TARGATED THERAPY FOR BRAIN TUMORS

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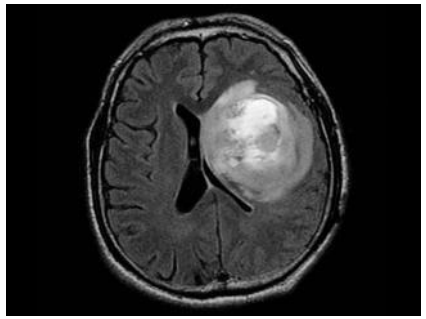
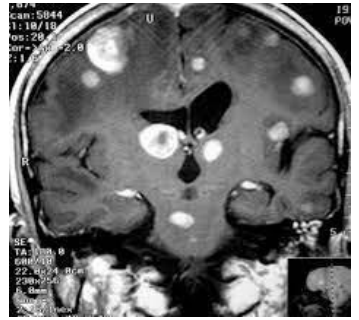
Primary and metastatic Brain Tumors





Primary Brain Tumors

- ~ 24,000 malignant brain tumors per year
- ~ 17,000 deaths per year

Brain metastases

- ~98,000-200,000 patients diagnosed annually
- Up to 30% of patients with stage IV cancer
- Median survival 3-6 months

- Largely excluded from clinical trials
- Represent an active focus of clinical research
- Upcoming evidences of Immunotherapy activity in BM

2021 WHO Classification of Tumors of CNS

Newly Recognized Tumor Types
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
High-grade astrocytoma with piloid features
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (provisional type)
Myxoid glioneuronal tumor
Multinodular and vacuolating neuronal tumor
Supratentorial ependymoma, *YAP1* fusion-positive
Posterior fossa ependymoma, group PFA
Posterior fossa ependymoma, group PFB
Spinal ependymoma, *MYCN*-amplified
Cribriform neuroepithelial tumor (provisional type)
CNS neuroblastoma, *FOXR2*-activated
CNS tumor with *BCOR* internal tandem duplication
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant
Intracranial mesenchymal tumor, FET-CREB fusion positive (provisional type)
CIC-rearranged sarcoma
Primary intracranial sarcoma, *DICER1*-mutant
Pituitary blastoma

CNS WHO Grades of Selected Types	
Astrocytoma, IDH-mutant	2, 3, 4
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	2, 3
Glioblastoma, IDH-wildtype	4
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	1
Polymorphous low-grade neuroepithelial tumor of the young	1
Diffuse hemispheric glioma, H3 G34-mutant	4
Pleomorphic xanthoastrocytoma	2, 3
Multinodular and vacuolating neuronal tumor	1
Supratentorial ependymoma[a]	2, 3
Posterior fossa ependymoma[a]	2, 3
Myxopapillary ependymoma	2
Meningioma	1, 2, 3
Solitary fibrous tumor	1, 2, 3

Grade is based on natural history and for some tumor types, definite grading criteria and understanding of natural history are not yet known. Note the use of Arabic numerals.
[a]For morphologically defined ependymomas.

Louis DN, et al. Neuro-oncology. 2021 Aug 1;23(8):1231-51.

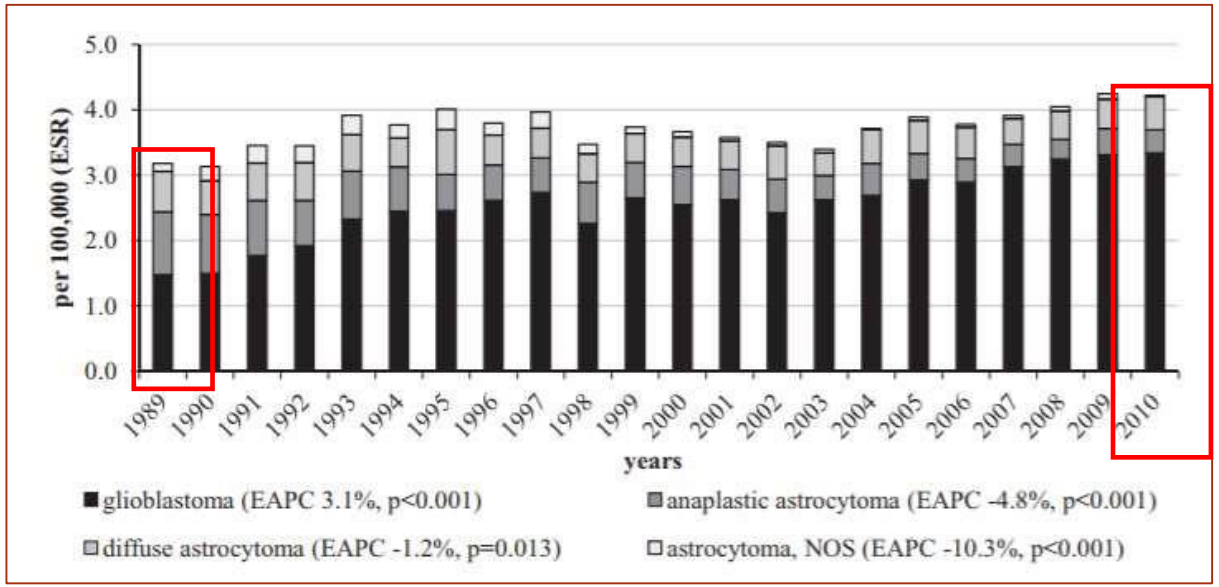
Challenges to curing primary brain tumors

- Brain tumors are among the most feared of all forms of cancer.
- More than two-thirds of adults diagnosed with glioblastoma — the most aggressive type of brain cancer — will die within 2 years of diagnosis.
- Brain cancers are also the most common and most lethal of all paediatric solid tumors.
    - Furthermore, children with these tumors who survive and enter adulthood will often be affected by the long-term consequences of exposing the developing brain to medical interventions, including surgery, radiotherapy and/or chemotherapy

Aldape K, et al. Nature reviews Clinical oncology. 2019 Aug;16(8):509-20.

Changing incidence and improved survival of gliomas

Vincent K.Y. Ho [a,*], Jaap C. Reijneveld [b], Roelien H. Enting [c], Henri P. Bienfait [d],

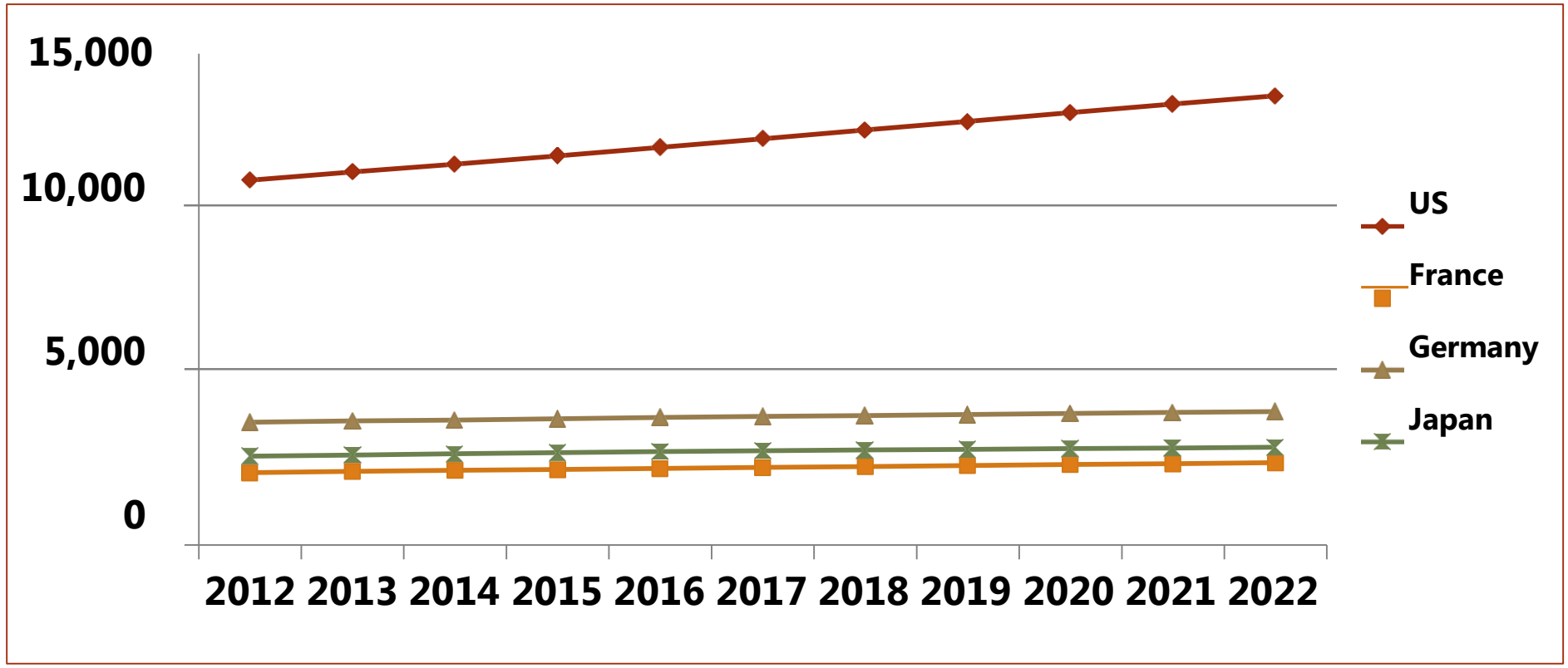


Age-standardised incidence rates for astrocytic tumours in the Netherlands from 1989 to 2010.

Incidence of gliomas in adults increased over time, from 4.9 per 100,000 in 1989 to 5.9 in 2010. Two thirds were astrocytoma, 10% oligodendroglioma/oligoastrocytoma, 3% ependymoma and 21% were unspecified. Within the group of astrocytic tumours, the proportion of glioblastoma rose, while the proportion of anaplastic and unspecified astrocytoma decreased. Over the course of the study period, glioblastoma patients more often received multimodality treatment with chemotherapy concomitant and adjuvant to radiotherapy. The crude two-year survival rate of glioblastoma patients improved significantly, from 5% in the time period 1989–1994 to 15% in 2006–2010, with median survival increasing from 5.5 to 9 months. The incidence of low-grade gliomas did not change over time. Survival rates for low-grade oligodendroglial and mixed tumours show a modest improvement.

Incidence in Future?

- Number of newly diagnosed cases of glioblastoma is expected to increase in the US, France, Germany, and Japan



Decision Resources: Glioblastoma Multiforme. September 2013

EPIDEMIOLOGY

Glioblastoma (GBM)

Most common primary brain tumor of adults

Most aggressive (15 months median overall survival)

Incidence: 4-5/100.000/year

Male to female ratio = 1.3:1

Median age at diagnosis

- Primary glioblastoma: 64 years
- Secondary glioblastoma: 45 year

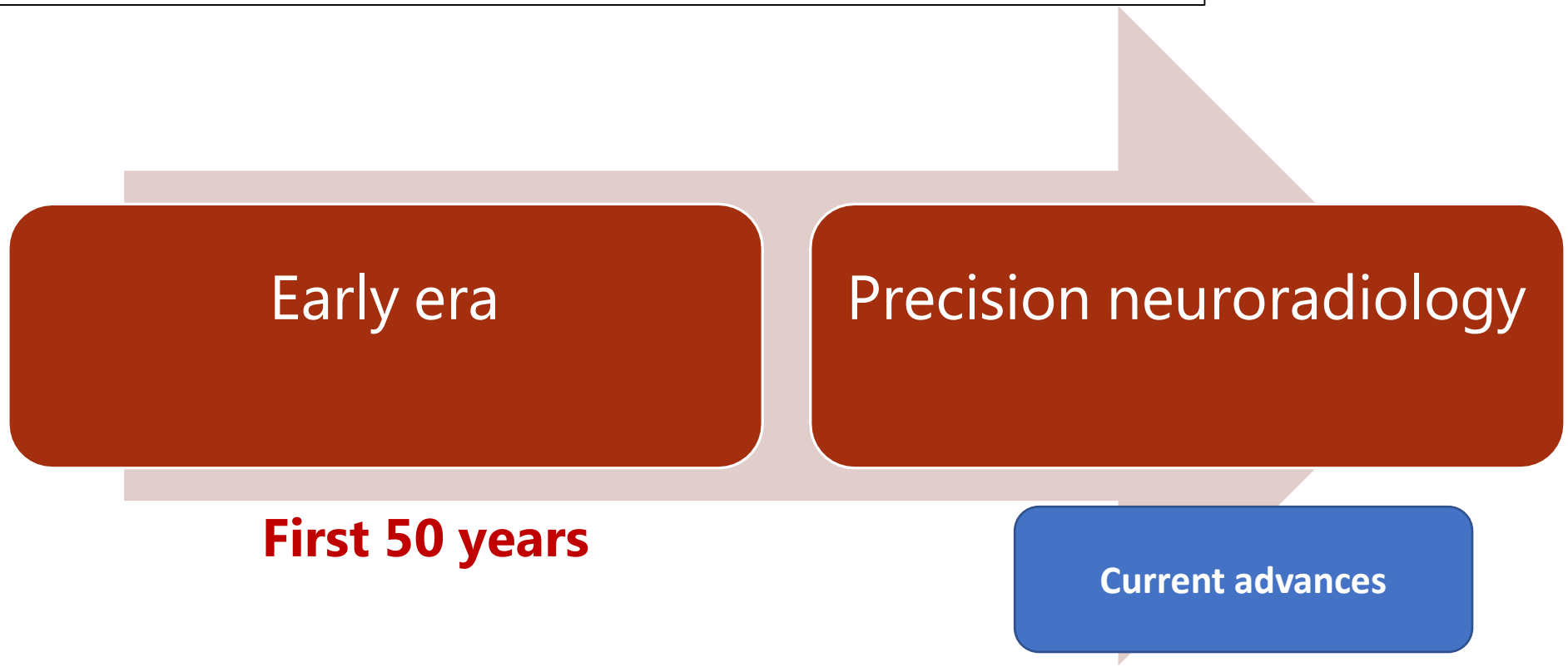
Low grade gliomas (LGGs)

