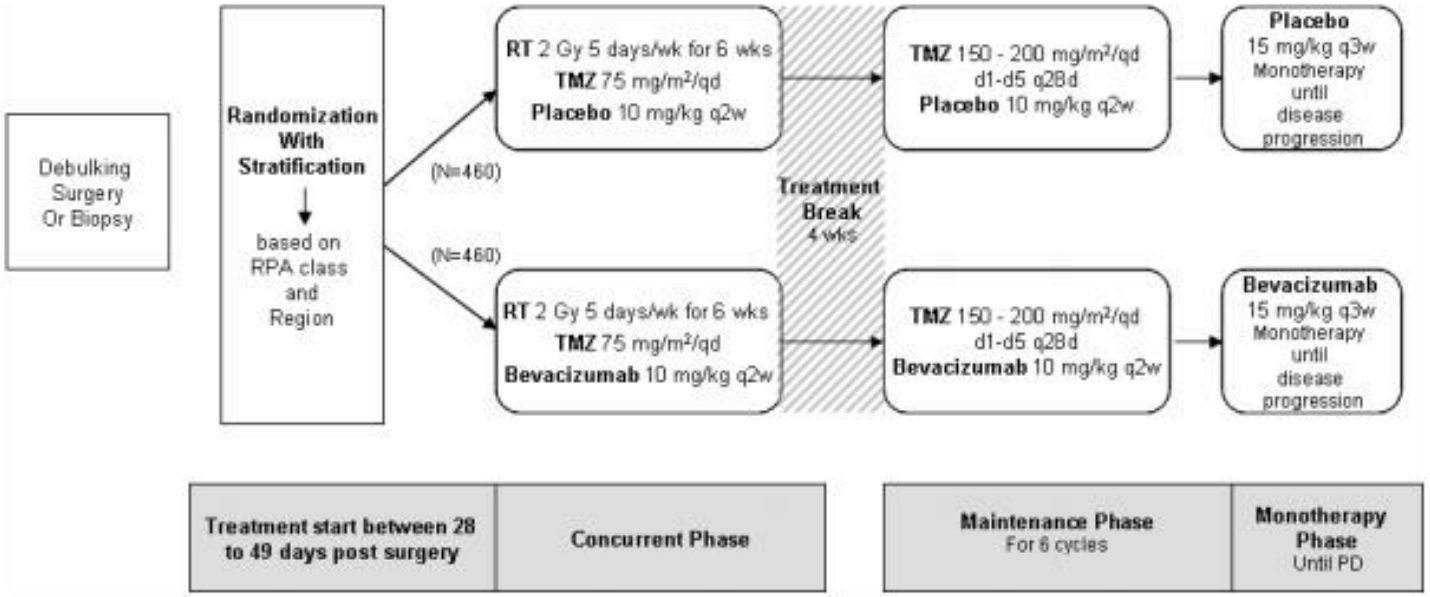
ORIGINAL ARTICLE

Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma

N ENGL J MED 370;8 NEJM.ORG FEBRUARY 20, 2014

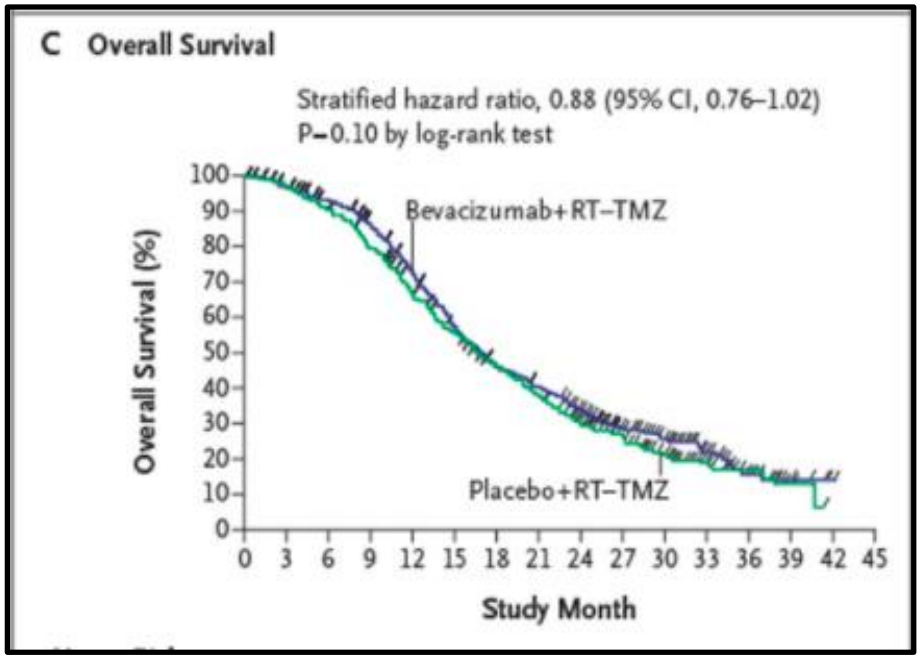
AVAGLIO STUDY

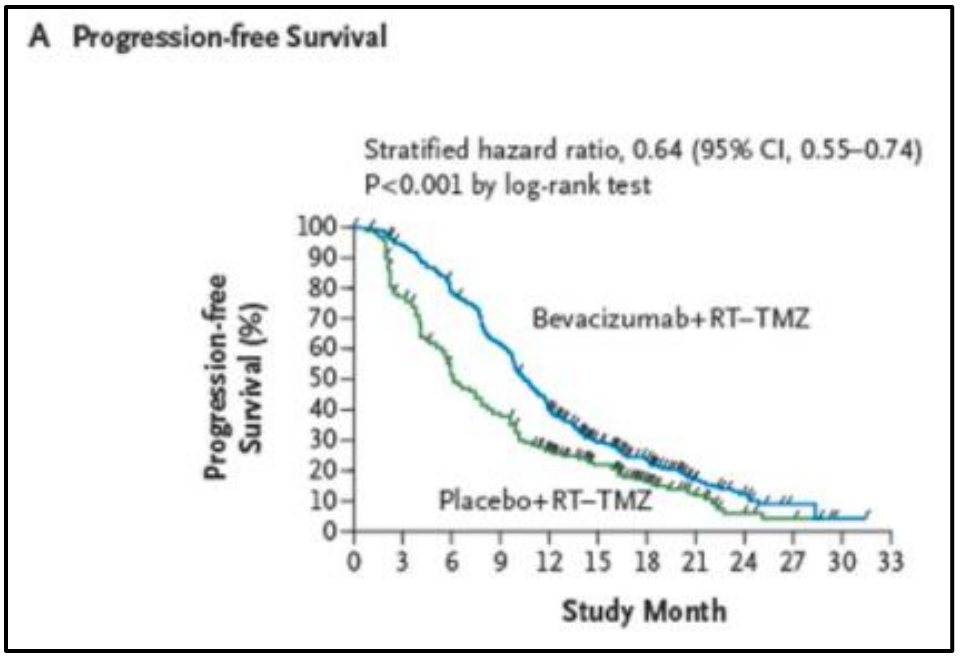
Figure 1: study design



RT: radiation, **TMZ**: temozolomide

Role of Bevacizumab in newly diagnosed GBM:AVAGLIO





Conclusions

- Bevacizumab + radiotherapy–temozolomide did not improve survival in patients with GBM.
- Improved progression-free survival on addition of Bev
- Maintenance of baseline quality of life and performance status were observed with bevacizumab.
- Rate of adverse events was higher with bevacizumab than with placebo.

Advances in GBM Treatment

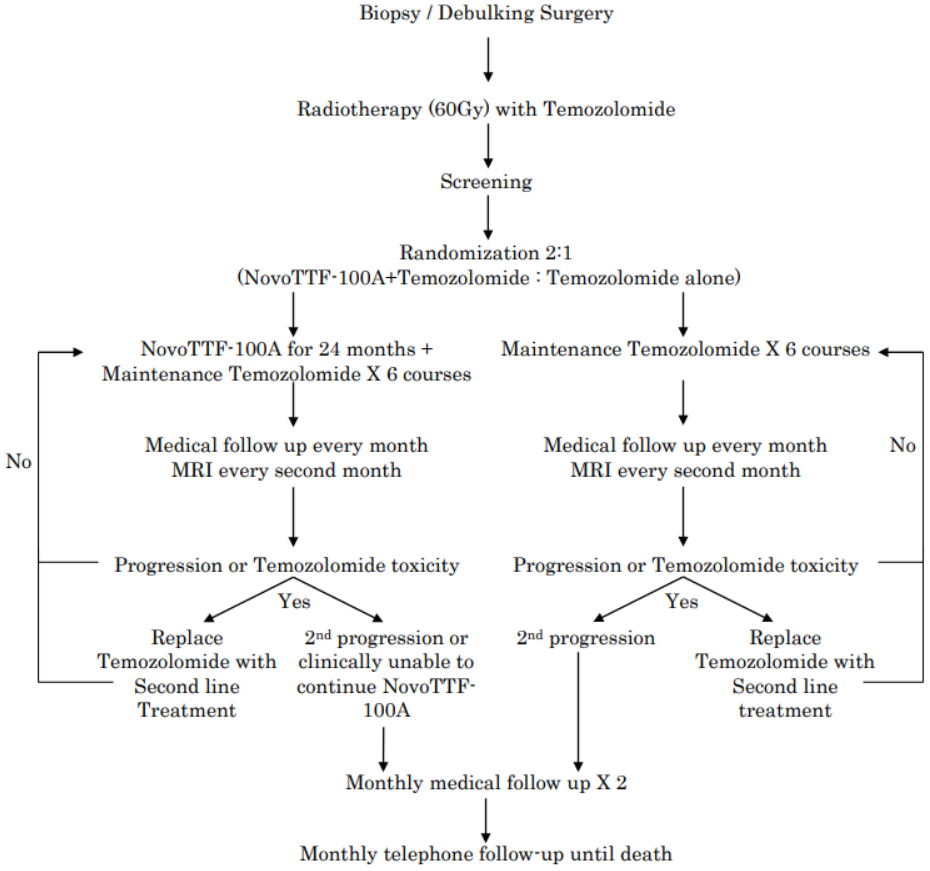
TTF: Tumour Treatment Fields

JAMA | Original Investigation

Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma

A Randomized Clinical Trial

JAMA. 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718

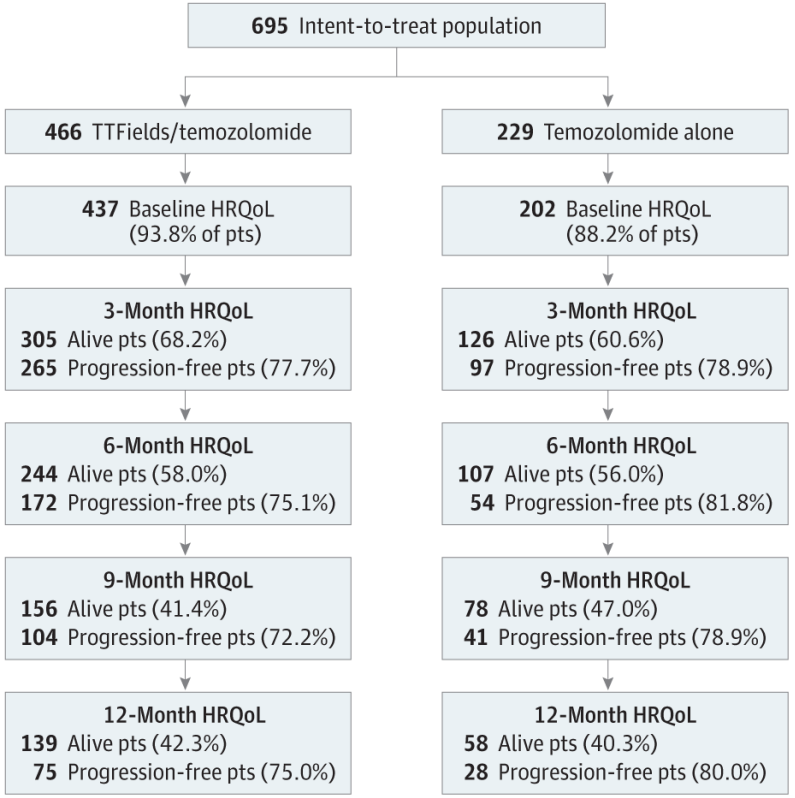


JAMA Oncology | Original Investigation

Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma

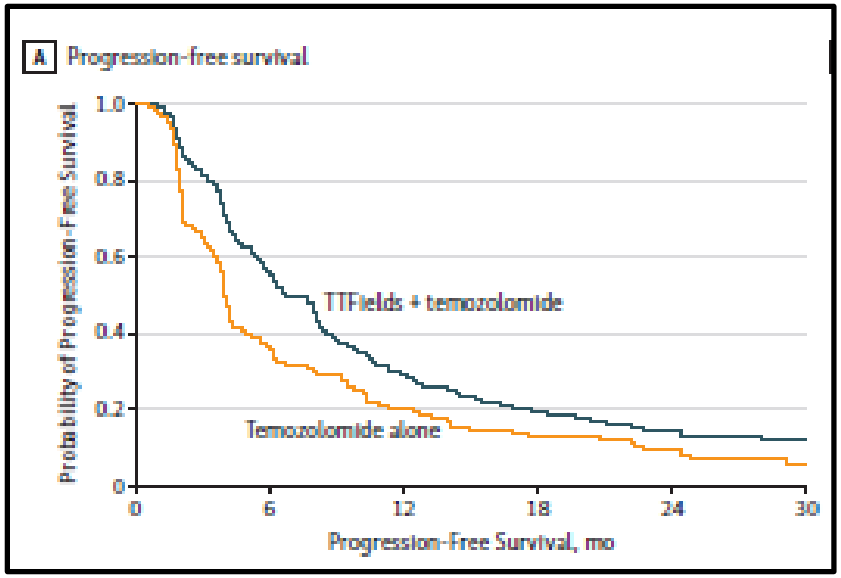
A Secondary Analysis of a Randomized Clinical Trial