5-10% of all gliomas

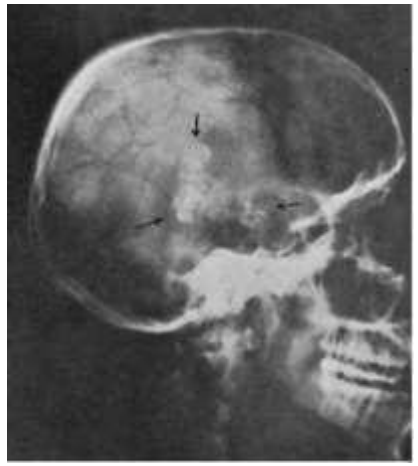
Age at diagnosis: 30-50 years

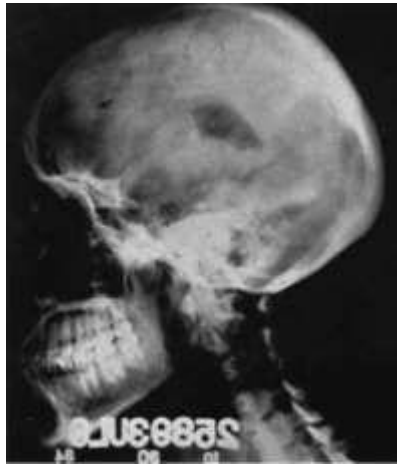
Most common symptom: seizures

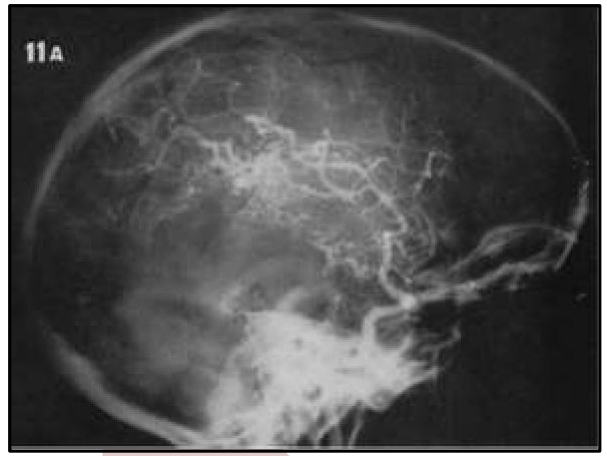
History and Evolution of Brain Tumor Imaging: Insights through *Radiology*[1]



Early era







Plain radiograph

Pneumatoencephalograms

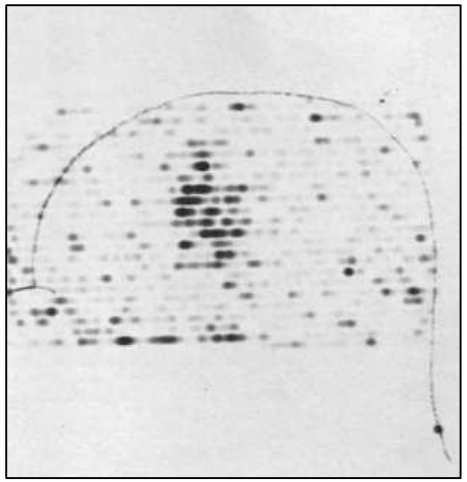
Cereberal angiography

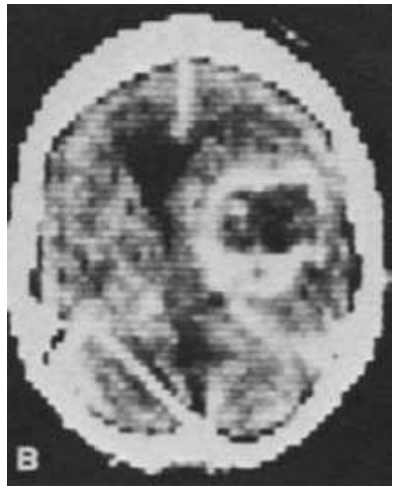
After discovery of Xrays

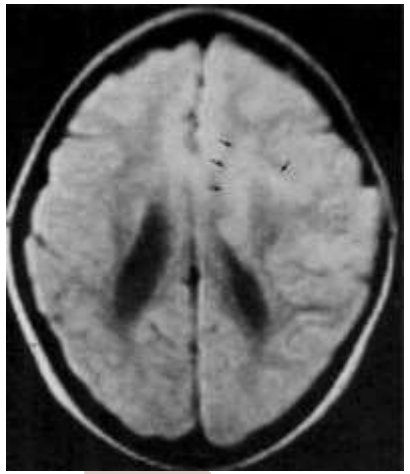
1918

1928

Precision neuroradiology







Radiotracer uptake

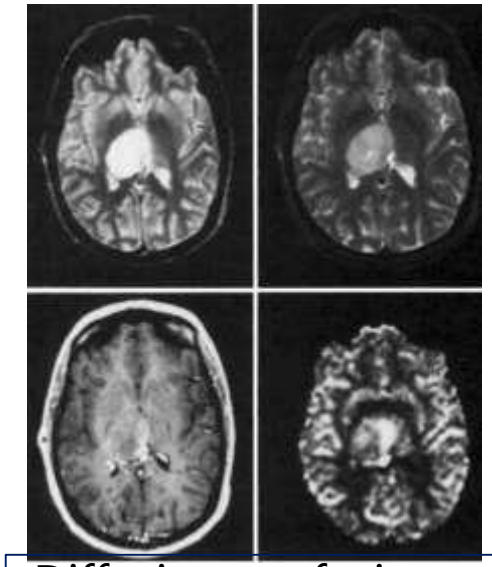
CT Scan

MRI

1971

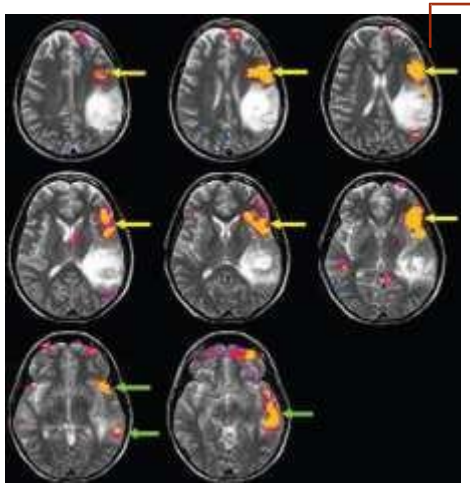
1977

Newer imaging modalities

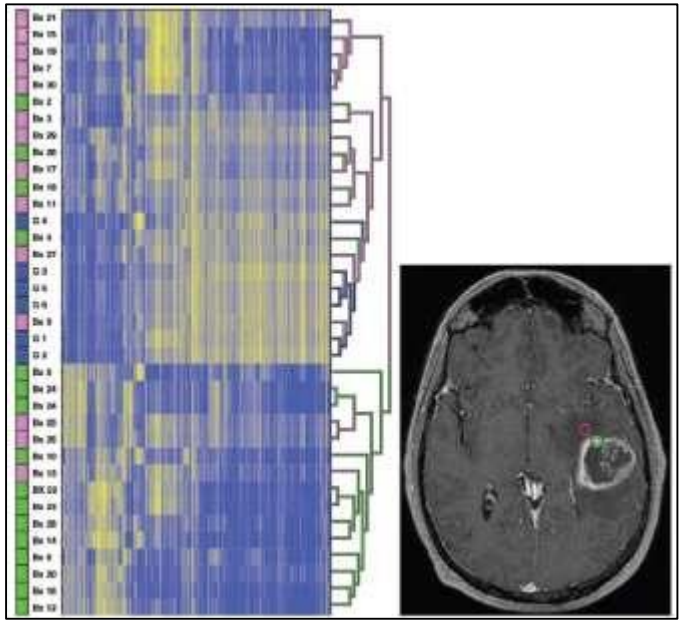


Diffusion-perfusion MRI

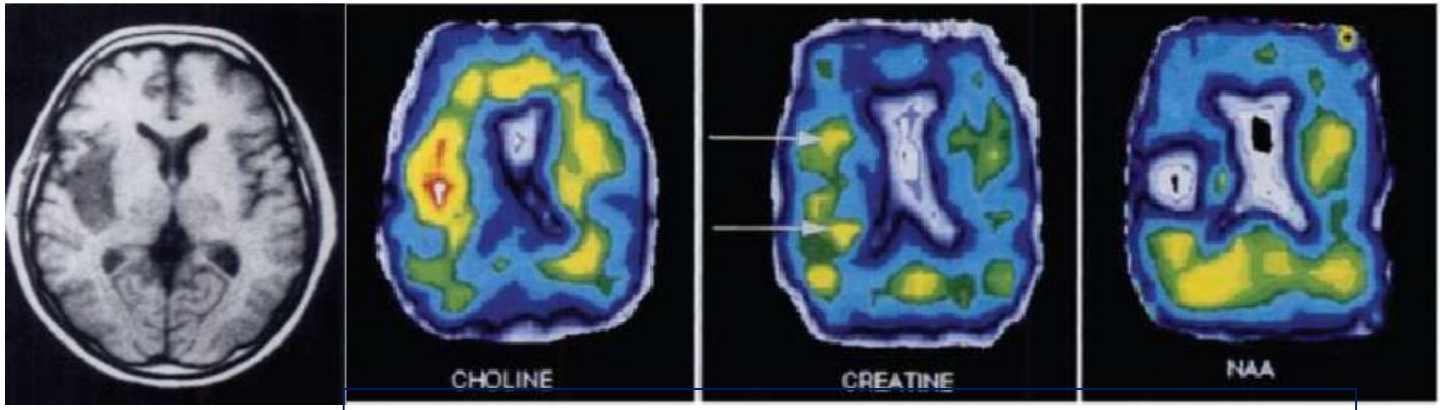
Eloquent areas



Functional MRI



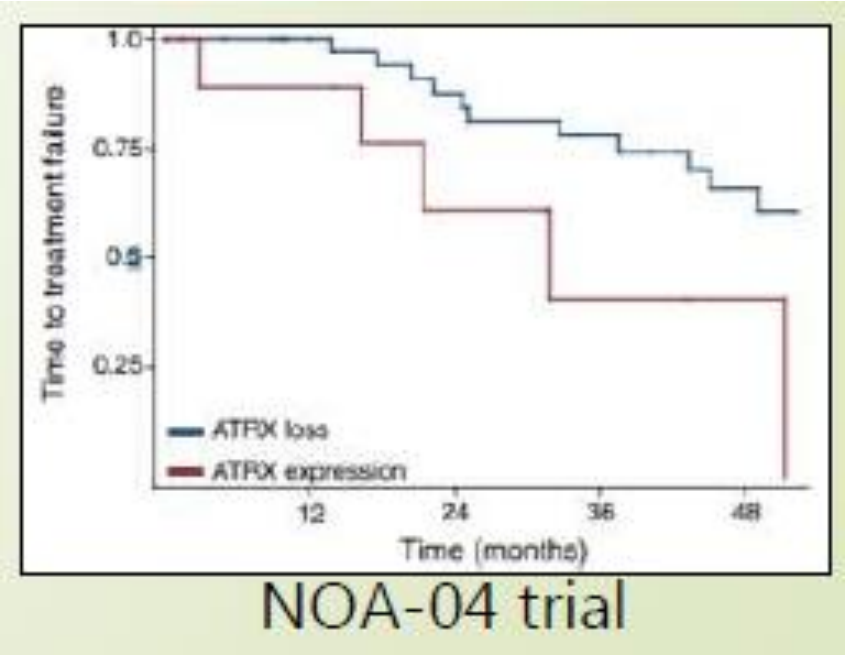
Radio Genomics



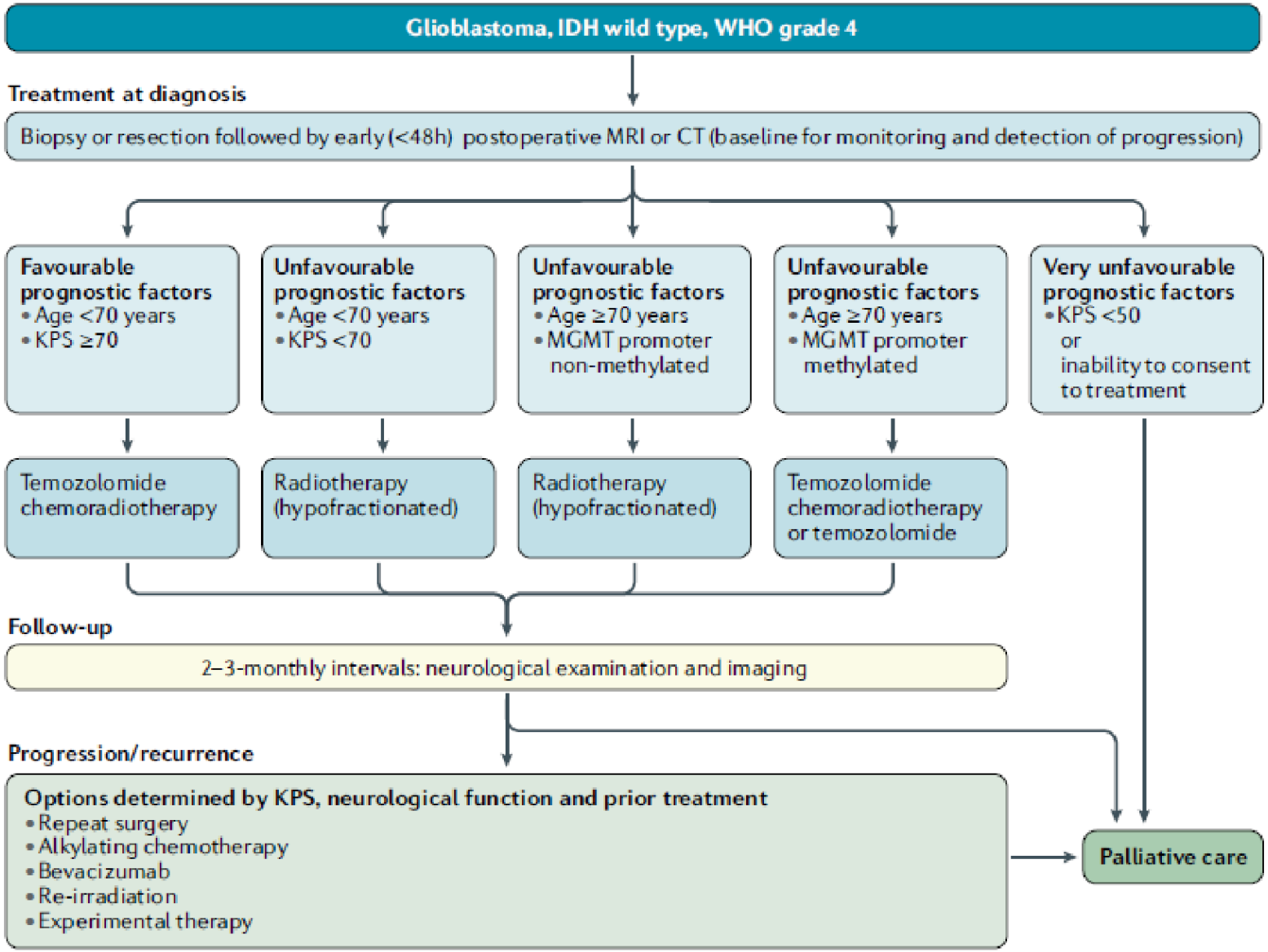
Magnetic resonance spectroscopy (MRS)