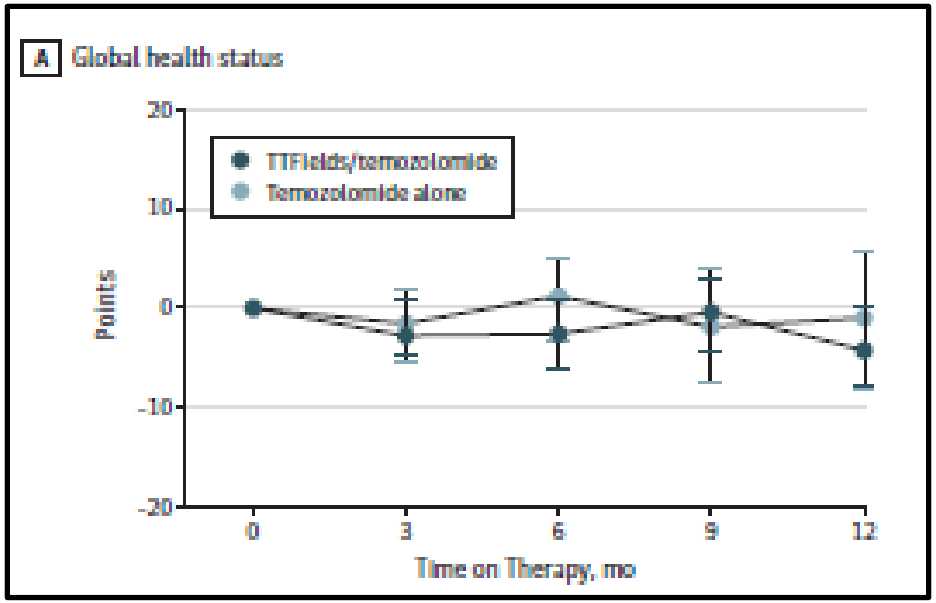
JAMA Oncol. 2018;4(4):495-504. doi:10.1001/jamaoncol.2017.5082

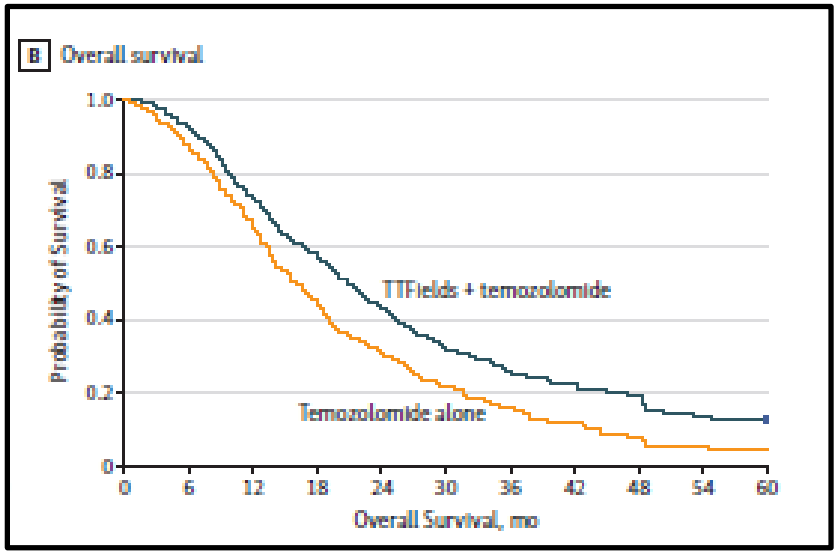


Advances in GBM Treatment

TTF: Tumour Treatment Fields

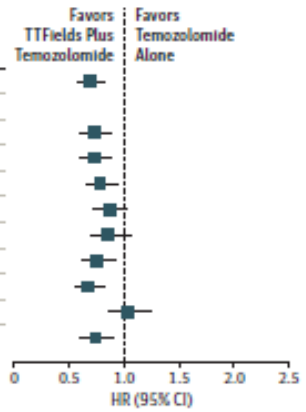






A Deterioration-free survival

Source	Median, mo: TTFields Plus Temozolomide	Median, mo: Temozolomide Alone	HR (95% CI)
Progression-free survival	6.7	4.0	0.69 (0.57-0.83)
Deterioration-free survival			
Global health status	4.8	3.3	0.73 (0.60-0.88)
Physical functioning	5.1	3.7	0.73 (0.60-0.88)
Cognitive functioning	4.4	3.6	0.78 (0.64-0.94)
Role functioning	4.3	3.8	0.86 (0.71-1.02)
Social functioning	4.5	3.9	0.84 (0.70-1.06)
Emotional functioning	5.3	3.9	0.75 (0.62-0.91)
Pain	5.6	3.6	0.67 (0.56-0.81)
Itchy skin	3.9	4.0	1.03 (0.85-1.25)
Weakness of legs	5.6	3.9	0.74 (0.61-0.89)



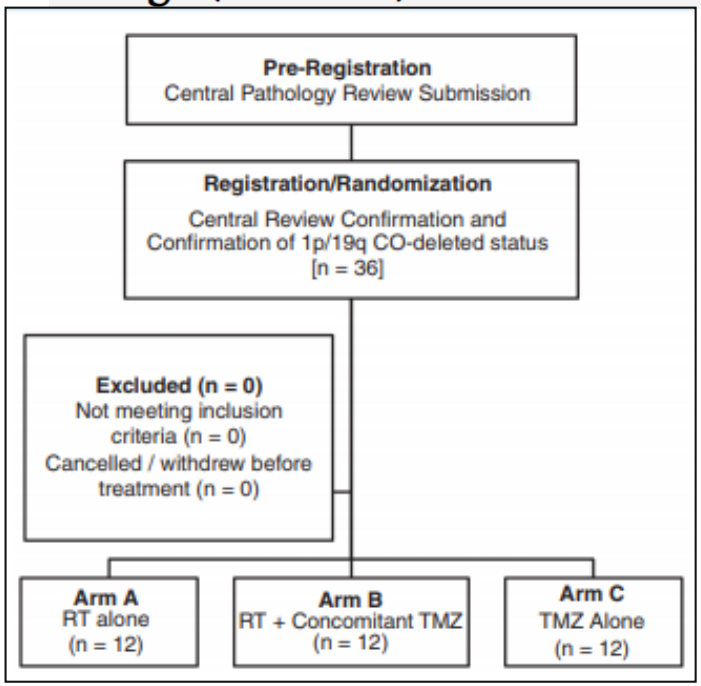
CONCLUSIONS:

- Addition of TTF maintenance to standard therapy resulted statistically significant improvement in PFS & OS
- Addition of TTFields results improved survival without a negative influence on HRQoL except for more

CODEL Trial for Grade –III Oligodendrogliomas

Neurology®
The most widely read and highly cited peer-reviewed neurology journal
Subscribe My Alerts Log in
AMERICAN ACADEMY OF NEUROLOGY®
Home Latest Articles Current Issue Past Issues Residents & Fellows
April 05, 2016; 86 (16 Supplement) APRIL 20, 2016

CODEL (Alliance-N0577; EORTC-26081/22086; NRG-1071; NCIC-CEC-2): Phase III Randomized Study of RT vs. RT+TMZ vs. TMZ for Newly Diagnosed 1p/19q-Codeleted Anaplastic Oligodendroglial Tumors. Analysis of Patients Treated on the Original Protocol Design (PL02.005)



- N= 36 pts
  RT alone =12; RT+TMZ=12;TMZ:12
- Median follow-up of 3.5 yrs
- **Progression**
  7/12(58%) TMZ-alone pts progressed
  3/24(12.5%) RT-Arm pts progressed (p = 0.007)
- **Death From progression**
  4/12(33%) TMZ-alone pts
  1/24 (4%) RT-Arm pts (p = 0.03)
- **Median PFS**
  Median PFS in TMZ-alone pts (2.5 yrs)
  Median PFS not reached for RT-Arm pts; HR=7.0, p<=0.001)

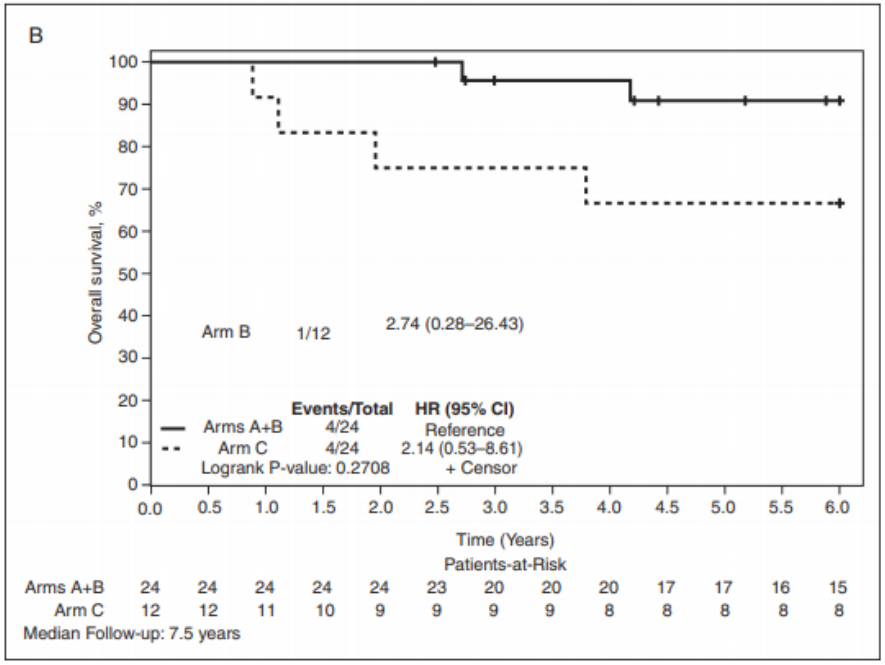
CODEL Trial for Grade –III Oligodendrogliomas

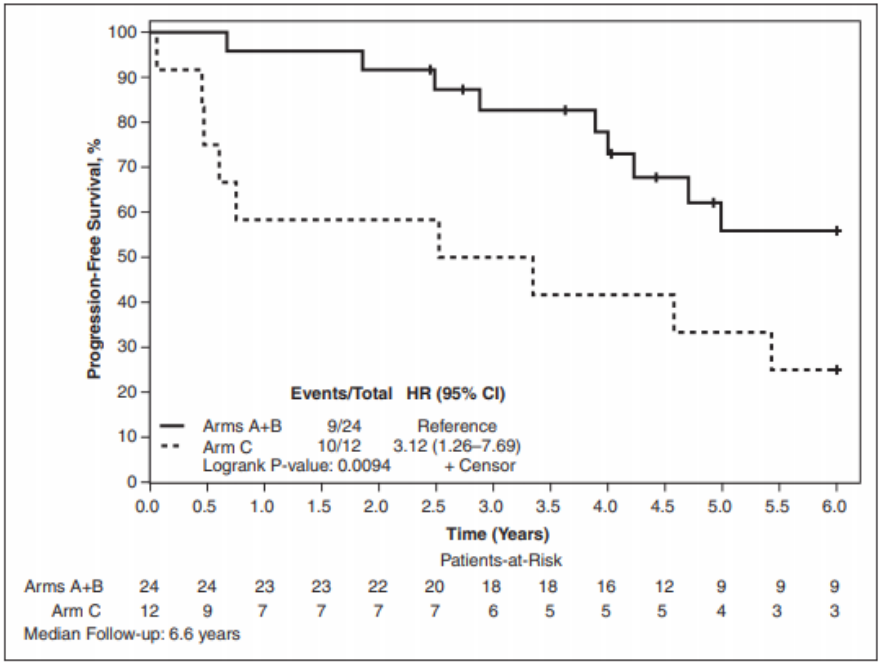
Neuro-Oncology
23(3), 457–467, 2021 | doi:10.1093/neuonc/noaa168 | Advance Access date 17 July 2020

CODEL: phase III study of RT, RT + TMZ, or TMZ for newly diagnosed 1p/19q codeleted oligodendroglioma. Analysis from the initial study design

Median follow-up of 7.5 years

- 83.3% (10/12) TMZ-alone patients progressed
- 37.5% (9/24) on the RT arm progressed





CODEL Trial for Grade –III Oligodendrogliomas

Conclusions

- TMZ-alone patients experienced significantly shorter PFS than patients treated on the RT arms.

- The RT-alone control arm was changed to RT + adjuvant procarbazine/lomustine/vincristine (PCV) following reports from EORTC 26951 and RTOG 9402, which showed a survival benefit of added PCV for this cohort.

- The ongoing CODEL trial has been redesigned to compare RT + PCV versus RT + TMZ.