Molecular testing

- IDH1 and IDH2 (isocitrate dehydrogensase) mutations
  - Good prognostic marker
  - Can be done by IHC, PCR or pyrosequencing
- 1p19q co-deletion
  - Mainly seen in ODG
  - Good prognostic factor
  - Can be done by PCR, FISH
- ATRX gene mutation (alpha thalassemia-mental retardation, X linked)
  - Seen in 45% of anaplastic astrocytoma
  - Considered as hallmark of astrocytoma
  - ATRX loss is a good prognostic factor
  - Can be done by IHC,FISH, PCR



NOA-04 trial



EVIDENCE-BASED GUIDELINES

OPEN

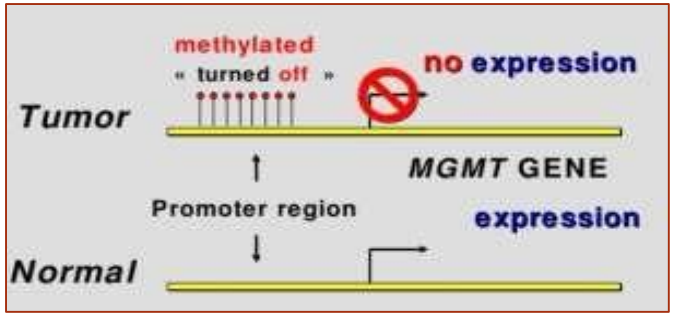
EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood

Michael Weller[1✉], Martin van den Bent[2], Matthias Preusser[3], Emilie Le Rhun[4,5,6,7], Jörg C. Tonn[8], Giuseppe Minniti[9], Martin Bendszus[10], Carmen Balana[11], Olivier Chinot[12], Linda Dirven[13,14], Pim French[15], Monika E. Hegi[16], Asgeir S. Jakola[17,18], Michael Platten[19,20], Patrick Roth[1], Roberta Rudà[21], Susan Short[22], Marion Smits[23], Martin J. B. Taphoorn[13,14], Andreas von Deimling[24,25], Manfred Westphal[26], Riccardo Soffietti[21], Guido Reifenberger[27,28] and Wolfgang Wick[29,30]

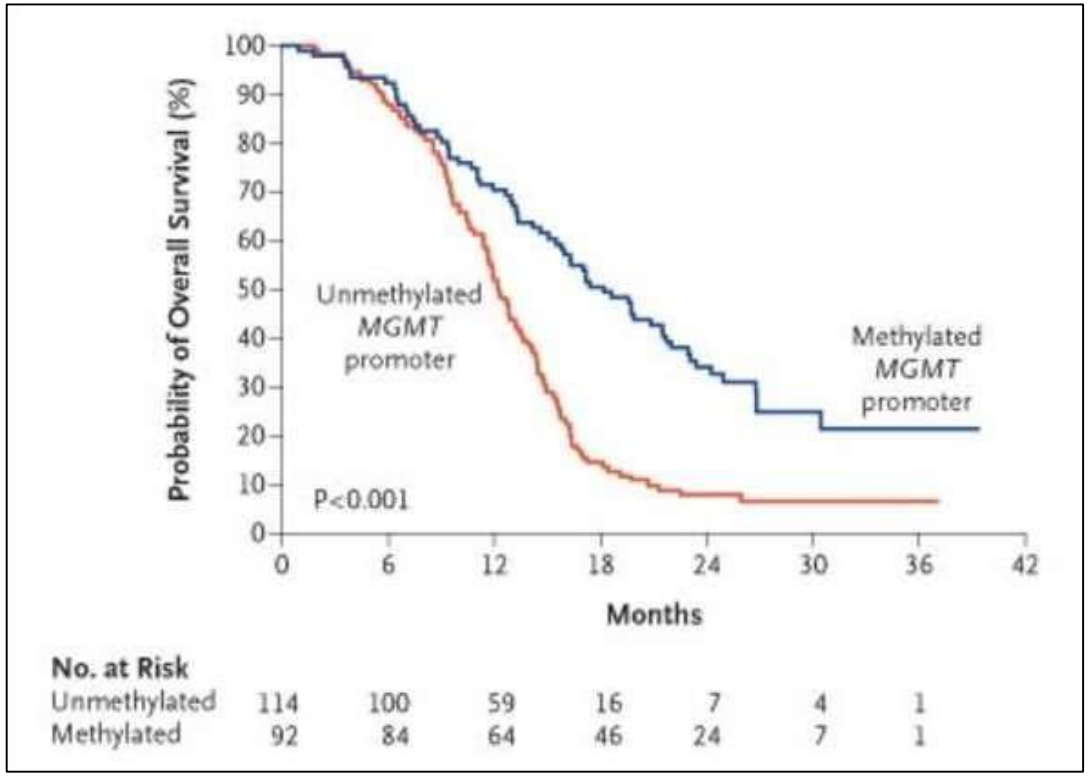
NATURE REVIEWS | CLINICAL ONCOLOGY

MGMT (O-6 methylguanine methyltransferase) promotor status

- Is crucial for genome stability
- It repairs methylation of DNA
- It also reverses the cytotoxic effects of alkylating agent

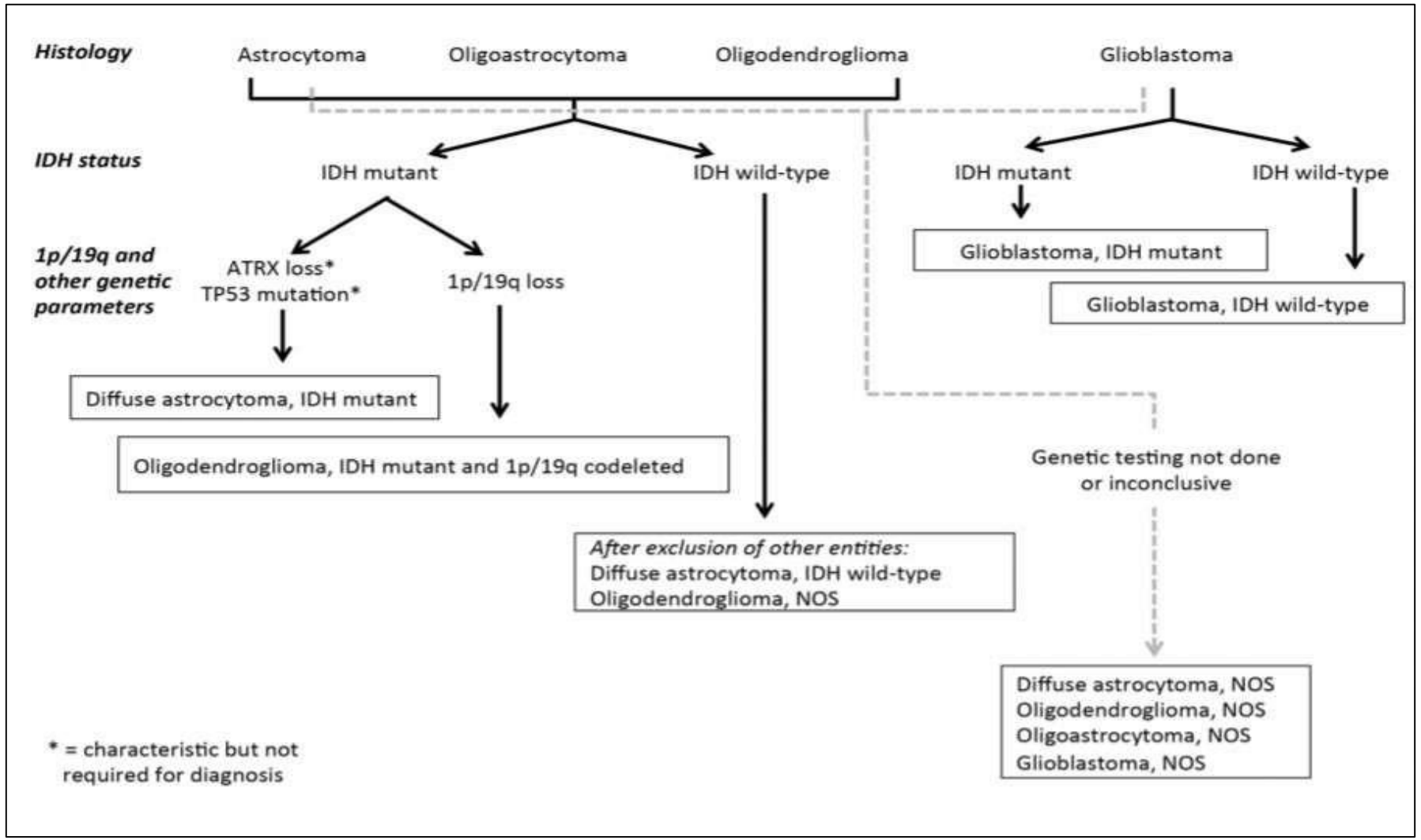


- Inactivation of MGMT makes it sensitive to alkylating agent
- Is a prognostic and predictive marker
- Done by PCR, pyrosequencing



M Hegi et al NEJM, 2005

CLASSIFICATION OF BRAIN TUMORS



Challenges in Response Assessment:

Pseudoprogression

Apparent increase of tumor lesion imaging that is not due to actual tumor growth

Observed in 5%–31% patients* after RT/chemotherapy

- -Also been observed after treatment with immunotherapies, but is often followed by tumor regression
- -Apparent increases in tumor lesions in these cases may be a result of immune-cell infiltration of the tumor

Pseudoresponse

Apparent decrease of tumor lesion on on imaging that does not reflect true tumor reduction

Often occurs with antiangiogenic agents such as bevacizumab

Current Standard of Care

Local + Distant Control

Maximum Surgical Resection

↓

Radiation + Temozolomide

↓

TMZ for ≥6 months

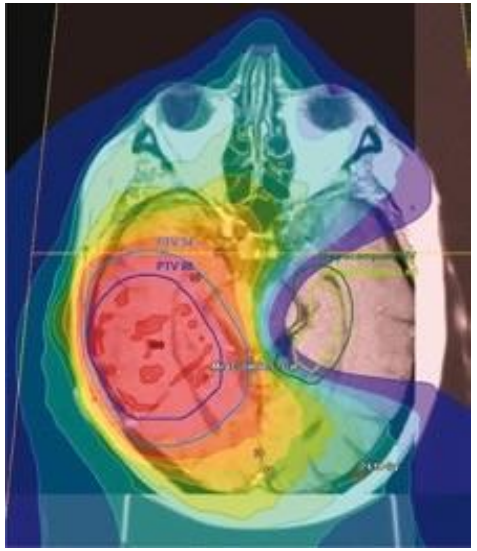
NCCN. Clinical practice guidelines in oncology: central nervous system cancers. v.2.2021. nccn.org.

NEUROSURGERY

- Objective: Maximal safe resection & histological + molecular confirmation
  - The extent of resection is a prognostic factor but the prevention of new permanent neurological deficits has higher priority
  - Only complete tumour resection (at least all contrast-enhancing tumour on MRI) has a positive prognostic impact on gliomas
- Indication for either tumour resection or stereotactic biopsy depending on:
  - Tumour localisation, risk factors, age and comorbidities
- Preoperative +/- intraoperative advanced neuroimaging to plan neurosurgery improves oncological and neurological outcomes

Radiotherapy for gliomas

High precision:
- Thermoplastic mask/non-invasive frame system immobilisation
- Image guidance positioning