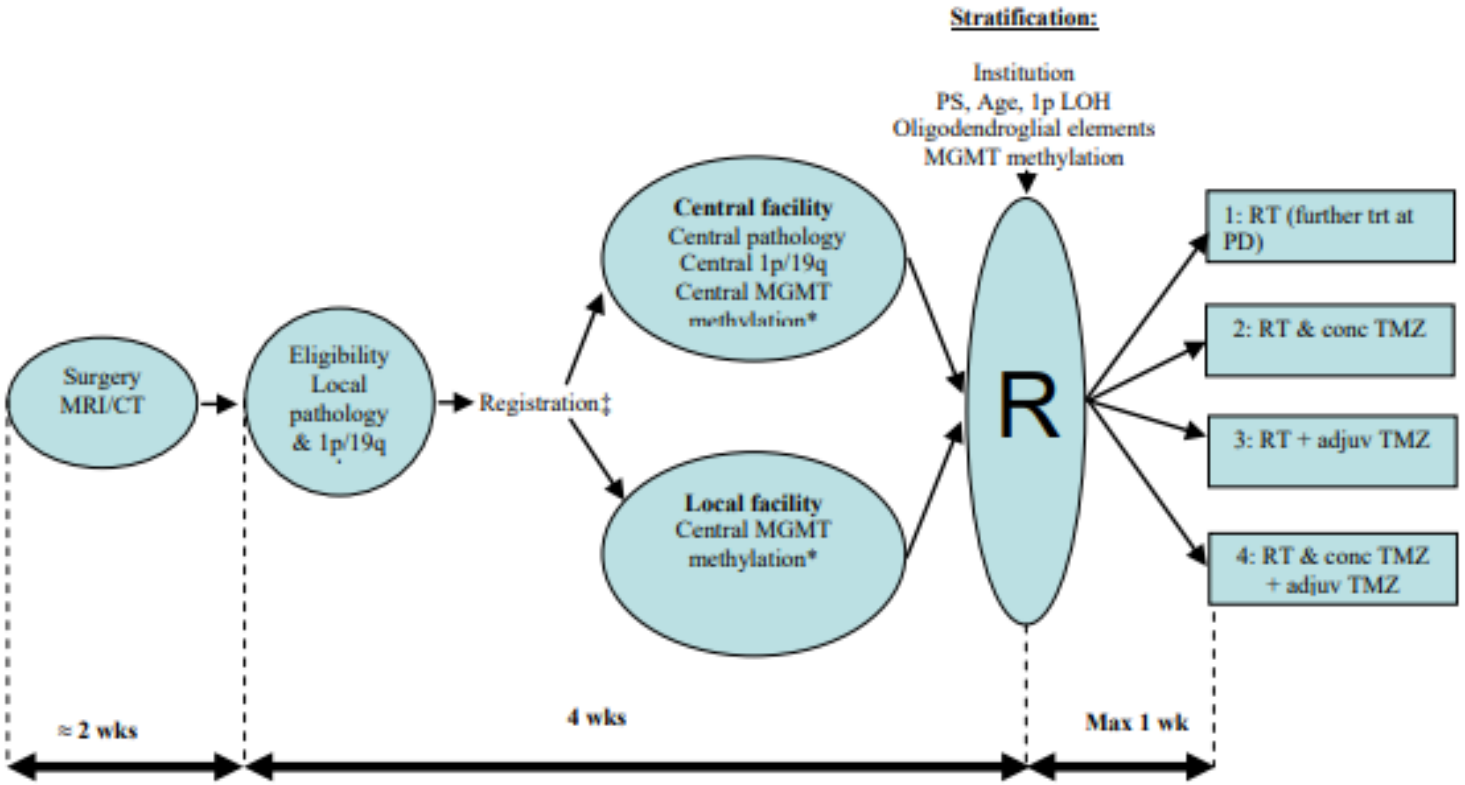
Redesigned CODEL Trial for Grade –III Oligodendrogliomas

Arm	Intervention/treatment
Experimental: Arm A (RT, procarbazine, lomustine, vincristine) Patients undergo 3D-CRT or IMRT on days 1-5 for 5-7 weeks. Patients also receive procarbazine hydrochloride PO on days 8-21, lomustine PO on day 1 and vincristine sulfate IV on days 8 and 29 of courses 3-8. Treatment repeats every 6-7 weeks for up to 6 courses in the absence of disease progression or unacceptable toxicity.	Radiation: radiotherapy Drug: procarbazine Days 8-21: 60 mg/m^2 orally Drug: CCNU Day 1: 110 mg/m^2 orally Drug: vincristine Days 8 and 29: 1.4 mg/m^2 IV
Experimental: Arm B (RT, temozolomide) Patients undergo RT as in arm I and receive temozolomide PO QD on days 1-5 for 5-7 weeks. Beginning 4 weeks after completion of concurrent chemoradiotherapy, patients receive adjuvant temozolomide PO QD days 1-5. Treatment with adjuvant temozolomide repeats every 4 weeks for 6-12 courses in the absence of disease progression and unacceptable toxicity.	Drug: concomitant temozolomide (TMZ) 75 mg/m^2, orally daily Radiation: radiotherapy Drug: adjuvant temozolomide (TMZ) 150 or 200 mg/m^2 orally

CATNON trial : No co-deleted Anaplastic Gliomas

Trial Design

Arm 1: Radiotherapy and further treatment including chemotherapy if indicated at progression
Arm 2: Radiotherapy & concurrent temozolomide
Arm 3: Radiotherapy + adjuvant temozolomide for 12 cycles
Arm 4: Radiotherapy & concurrent temozolomide + adjuvant temozolomide for 12 cycles

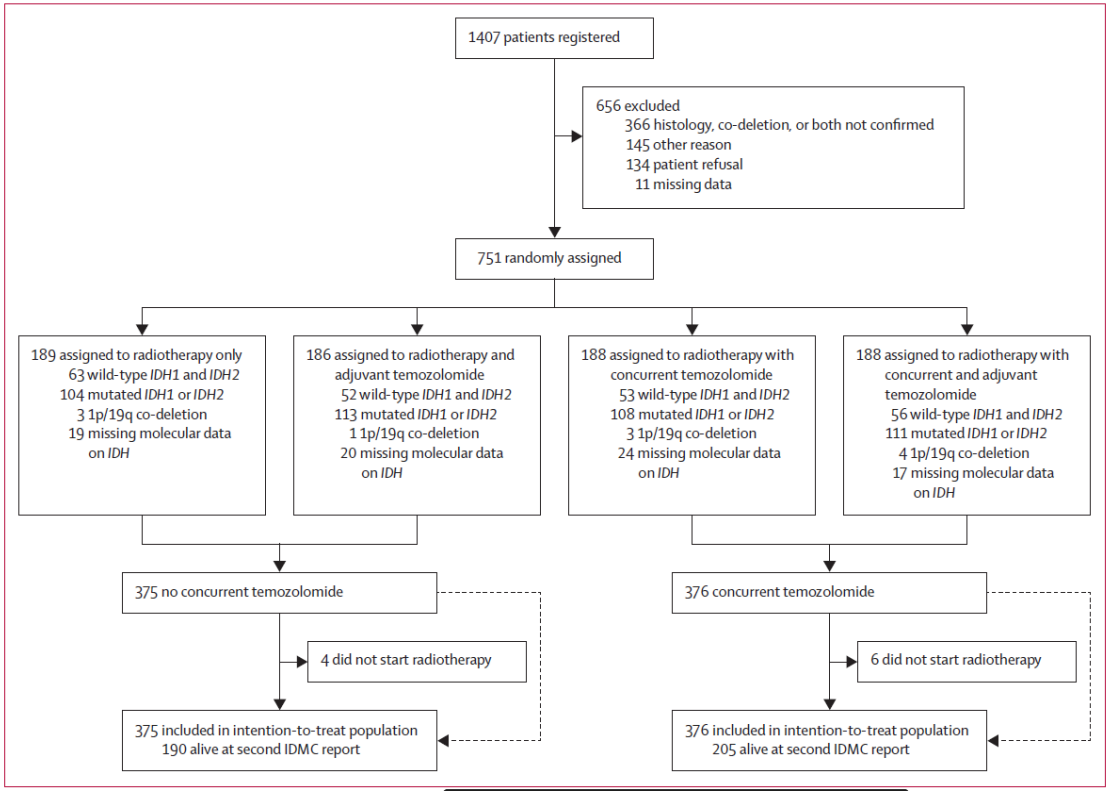


CATNON trial : No co-deleted Anaplastic Gliomas

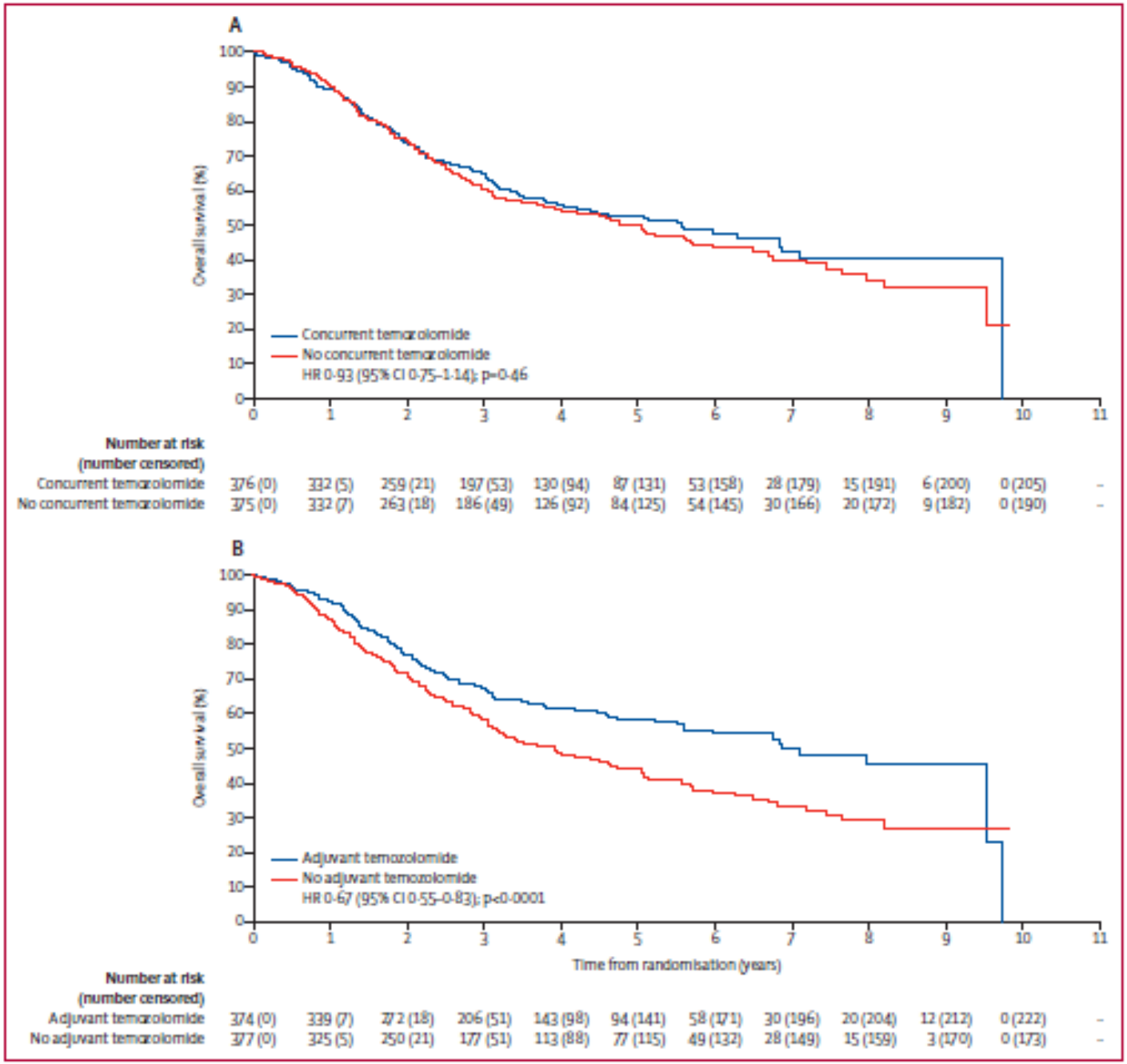
Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study