Dose distribution for potential hippocampal avoidance

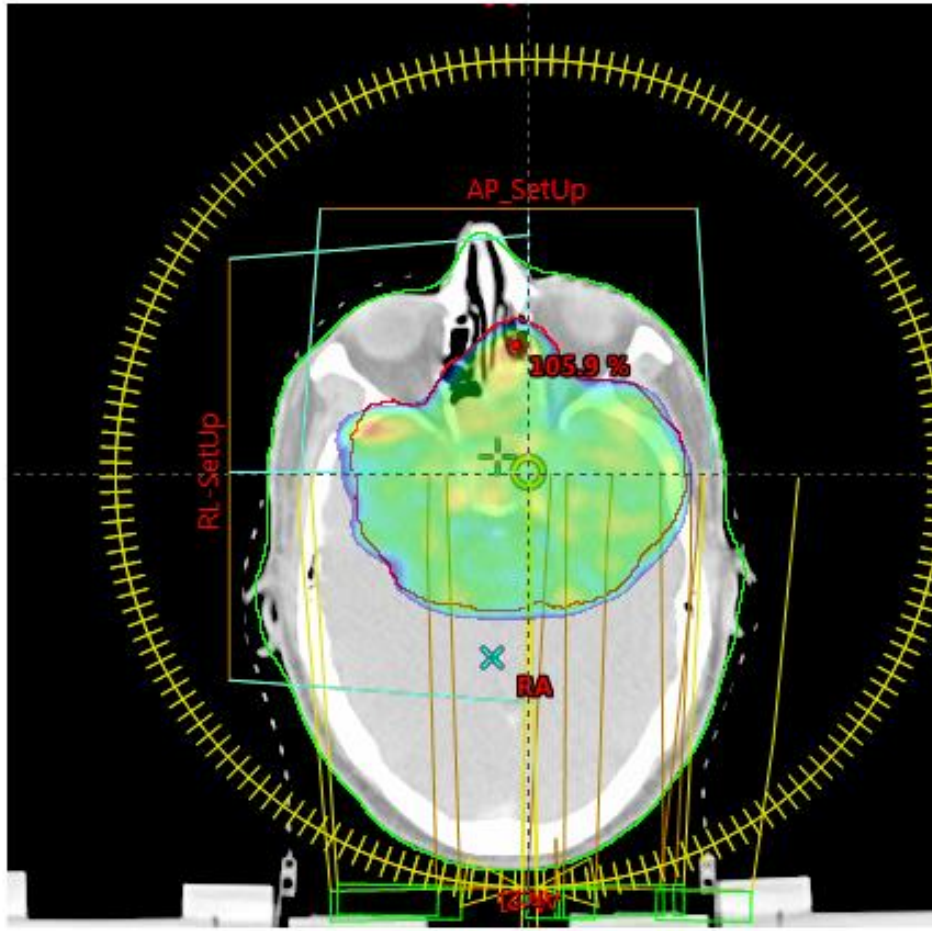
Adverse effects of radiotherapy

Fractionated RT is well tolerated

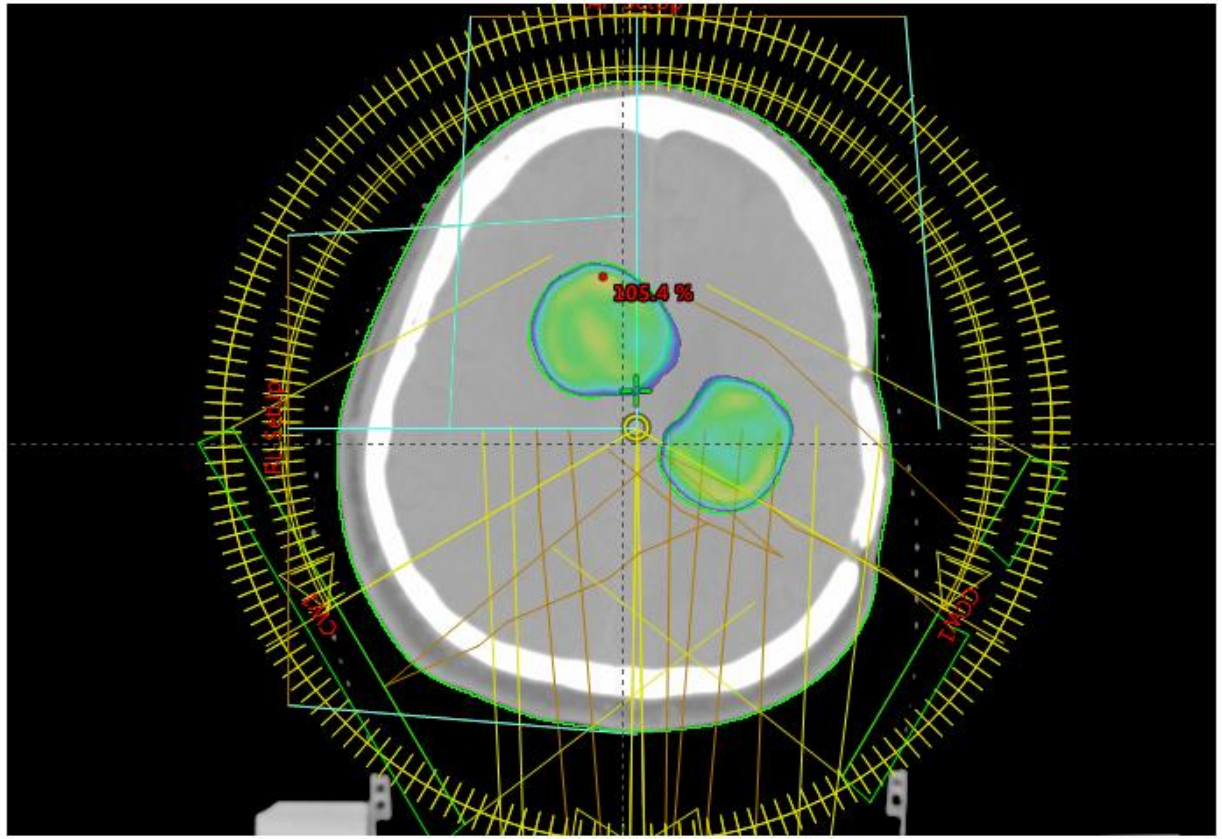
Acute toxicity:
- Alopecia
- Fatigue

Late toxicity:
- Radiation necrosis
- Decline in cognitive function
  - Prevention: Avoidance of hippocampus

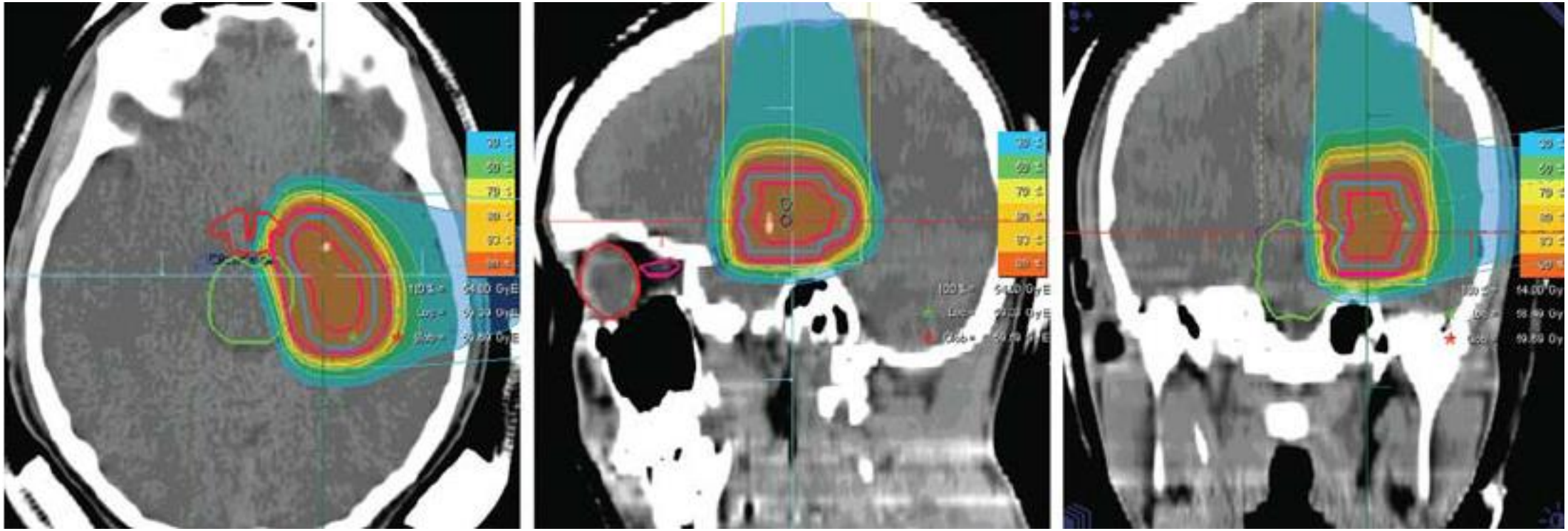
RA



RA Plan



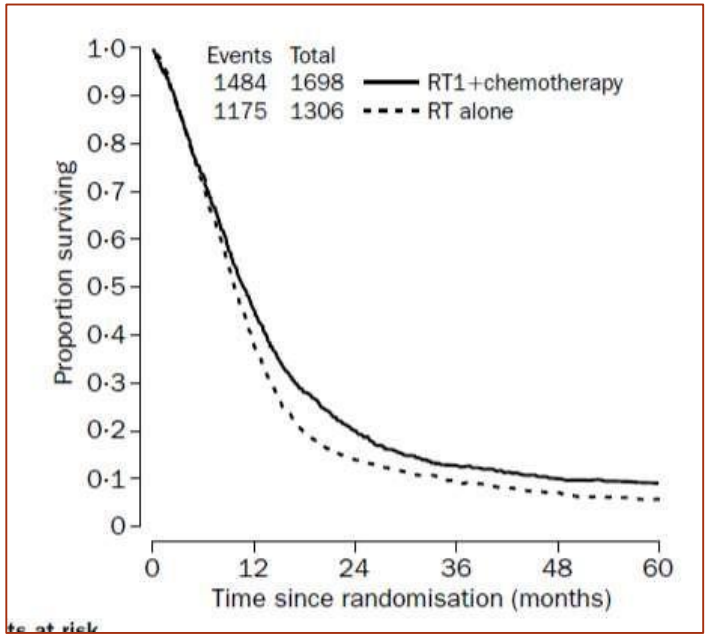
PROTON BEAM THERAPY



Chemotherapy in high grade glioma

Nitrosoureas

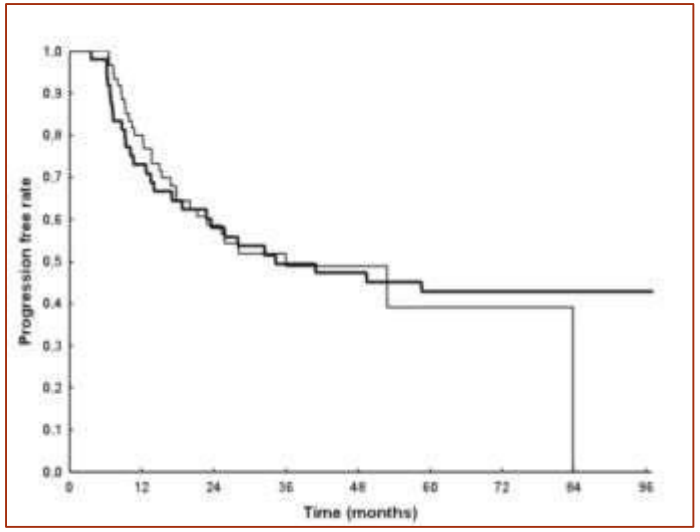
- Historically were standard choice of chemotherapy
- Lipid-soluble agents and can cross the BBB
- BCNU has mainly been evaluated as single-agent therapy
- Dose 150 to 200 mg/m2 i.v6 to 8 weekly
- Toxicities myelosuppression, drug-induced pulmonary fibrosis increases with cumulative dosages

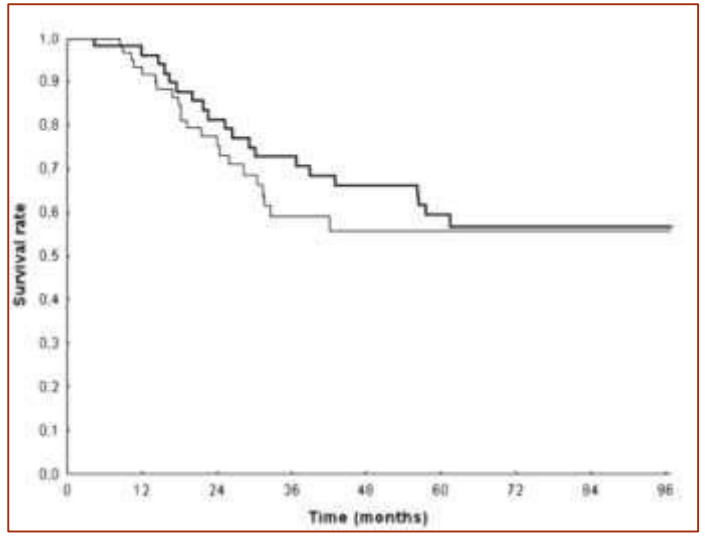


Ref	Accrual dates	Treatment groups included	Eligible histology	Eligible surgery	Delay*	Radiotherapy details	Chemotherapy details	n†
26	1969–72	2/4‡	Anaplastic glioma	Definitive surgical resection	6	Whole brain; 50–60 Gy; 30–35 fractions; 6–7 weeks	Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks	193
27	1971–73	2/3‡	High-grade astrocytoma	Resection, biopsy	2	Whole brain; 40–45 Gy; 25 fractions; 4–5 weeks; cobalt-60	Lomustine 130 mg/m² orally, every 6 weeks	205§
29	1972–76	All	Glioblastoma multiforme	Total or subtotal resection	2	Tumour and margin; 50 Gy; 25–30 fractions; 5 weeks	Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks; lomustine 130 mg/m² orally, every 6–8 weeks	105
30	1974–79	3/4‡	Astrocytoma, grade III/IV (Kernohan)	Resection, biopsy	4	Whole brain; 60 Gy; 35 fractions; 7 weeks; megavoltage	Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks; methyl lomustine 125 mg/m² orally, every 8 weeks; dacarbazine 150 mg/m²×5 intravenously, every 4 weeks‖	511
28	1972–75	3/4‡	Malignant glioma	Definitive surgery	3	Whole brain; 60 Gy; 30–35 fractions; 6–7 weeks; megavoltage	Methyl lomustine 220 mg/m² orally, every 6–8 weeks; carmustine 80 mg/m²×3 intravenously, every 6–8 weeks	355
32	1974–78	2/4¶	Malignant glioma	Definitive surgery	3	Tumour and margin; 60 Gy; 30–35 fractions; 6–7 weeks	Carmustine 80 mg/m²×3 intravenously, every 8 weeks; procarbazine 150 mg/m²×28 days, every 8 weeks	309
31	1975–78	**	Malignant glioma	Optimum resection	4	Tumour and margin; 55–60 Gy; 30 fractions; 6 weeks; betatron, telecobalt, linear accelerator	Lomustine 130 mg/m² orally; epipodophyllotoxin 60 mg/m² intravenously, every 6 weeks	116
33	1978–81	All	Glioblastoma; malignant astrocytoma grade III (WHO/Zulch)	At least subtotal resection	4	Tumour and margin; 51 Gy; 25–30 fractions; 5–6 weeks; cobalt-60	Mitolactol 400 mg/m², every 5 days during radiotherapy, with 1 month rest then repeat; mitolactol 400 mg/m², every 5 days during radiotherapy, with 6 weeks rest then (day 1) lomustine 100 mg/m² followed by dacarbazine 200 mg/m², every 5 days×7	91
34	NK	All	Glioma (high and low grade)††	Resection	3	Tumour and margin; 60 Gy; 30 fractions; 6 weeks; cobalt-60	Lomustine 100 mg/m² orally, every 6–8 weeks	125
Un-publ	1982–87	All	Malignant astrocytoma, glioblastoma, ependymo blastoma, oligondendroglioma	Optimum resection	3	Tumour and margin; 55–60 Gy; 30 fractions; 6 weeks; betatron, telecobalt, linear accelerator	Before radiotherapy: lomustine 130 mg/m² orally, plus epipodophyllotoxin 100 mg/m² intravenously, every 6 weeks 3 courses	235
35	1986–97	All	Astrocytoma grade III/IV (WHO/Zulch)	Resection, biopsy	6	Tumour and margin; 45 Gy; 20 fractions; 4 weeks; or 60 Gy; 30 fractions; 6 weeks; or 55 Gy; 34 twice-daily fractions‡‡	Lomustine 100 mg/m²; procarbazine 100 mg/m² orally×10; vincristine 1·5 mg/m², every 6 weeks	674
36	1989–91	All	Anaplastic astrocytoma, glioblastoma	Resection, stereotactic biopsy (stratified)	4	Tumour and margin; 60 Gy; 30–35 fractions; 6–7 weeks; cobalt-60 or megavoltage	Dacarbazine 700 mg/m²×6 orally during radiotherapy, then carmustine 150 mg/m² intravenously; dacarbazine 1000 mg/m² orally, every 6 weeks	270

Survival following adjuvant PCV or temozolomide for anaplastic astrocytoma

Alba A. Brandes,[1,2] Linda Nicolardi, Alicia Tosoni, Marina Gardiman, Paolo Iuzzolino,





Toxicity	PCV	Temozolamide
Hematolgical	9%	4%

Neuro-Oncology 8, 253–260, 2006

Targeted therapy

- Challenges limiting the efficacy :-

- difficulty in crossing blood brain barrier
- heterogeneity of tumors
- lack of accurate and reproducible biomarker
- difficulty in assessing target modulation

2009 for use in recurrent GBM:

- Bevacizumab received approval by the US Food and Drug Adminstration (FDA) in

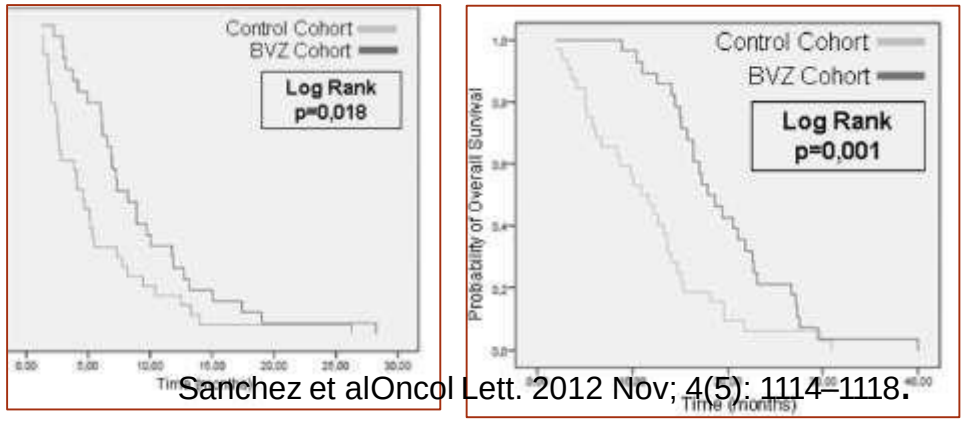
Trial	Study Arms	Ph	Study Setting	N	ORR, %	mPFS, mo	mOS, mo
BRAIN	BEV	II	Recurrent glioblastoma	167	28	4.2	9.2
	BEV + irinotecan				38	5.6	8.7
NCI	BEV	II	Recurrent glioblastoma	48	35	16 wks	31 wks
JO22506	BEV	II	Recurrent glioblastoma (Japan)	31	28	3.3	10.5
AVAglio[	BEV + RT + TMZ vs Placebo + RT + TMZ	III	Newly diagnosed glioblastoma	921	NA	10.6 vs 6.2*	16.8 vs 16.7†

- Only transitory clinical and radiographic benefit for a few month
- Main benefit is secondary to reduction in cerebral edema

Control group – TMZ
BVZ group- BVZ/CPT-11

BVZ/CPT-11

High dose bevacizumab 15 mg/kg 3 weekly
irinotecan 125mg/m2on D1, 8, 22, and 29



Sanchez et alOncol Lett. 2012 Nov; 4(5): 1114–1118.

Immunotherapy

- Based on concept of harnessing the patient's own immune system to stimulate an antitumor response
- Immunosuppression is inherently associated with glioblastoma and is mediated by a variety of mechanisms

Current Status of Immunotherapy and Gene Therapy for High-Grade Gliomas James C. Marsh, MD, Justin Goldfarb, MD, Timothy D. Shafman, MD, and Aidnag Z. Diaz, MD, MPH

Conclusions

Although phase III data are lacking, the existing preclinical, phase I, and phase II data suggest that immunotherapy potentially offers a new approach in the treatment of high-grade gliomas, both in the initial treatment setting and in the context of recurrent tumors.

Registration number	New/recurrent/metastatic	Therapy	Number of patients	Phase
EGFRvIII vaccine				
NCT01480479	New	Rindopepimut/GM-CSF	*n* = 700	Phase III
NCT00626015	New	EGFRvIII peptide vaccine, daclizumab	3 experimental versus 3 control	Pilot
[96]	New	DC vaccine targeting EGFRvIII antigen	*n* = 12	Phase I
[38]	New	EGFRvIII peptide vaccine	*n* = 18	Phase II
[39]	New	EGFRvIII peptide Vaccine, TMZ	*n* = 22	Phase II
[40]	New	Rindopepimut (CDX-110)	*n* = 65	Phase II
Heat-shock protein (HSP) vaccine				
NCT01814813	Recurrent	HSPPC-96 C, bevacizumab	*n* = 222	Phase II
[54]	Recurrent	HSPPC-96 vaccine	*n* = 41	Phase II
[97]	New	HSP70 vaccine	*n* = 12	Pilot
Dendritic cell (DC) vaccines				
NCT00846456	New	DC vaccine against cancer stem cells	*n* = 11	Pilot
NCT00068510	New + recurrent	C vaccine, toll-like receptor agonists	*n* = 23	Phase I
NCT00045968	New	DCVax®-L	*n* = 300	Phase III
[98]	New	DC vaccine	*n* = 10	Pilot
[99]	New	DC vaccine	*n* = 8	Pilot
[100]	New	DC vaccine	*n* = 5	Pilot
[101]	Recurrent	DC vaccine	*n* = 9	Phase I
[47]	New + recurrent	multi-epitope pulsed DC vaccine	*n* = 21	Phase I
[102]	New + recurrent	DC vaccine	*n* = 17	Phase I/II
Adoptive T-cell therapy				
NCT02209376	New + recurrent	CAR T-cells to EGFRvIII	*n* = 12	Phase I
NCT00693095	New	CMV-autologous lymphocyte transfer	*n* = 12	Phase I
NCT01109095	Recurrent	CMV-specific cytotoxic T lymphocytes	*n* = 16	Phase I
NCT01454596	Recurrent	CAR T-cells to EGFRvIII	*n* = 160	Phase I/II
NCT02208362	Recurrent + refractory	Enriched T-cells expressing IL13Ra2	*n* = 44	Phase I
[93]	Recurrent	CMV-specific T-cells	*n* = 19	Phase I

Recurrent Glioblastoma: Nearly Universal and Still a Challenge

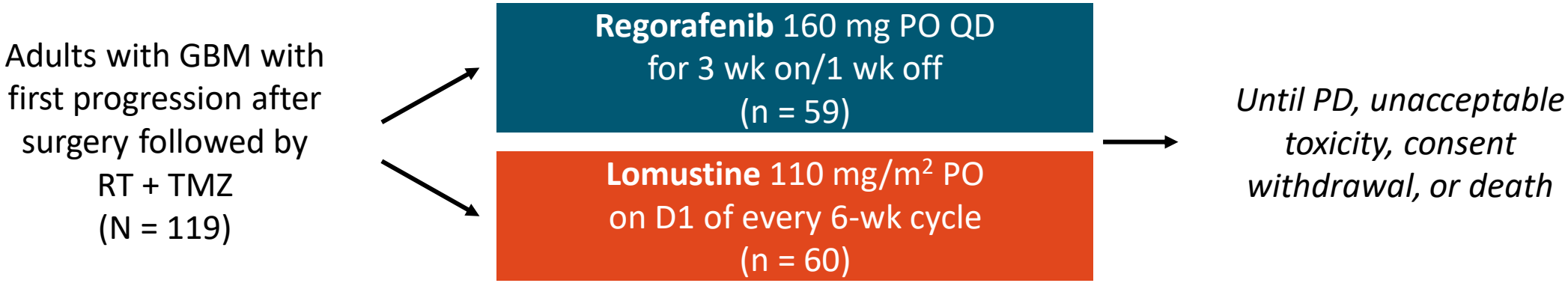
Agent	Class	N	Response Rate, %	Median OS	Median PFS/TTP	6-Mo PFS Rate, %
BCNU[1]	Alkylator	40	15	7.53 mo	TTP: 13.3 wk	17.5
Gefitinib[2.3]	EGFR	57/38	0-13	39.4 wk	TTP: 8 wk	9-13.2
Erlotinib[4-6]	EGFR	48/38 /16	6.3	6-9.7 mo	PFS: 2 mo TTP: 145 d	3-20
Imatinib[7,8]	PDGFR	50/35	3-6	5.9 mo	PFS: 1.8 mo	6-8
Temsirolimus[9,10]	mTOR	43/65	0-5	4.4 mo	TTP: 9 wk TTP: 2.3 mo	2-8
Pooled ph II[11]	Various, 1998-2002	291	7*	26 wk	PFS: 7 wk	9

*Response rate reported for n = 437 patients who received TMZ or other therapies.

1. Brandes, Neurology 2004;63:1281. 2. Rich. JCO. 2004;22:133. 3. Lieberman. ASCO 2003. Abstr 421. 4. Yung. Neuro Oncol. 2010;12:1061. 5. Raizer. Neuro Oncol. 2010;12:95. 6. Vogelbaum. ASCO 2004. Abstr 1558. 7. Raymond. JCO. 2008;26:4659. 8. Wen. Clin Cancer Res. 2006;12:4899. 9. Chang. Invest New Drugs. 2005;23:357. 10. Galanis. JCO. 2005;23:5294. 11. Lamborn. Neuro Oncol. 2008;10:162.

Regorafinib (REG, Multi-TKI): Improves 6-Mo PFS, OS in rGBM?

- Randomized, multicenter, open-label phase II trial in Italy

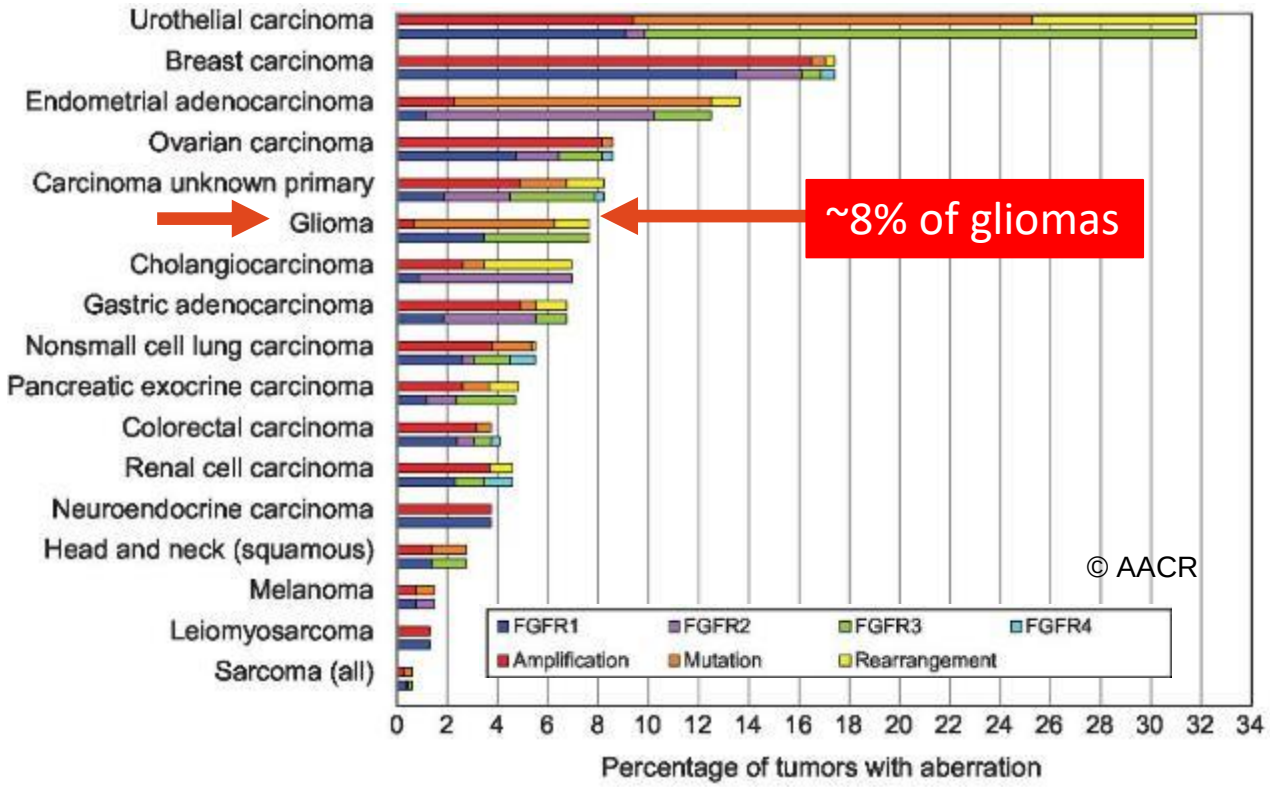


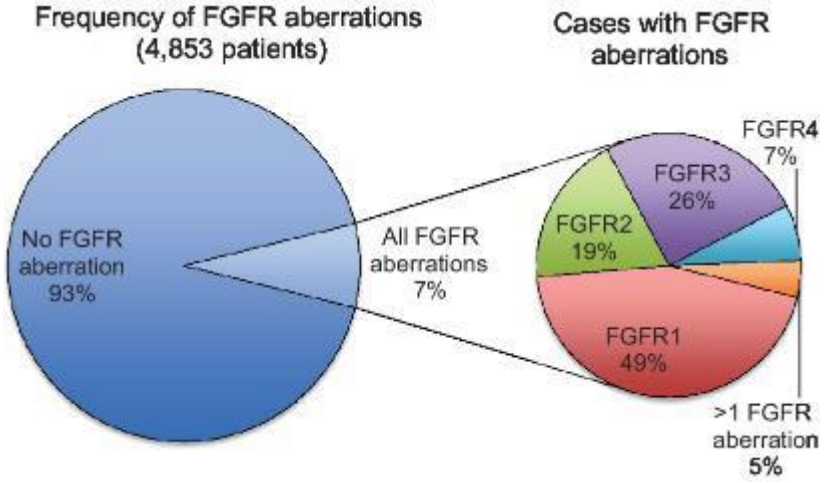
Treatment Arm	6-Mo PFS Rate, %	Median OS, Mo
Regorafenib (n = 59)	16.9	7.4
Lomustine (n = 60)	8.3	5.6

- Positive treatment arm or
- Negative control arm?
- GBM AGILE trial ongoing (NCT03970447)
  - nGBM and rGBM

Lombardi. Lancet Oncol. 2019;20:110.

FGFR Abnormalities in Solid Tumors: Fusions





Singh. Science 2012;337:1231. Di Stefano. Clin Cancer Res. 2015;21:3307. Lasorella. Neuro Oncol. 2017;19:475. Helsten. Clin Cancer Res. 2016;22:259.