Lancet Oncol 2021

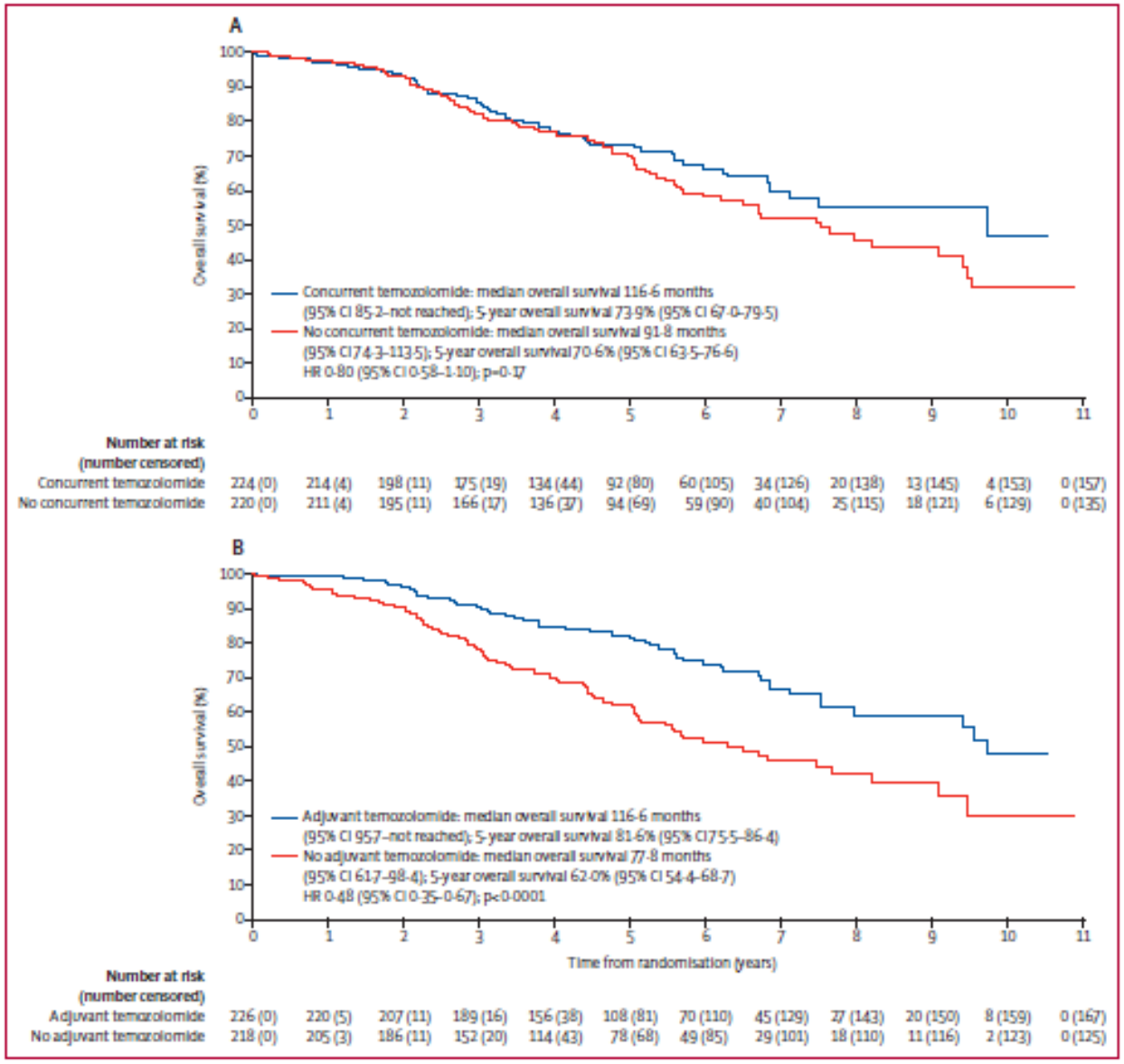
Institutions:137



Overall Survival regardless of *IDH1* and *IDH2* mutational status



Overall survival based on IDH mutations



Interpretation

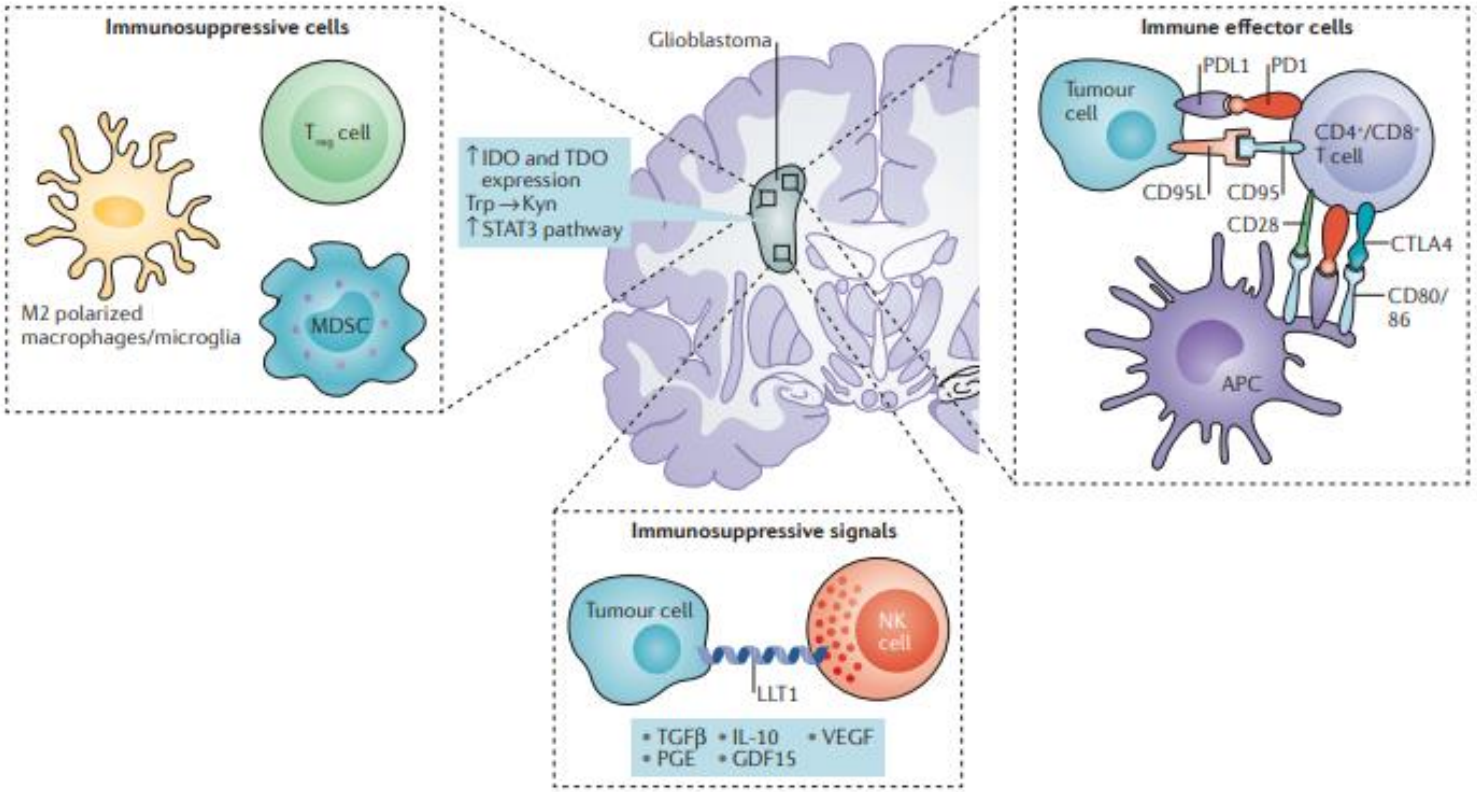
- Adjuvant TMZ, but not concurrent TMZ , was associated with a survival benefit in patients with 1p/19q non-co-deleted anaplastic glioma.
- Clinical benefit was dependent on *IDH1* and *IDH2* mutational status.