FGFR Abnormalities and Infigratinib

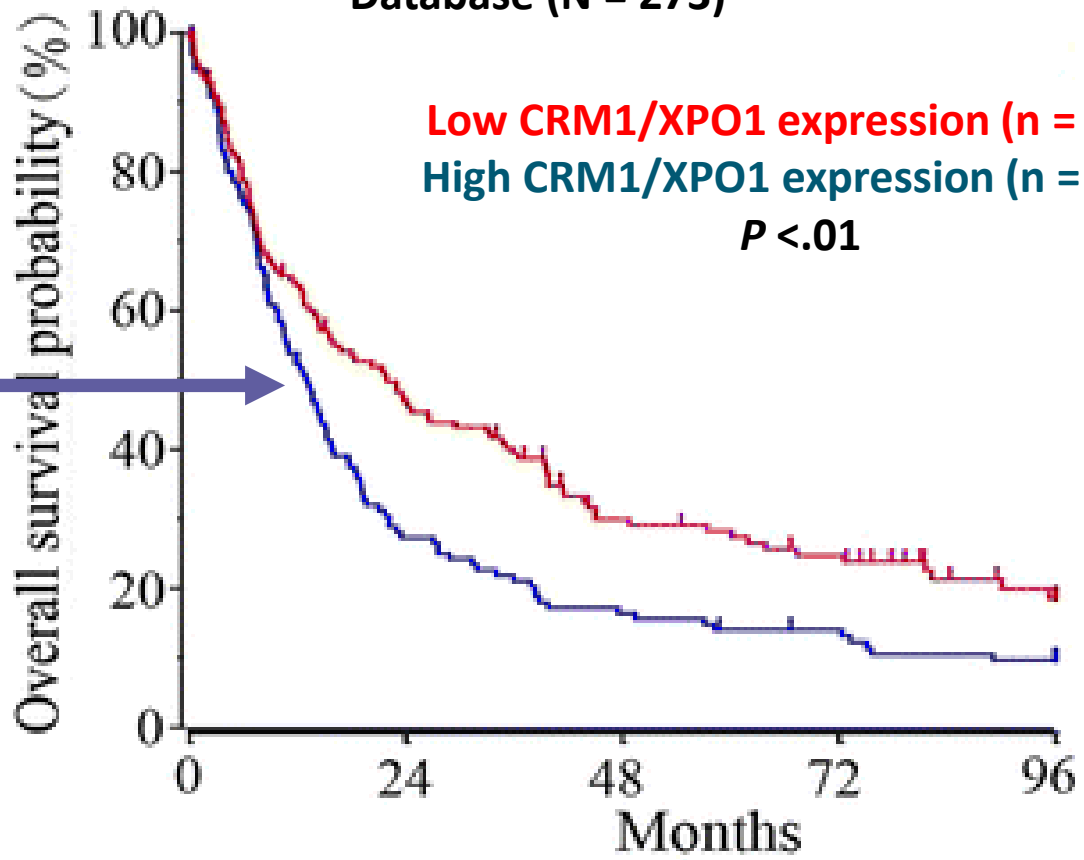
- *FGFR-TACC* fusions
  - Predict response to FGFR TKIs in vitro and in vivo[1,2]
  - Role of *FGFR* amplifications or other mutations less clear
- Infigratinib: FGFR1-3 TKI in development for *FGFR*-driven cancers with high disease control rates, with accelerated FDA approval for *FGFR* fusion–positive advanced cholangiocarcinoma[3,4]
- Conducted international phase II study for *FGFR*-altered recurrent glioma

1. Di Stefano. Clin Cancer Res. 2015;21:3307. 2. Singh. Science. 2012;337:1231.
3. Javle. JCO. 2018;36:276. 4. Pal. Cancer Discov. 2018;8:812.

Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export

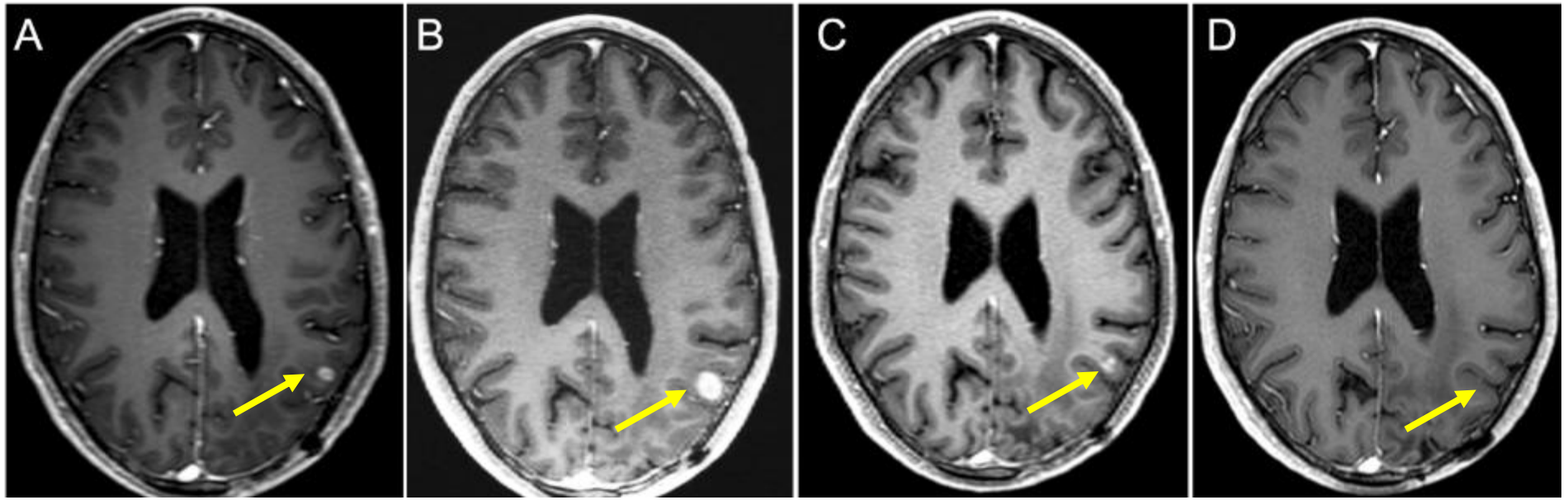
- Exportin 1 (XPO1)[1]
  - Major nuclear exporter
  - Protein mislocalization
  - **Higher expression correlates with worse prognosis in GBM[2]**
- Selinexor[3]
  - Selective XPO1 inhibitor
  - FDA accelerated approval for MM (2019)[4], DLBCL (2020)[5]

OS in Patients With Glioma From R2 Genomics Database (N = 273)[2]



1. Green. Neuro Oncol. 2015;17:697. 2. Liu. J Hematol Oncol. 2016;9:108. 3. Argueta. Oncotarget. 2018;9:25529.
4. FDA. FDA grants accelerated approval to selinexor for multiple myeloma. 5. FDA. FDA approves selinexor for relapsed/refractory diffuse large B-cell lymphoma.

Durable Response to Selinexor



Pre-baseline | Baseline | Partial Response | Complete Response

Subsequent trial in newly diagnosed and recurrent GBM ongoing (XPORT)

Lassman. Clin Cancer Res. 2022;28:452.

Conclusion of KING Trial

- At 80 mg weekly, single-agent selinexor induced responses and clinically relevant PFS6 with manageable side effects requiring dose reductions.
- Ongoing trials are evaluating safety and efficacy of selinexor in combination with other therapies for newly diagnosed or recurrent glioblastoma.

ICI therapy in recurrent GBM

Phase I data, Recurrent GBM:

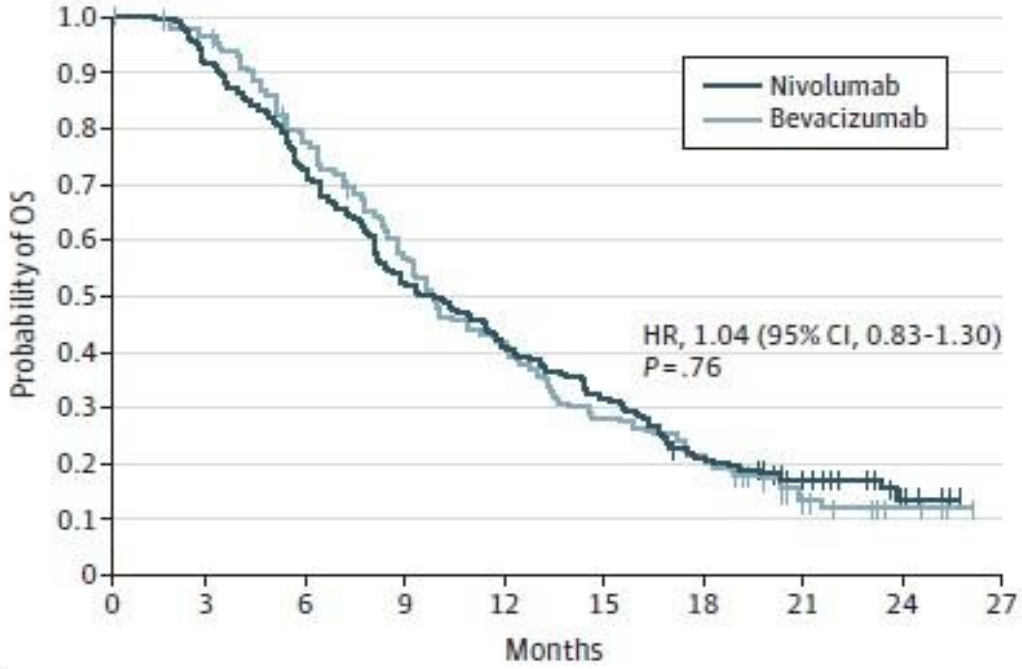
Immune checkpoint inhibitors in first recurrence after radiation/temozolomide (bevacizumab-naïve)

Pembrolizumab (PD-1)	Nivolumab (PD-1)	Durvalumab (PD-L1)
• n=26	• n=10	• n=30
• 4% ORR (1 patient)	• 10% ORR (1 patient)	• 13% ORR (4 patients)
• **OS-12 mo = 74%**	• **OS-9 mo = 60%**	• **OS-12 mo = 44%**
• 15% grade 3/4 AEs	• No grade 3/4 AEs	• 10% grade 3/4 AEs

Reardon DA et al, SNO Annual Meeting 2016
Lim M et al, ASCO 2016

A Probability of OS by intervention

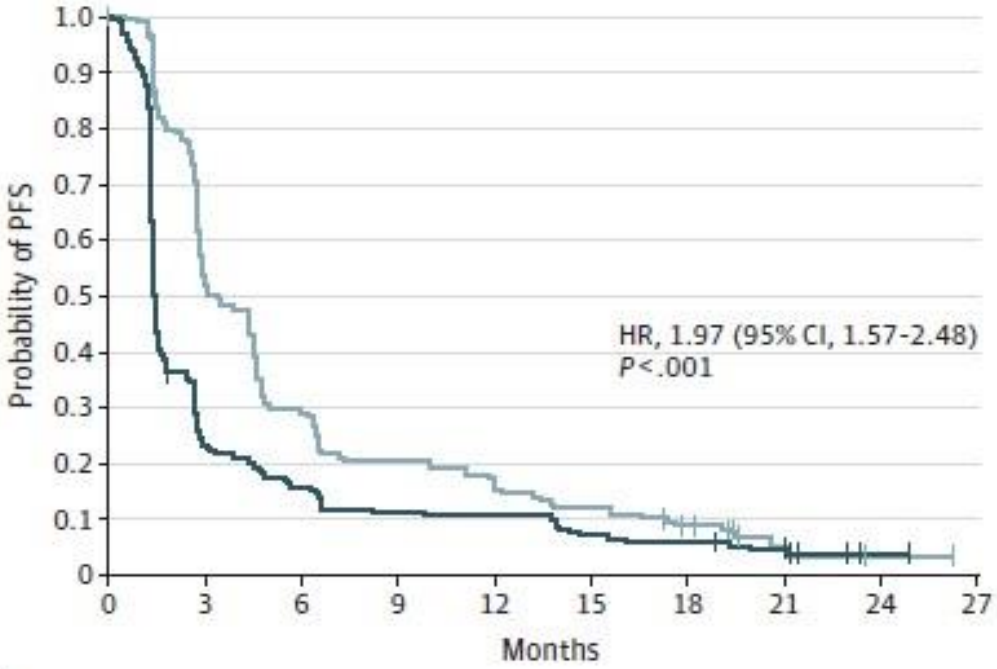
Intervention	Events, No.	Median OS (95% CI), months	OS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	154	9.8 (8.2-11.8)	72.3 (65.2-78.2)	41.8 (34.7-48.8)	21.7 (16.1-27.9)
Bevacizumab	147	10.0 (9.0-11.8)	78.2 (71.2-83.6)	42.0 (34.6-49.3)	21.6 (15.8-28.0)



No. at risk										
Nivolumab	184	168	133	96	77	59	39	24	9	0
Bevacizumab	185	169	135	99	72	48	37	14	5	0

B Probability of progression-free survival

Intervention	Events, No.	Median PFS (95% CI), months	PFS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	171	1.5 (1.5-1.6)	15.7 (10.8-21.5)	10.5 (6.5-15.5)	5.8 (3.0-10.0)
Bevacizumab	146	3.5 (2.9-4.6)	29.6 (22.7-36.9)	17.4 (11.9-23.7)	8.9 (5.1-14.1)



No. at risk										
Nivolumab	184	41	27	19	18	12	10	7	1	0
Bevacizumab	185	88	46	32	27	19	12	3	1	0

Reardon DA et al, Jama Oncology 2020

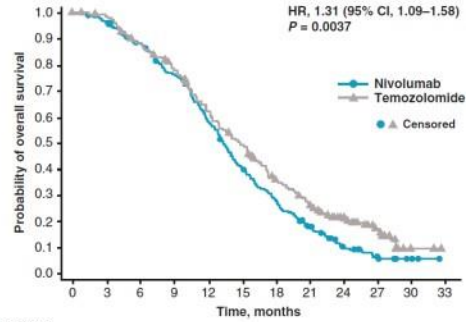
ICI therapy in newly diagnosed GMB

Neuro-Oncology
XX(XX), 1–12, 2022 | https://doi.org/10.1093/neuonc/noac099 | Advance Access date 14 April 2022

Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated *MGMT* promoter: An international randomized phase III trial

A

	Events, n	Median overall survival (95% CI), mo
Nivolumab plus radiotherapy	244	13.4 (12.6–14.3)
Temozolomide plus radiotherapy	218	14.9 (13.3–16.1)

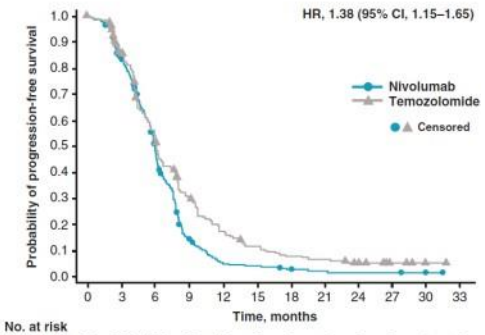


No. at risk

Nivolumab	280	270	243	209	158	110	76	44	19	9	2	0
Temozolomide	280	272	242	212	166	131	92	67	37	19	2	0

B

	Events, n	Median progression-free survival (95% CI), mo
Nivolumab plus radiotherapy	251	6.0 (5.7–6.2)
Temozolomide plus radiotherapy	240	6.2 (5.9–6.7)



No. at risk

Nivolumab	280	225	130	36	13	10	6	4	3	3	1	0
Temozolomide	280	227	141	76	43	28	19	16	11	5	1	0

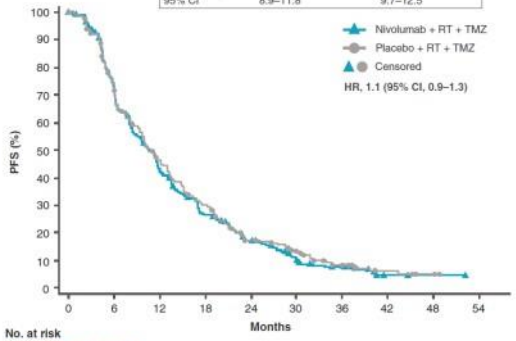
Omuro A et al, NeuroOncol 2022

Neuro-Oncology
24(11), 1935–1949, 2022 | https://doi.org/10.1093/neuonc/noac116 | Advance Access

Phase III trial of chemora… plus nivolumab o… glioblastom…

A

	Nivolumab + RT + TMZ n = 358	Placebo + RT + TMZ n = 358
No. of events	274	283
PFS, median, mo (95% CI)	10.6 (8.9–11.8)	10.3 (9.7–12.5)

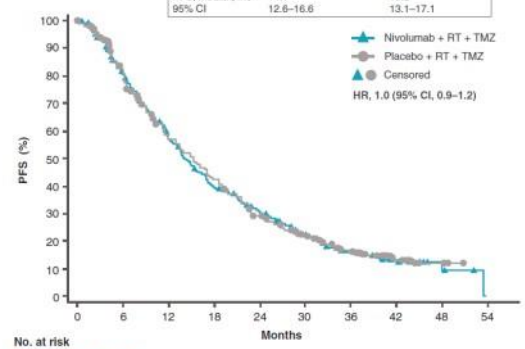


No. at risk

Nivolumab + RT + TMZ	358	294	222	167	130	100	77	67	47	36	22	15	13	9	2	1	1	1	0					
Placebo + RT + TMZ	358	300	238	185	142	116	90	66	48	40	30	18	13	6	5	4	2	0	0					

B

	Nivolumab + RT + TMZ n = 358	Placebo + RT + TMZ n = 358
No. of events	259	267
PFS, median, mo (95% CI)	14.1 (12.6–16.6)	15.2 (13.1–17.1)



No. at risk

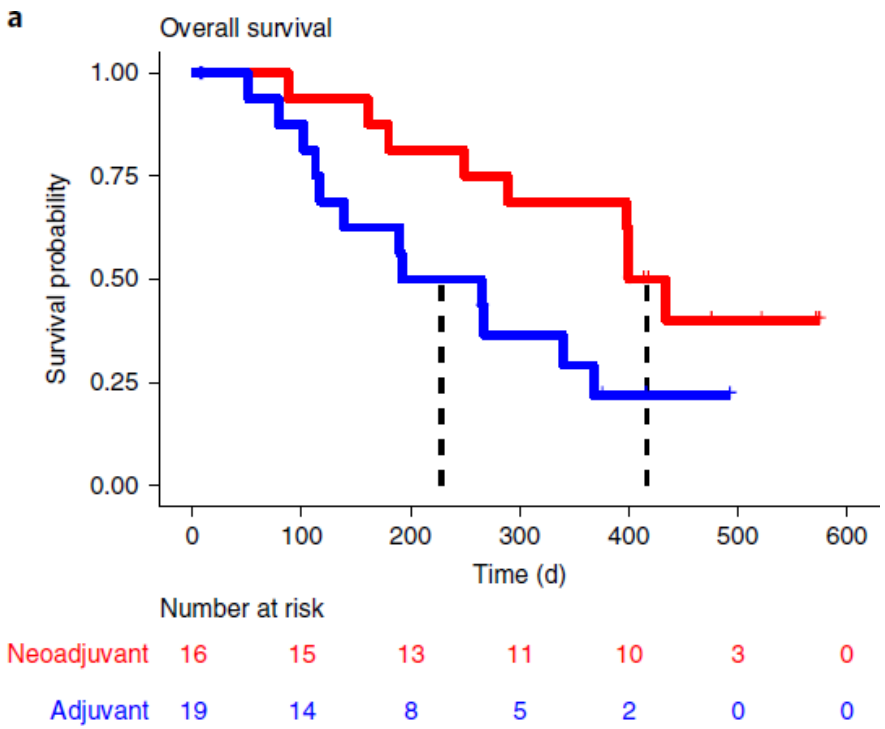
Nivolumab + RT + TMZ	358	309	260	214	174	143	118	104	87	73	54	35	26	20	15	5	4	2	0					
Placebo + RT + TMZ	358	321	268	220	182	161	135	112	89	72	57	43	34	24	16	5	3	0	0					

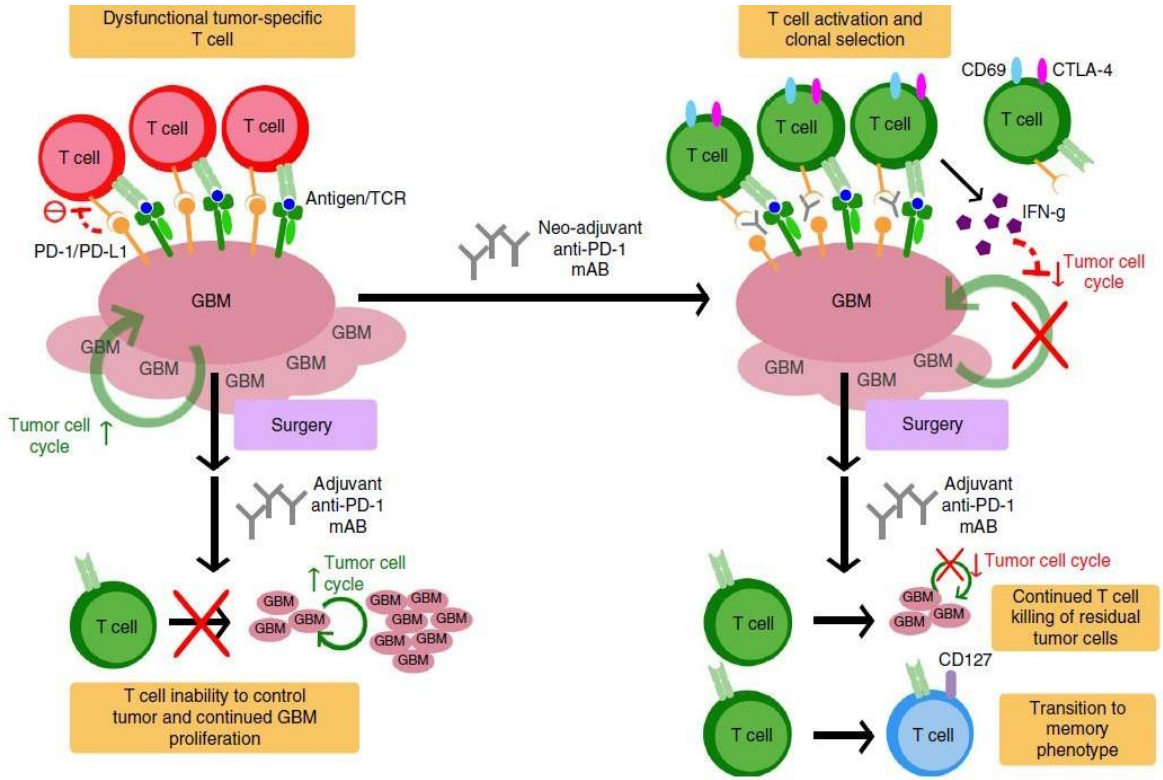
Lim M et al, NeuroOncol 2022

nature medicine
FOCUS | ARTICLES
https://doi.org/10.1038/s41591-018-

Neoadjuvant anti-PD-1 immunotherapy
a survival benefit with intratumor
immune responses in recur

Timothy F. Cloughesy[1,2,3,18*], Aaron Y. Mo
Alexander H. Lee[2,5], Tom B. David
Julie A. Rytlewski[8], Cather
Sarah C. Gaffey[11], Ada
Barbara J. O'Br
Isabel C
P





Clinical trials of ICIs

Number	Treatment	Type of Study	Setting	N of patients
NCT02337686	Pembrolizumab	Phase II	Recurrent glioblastoma (rGBM)	20
NCT02667587	Nivolumab	Phase III	Newly diagnosed MGMT-methylated GBM	716
NCT02617589	Nivolumab	Phase III	Newly diagnosed MGMT-unmethylated GBM	560
NCT03047473	Adjuvant avelumab	Phase II	Newly diagnosed GBM	30
NCT02852655	Neoadjuvant pembrolizumab	Phase I	Surgically accessible recurrent/progressive GBM	25
NCT02974621	Cediranib	Phase II	rGBM	70
NCT03197506	Neoadjuvant pembrolizumab combined with adjuvant RT/TMZ/pembrolizumab	Phase II	Newly diagnosed GBM	50
NCT03158389	Matches one of 7 drugs to patients (APG101, idasanutlin,alectinib, vismodegib, atezolizumab, Palbociclib, and temsirolimus) in view of molecular markers after surgery.	Phase I/II	MGMT-unmethylated GBM	350
NCT03174197	Atezolizumab	Phase I/II	Newly diagnosed GBM	80
NCT03925246	Nivolumab	Phase II	Recurrent IDH mutant GBM	43
NCT03341806	Avelumab	Phase I	rGBM	13
NCT03426891	Pembrolizumab	Phase I	Newly diagnosed GBM	21
NCT04323046	Ipilimumab/nivolumab+adjuvant nivolumab	Phase I	Recurrent/progressive high-grade glioma	45
NCT03532295	Epacadostat+INCMGA00012	Phase II	rGBM	55
NCT03718767	Adjuvant nivolumab	Phase II	IDH mutant glioma	95
NCT03899857	pembrolizumab	Phase II	newly diagnosed GBM	56
NCT03493932	Nivolumab with BMS-986016	Phase I	rGBM	20
NCT03961971	MBG453 + Spartalizumab	Phase I	rGBM	15
NCT04047706	BMS 986,205+ nivolumab	Phase I	Newly diagnosed GBM	30
NCT04145115	ipilimumab+nivolumab	Phase II	Somatically hypermutated glioblastoma	37
NCT04225039	schedule	Phase II	rGBM	32
NCT04826393	ASP8374 + cemiplimab	Phase Ib	Recurrent high-grade glioma	24
NCT04396860	ipilimumab nivolumab	Phase II/III	Newly diagnosed IDH wild type MGMT-unmethylated glioblastoma.	485
NCT04608812	OS2966	Phase I	Newly diagnosed GBM	24
NCT04729959	Tocilizumab±atezolizumab	Phase II	rGBM	12
NCT04817254	ipilimumab	Phase II	Newly diagnosed GBM or gliosarcoma	48
NCT04656535	AB154 + AB122	Phase 0/I	rGBM	46
NCT04922723	daratumumab	Phase I/II	Newly diagnosed GBM	16
NCT04952571	Camrelizumab+ bevacizumab	Phase II	rGBM	94

Medulloblastoma

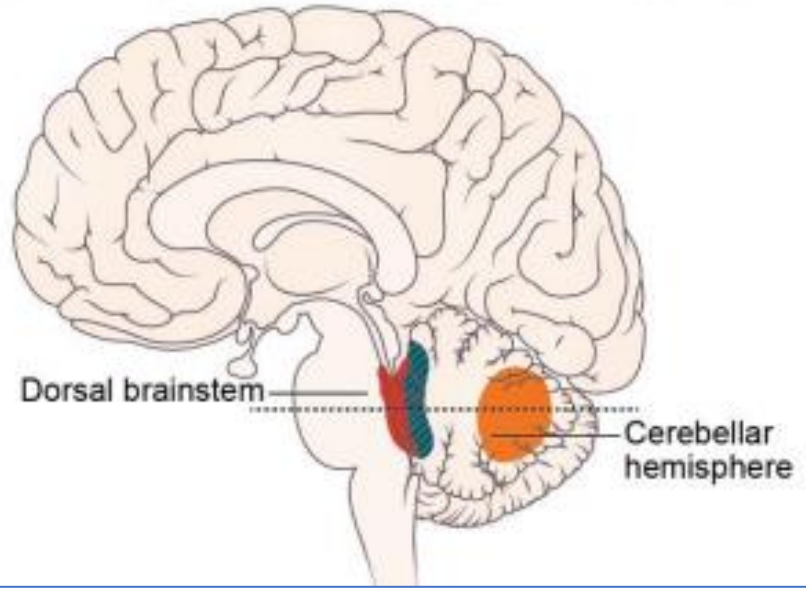
- Medulloblastoma is a central nervous system (CNS) tumor of cerebellar origin that comprises approximately 1% of all brain tumors.
- However, medulloblastoma is the most common malignant brain cancer in children, accounting for 25–30% of childhood brain tumors and over 40% of posterior fossa childhood tumors.
- Most patients present before 16 years of age, with over 70% before 10, a third of which are younger than 3 years old; very few cases present under 1 year old.
- The median age of diagnosis in children is about 5–7 years

Fang FY, et al. Cancers. 2022 May 3;14(9):2285.

Molecular Subtyping

Meduloblastoma subtypes

	Wnt	Shh	Group 3	Group 4
Molecular features	•CTNNB1 •Monosomy 6	•GL1 •SUFU •PTCH1 •TP53 •SMO	•FSTL5 •MYC •VEGFA	•KDM6A •MYC •OTX
5-year survival rate	95-100%	40% (p53 mutant) & 80% (p53 wildtype)	~30-60%	75%
Anatomical location	Dorsal brainstem	Cerebellar hemisphere	Midline	Midline



Fang FY, et al. Cancers. 2022 May 3;14(9):2285.

Clinical trials and therapies in development for the four pediatric medulloblastoma subtypes

WNT Subtype	
Clinical trial: Reducing doses of craniospinal radiation and chemotherapy	NCT01878617: A Clinical and Molecular Risk-Directed Therapy for Newly Diagnosed Medulloblastoma
	NCT02066220: International Society of Paediatric Oncology (SIOP) PNET 5 Medulloblastoma
	NCT02724579: Reduced Craniospinal Radiation Therapy and Chemotherapy in Treating Younger Patients with Newly Diagnosed WNT-Driven Medulloblastoma
Proposed therapy: WNT antagonists	Phoenix, et al. (2016) [31] reported that WNT antagonists block the formation of a blood-brain barrier, and thereby promote chemotherapy penetration and high intratumoral drug concentrations.
SHH Subtype	
Proposed therapy: nanoparticles	Valcourt, et al. (2020) [32] and Caimano, et al. (2021) [33] reported their development of nanoparticles that encapsulate SMO or GLI inhibitors to improve drug delivery to this tumor subtype.
Group 3 Subtype	
Proposed therapy: Ribavirin	Huq, et al. (2021) [34] reported therapeutic potential for ribavirin to reduce medulloblastoma cell growth and prolong survival.
Proposed therapy: Anti-vascularization therapy	Thompson, et al. (2017) [35] reported increased vascularity in Group 3 tumors and proposed using anti-VEGFA anti-vascularization therapy to inhibit tumor growth.
Group 4 Subtype	
Proposed therapy: anti-ERBB4-SRC receptor tyrosine kinase	Forget, et al. (2018) [36] demonstrated that the combination of TP53 inactivation and aberrant signaling of the ERBB4-SRC receptor tyrosine may induce Group 4-like tumor growth. They suggested molecular therapies to inhibit these effects.