Vaccine-based immunotherapeutic approaches to gliomas and beyond

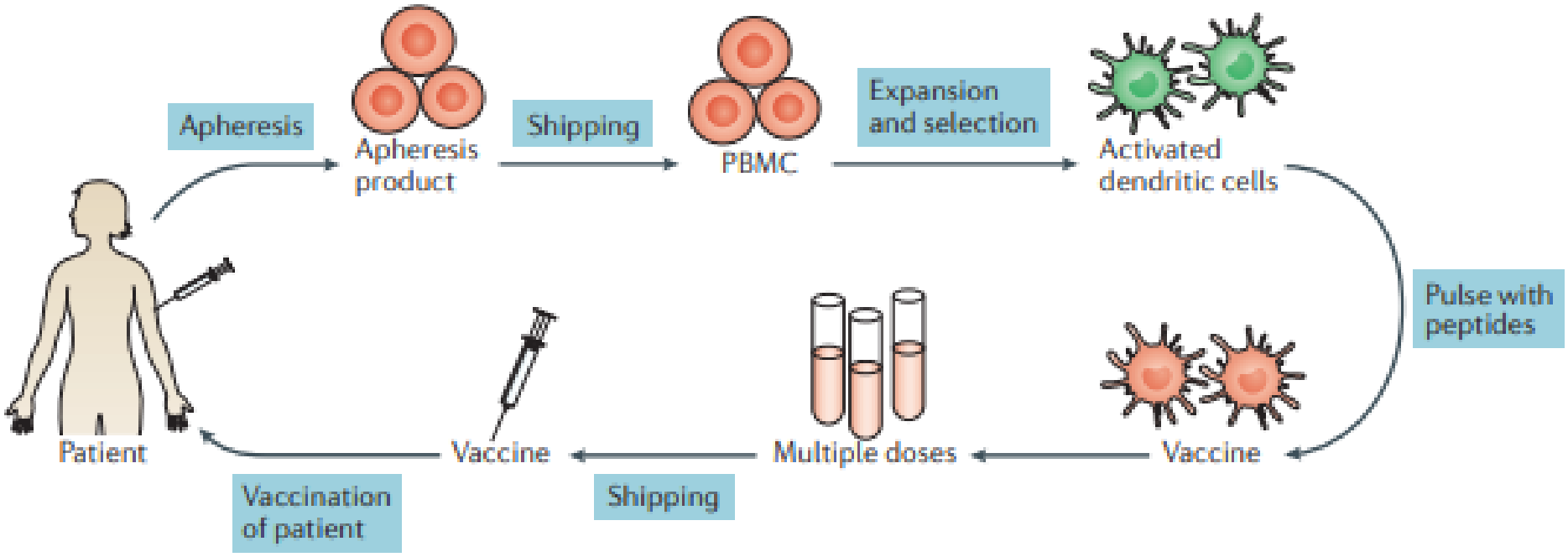
Michael Weller[1], Patrick Roth[1], Matthias Preusser[2], Wolfgang Wick[3], David A. Reardon[4], Michael Platten[3,5] and John H. Sampson[6]

nature reviews neurology

| Glioma-associated pathways of local and systemic immunosuppression



Logistical requirements for autologous immune or immune cell-based vaccination for glioblastoma



Completed trials of vaccination therapy for GBM

Trial name and ClinicalTrials.gov identifier	Active treatment	Control	Sample size	Primary end point	Result
Phase III					
ACT-IV[135] NCT01480479	Rindopepimut plus GM-CSF	KLH plus GM-CSF	700	Overall survival	Negative
Phase II					
ReACT[136] NCT01498328	Rindopepimut plus bevacizumab	KLH and GM-CSF plus bevacizumab	70	Progression-free survival	Positive (trend)
HeatShock[137] NCT00905060	HSPPC-96 plus temozolomide	None	46	Safety and survival	Results pending
HSPPC-96 (REF. 138) NCT00293423	HSPPC-96	None	41	Safety, toxicity	Safe vaccine
GBM-Vax[139] NCT01213407	Trivax (a DC-based vaccine) plus temozolomide plus radiotherapy, followed by maintenance temozolomide	Temozolomide plus radiotherapy, followed by maintenance temozolomide	87	Progression-free survival	Results pending
Phase I					
IMA-950 (REF. 140) NCT01222221	IMA-950 plus GM-CSF	None	45	Safety and T cell responses	Positive for primary end point
Phase III					
DCVax[64] NCT00045968	DCVax	Autologous PBMC	348		Progression-free survival
STING[67] NCT02546102	ICT-107	Autologous monocyte-enriched PBMC	414		Overall survival
Phase II					
ATTAC-II[141] NCT02465268	Cytomegalovirus RNA-pulsed DCs plus tetanus–diphtheria toxoid	Unpulsed PBMC and saline	150		Overall survival
ALLIANCE IND#15380 (REF. 142) NCT01814813	HSPPC-96 and concomitant bevacizumab versus HSPPC-96 followed by bevacizumab at progression	Bevacizumab	165		Overall survival
HSPPC-96 (REF. 82) NCT03018288	TMZ–RT→TMZ plus pembrolizumab and HSPPC-96	• TMZ–RT→TMZ plus pembrolizumab and placebo • A separate group of patients whose tumours did not fulfil all inclusion criteria also received TMZ–RT→TMZ plus pembrolizumab and placebo	108		Overall survival at 1 year
SurVaxM[143] NCT02455557	SurVaxM	None	50		Progression-free survival
Phase I					
NOA-16 (REF. 76) NCT02454634	IDH^{R132H} peptide vaccine	None	39		Safety and tolerability
GAPVAC[34] NCT02149225	APVAC1 and APVAC2 vaccine plus poly-ICLC and GM-CSF	None	16		Safety and biological activity
NCT02287428 (REF. 59)	Personalized neoantigen vaccine	None	15		Feasibility and safety

Tumour Grade and Estimated Median Survival

Grade and cell type	Median survival
Grade II	
Astrocytoma	7–10 years
Oligodendroglioma[a]	>10–15 years
Grade III	
Anaplastic astrocytoma	3.5 years
Anaplastic oligodendroglioma[a]	>10 years
Grade IV	
Glioblastoma	15 months, 2-year survival 27%
MGMT	
Methylated	23 months, 2-year survival: 49%
Unmethylated	13 months, 2-year survival: 12%

[a]With LOH 1p/19q. MGMT, methyl-guanine methyl transferase

Take Home Message

- Molecular markers: established role in the diagnosis and management of high-grade glioma

  - incorporated into the updated WHO 5th Edition Classification.

- There is new evidence to guide management of patients over 65 years of age with high-grade glioma.

  - Most of these patients will benefit from short-course radiotherapy with concurrent and adjuvant temozolomide.

- For unselected patients with high-grade glioma, the role of bevacizumab is limited.

- TTF : Shown efficacy in patients with newly diagnosed glioblastoma.
  - Not cost effective
  - Has not been widely adopted as a therapy for patients with this disease.

- Immunotherapeutic are under evaluation for high-grade glioma. We await the forthcoming results from randomized Phase III trials.

- Many targeted therapies have been evaluated for high-grade glioma, but so far have lacked clinical utility. Efforts incorporating novel strategies are ongoing.