Fang FY, et al. Cancers. 2022 May 3;14(9):2285.

Clinical trials involving immune checkpoint-targeting immunotherapy in medulloblastoma.

Trial ID	Title	Phase	Treatment	Target	Indications	Age	N	Status
NCT 04730349	A Study of Bempegaldesleukin (BEMPEG: NKTR-214) in Combination with Nivolumab in Children, Adolescents and Young Adults with Recurrent or Treatment-resistant Cancer (PIVOT IO 020)	1/2	i.v. nivolumab with bempegaldesleukin (BEMPEG: NKTR-214)	PD1, CD122	Ependymoma Ewing sarcoma High-grade glioma Leukemia and lymphoma Medulloblastoma Miscellaneous brain tumors Miscellaneous solid tumors Neuroblastoma Relapsed, refractory malignant neoplasms Rhabdomyosarcoma	<18 and 18–30 years	228	Not yet recruiting
NCT 03130959	An Investigational Immuno-therapy Study of Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Pediatric Patients with High Grade Primary CNS Malignancies (CheckMate 908)	2	Nivolumab, ipilimumab	PD1, CTLA-4	Various Advanced Cancer (including MB)	6 months–21 years	166	Active, not recruiting
NCT 03173950	Immune Checkpoint Inhibitor Nivolumab in People with Recurrent Select Rare CNS Cancers	2	i.v. nivolumab	PD1	Medulloblastoma Ependymoma Pineal region tumors Choroid plexus tumors Atypical/malignant meningioma	>18 years	180	Recruiting
NCT 02359565	Pembrolizumab in Treating Younger Patients with Recurrent, Progressive, or Refractory High-Grade Gliomas, Diffuse Intrinsic Pontine Gliomas, Hypermutated Brain Tumors, Ependymoma or Medulloblastoma	1	i.v. pembrolizumab	PD1	Constitutional Mismatch repair Deficiency syndrome Lynch syndrome Malignant glioma Recurrent brain neoplasm Recurrent childhood ependymoma Recurrent diffuse intrinsic pontine glioma Recurrent medulloblastoma Refractory brain neoplasm Refractory diffuse intrinsic pontine glioma Refractory ependymoma Refractory medulloblastoma	1–29 years	110	Recruiting
NCT 03838042	INFORM2 Study Uses Nivolumab and Entinostat in Children and Adolescents with High-risk Refractory Malignancies (INFORM2 NivEnt)	1/2	Nivolumab and entinostat	PD1	CNS Tumor Solid Tumor	6–21 Years	128	Recruiting
NCT 02502708	Study of the IDO Pathway Inhibitor, Indoximod, and Temozolomide for Pediatric Patients with Progressive Primary Malignant Brain Tumors	1	Oral indoximod with radiation therapy, temozolomide, or cyclophosphamide and etoposide	IDO	Glioblastoma multiforme Glioma Gliosarcoma Malignant brain tumor Ependymoma Medulloblastoma Diffuse intrinsic pontine glioma Primary CNS tumor	3–21 years	81	Completed
NCT 04049669	Pediatric Trial of Indoximod With Chemotherapy and Radiation for Relapsed Brain Tumors or Newly Diagnosed DIPG	2	Oral indoximod with combinations of temozolomide, cyclophosphamide, etoposide, lomustine and radiation therapy.	IDO	Glioblastoma Medulloblastoma Ependymoma Diffuse intrinsic pontine glioma	3–21 years	140	Recruiting

Voskamp MJ, et al. Cancers. 2021 Oct 27;13(21):5387.

Chemotherapy in WHO grade I astrocytoma

- Chemotherapy is often utilised as the initial therapeutic option in young children to avoid long term sequelae of RT
- Multi centric trial suggestive of 50% of reduction in volume of tumor vs none in placebo group

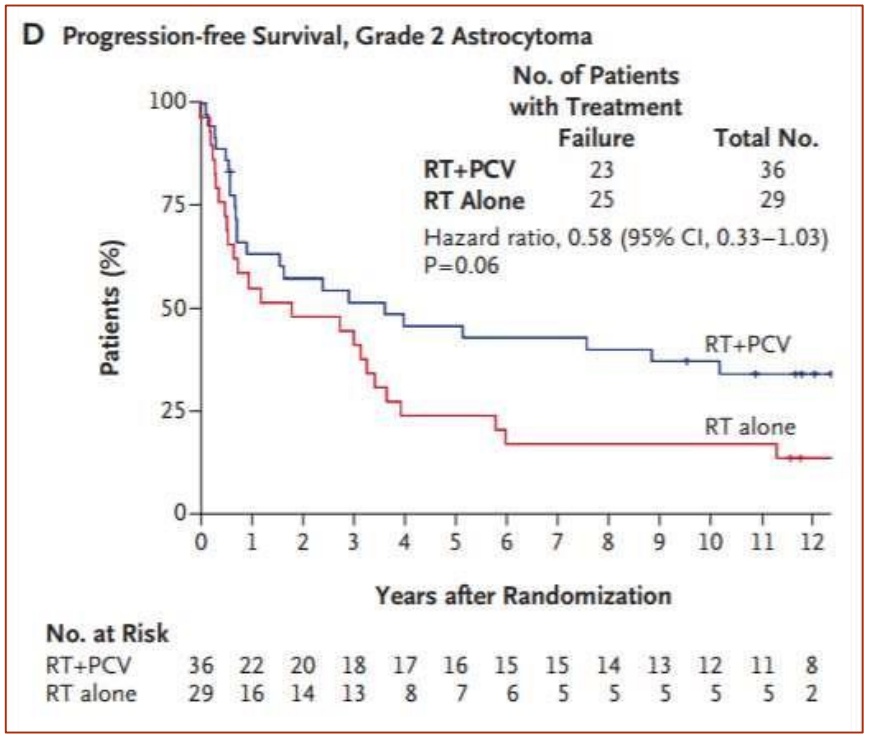
Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial

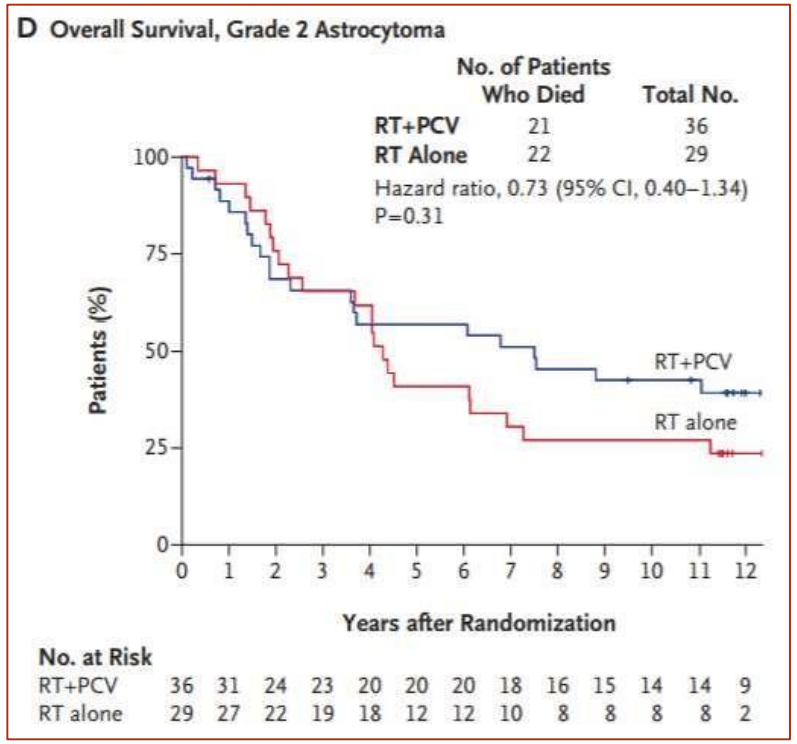
David Neal Franz, Elena Belousova, Steven Sparagana, E Martina Bebin, Michael Frost, Rachel Kuperman, Olaf Witt, Michael H Kohrman,

Chemotherapy in low grade diffuse gliomas

ORIGINAL ARTICLE

Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma





High risk diffuse LGGS

18 to 39 years of age with STR or biopsy

↓

EBRT 54 Gy/ 30#/6 wks

↓

PCV- 6 cycles

No trials comparing temozolamide with PCV for grade II

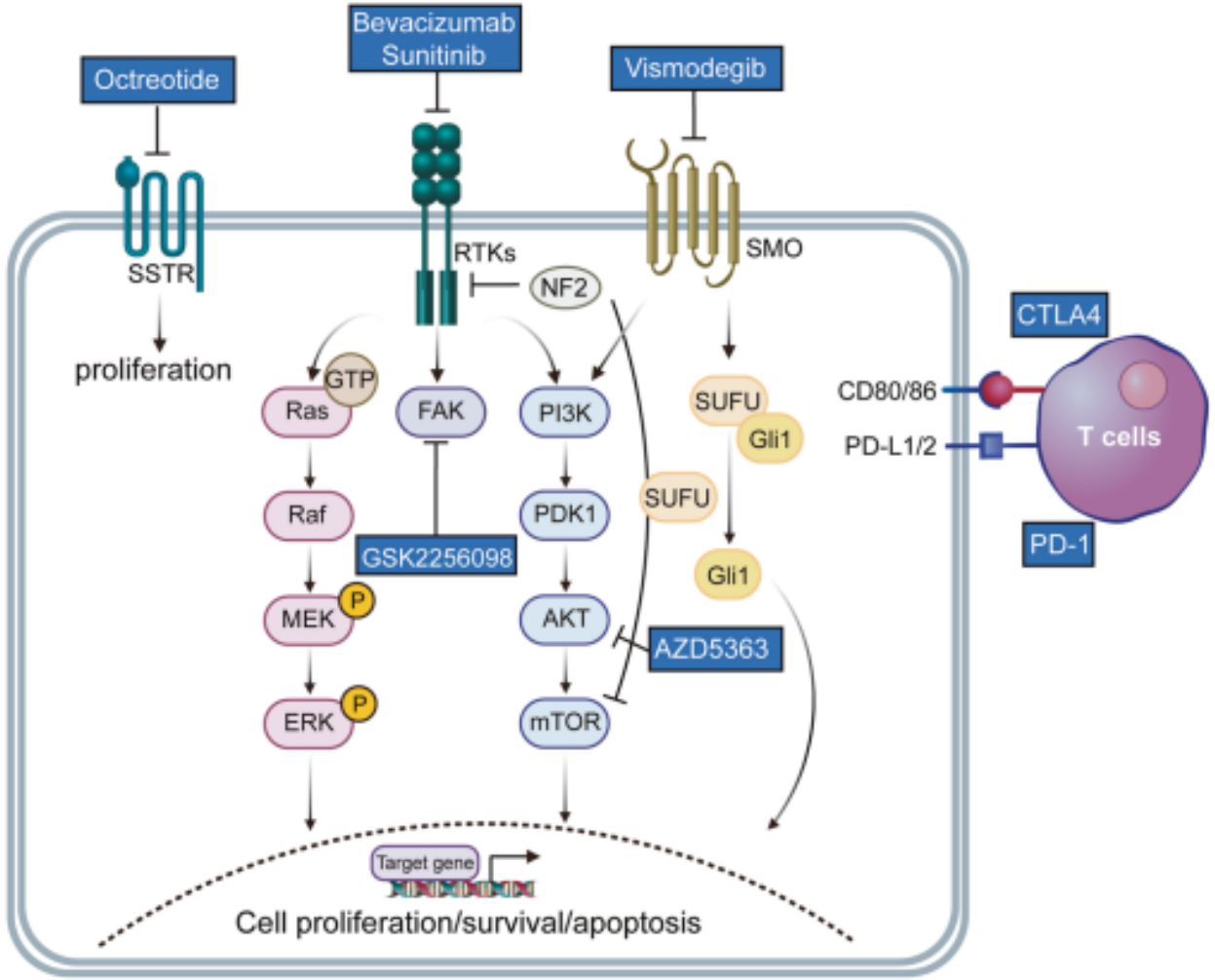
N Engl J Med. 2016;374(14):1344.

Meningioma

- Meningiomas are a primary intracranial tumor in adults, and this disease harbors an annual incidence rate of approximately 8.58 cases per 100,000 population.
- Incidence elevates with age, especially in those over 65 years.
- The overall proportion of WHO grade 1 was 80%, and about 20% are WHO grade 2 or 3.
- Among WHO grade 1/2 meningiomas, the incidence is 2.3 times higher in women than in men.

Li S, et al. Signal Transduction and Targeted Therapy. 2023 Jan 4;8(1):8.

- Summary of the activated signaling pathways and drug targets in meningioma



Li S, et al. Signal Transduction and Targeted Therapy. 2023 Jan 4;8(1):8.

Indications for systemic therapies of meningiomas

- Recurent or progressive WHO 1, 2, 3 mengingiomas not treatable (anymore) by surgery or radiotherapy
- Surgically inaccessible (e.g. skull base)
- Multiple meningioma
- En plaque
- Metastatic meningioma
- Clinical trials

SYSTEMIC TREATMENT FOR GRADE 2,3 MENINGIOMAS: DO WE HAVE A STANDARD?

A variety of systemic treatment agents such as temozolomide, **bevacizumab**, **somatostatin analogues**, **hydroxyurea**, irinotecan, everolimus, vatalanib (PTK787/ ZK-222584), **sunitinib**, mifepristone, interferon-α, imatinib, erlotinib, gefitinib, and the combination of cyclophosphamide, doxorubicin, and vincristine have been investigated with poor results

Treatment	Type of Study	n	Results
Hydroxyurea [65]	Retrospective	60	6-month PFS: 10%
Hydroxyurea [66]	Retrospective	35	6-month PFS: 3% Median OS: 8 months
Hydroxyurea plus imatinib [67]	Phase 2	15	Early interrupted for slow accrual No significant activity
Temozolomide [68]	Phase 2	16	6-month PFS: 0% Median OS: 7.5 months
Irinotecan [69]	Phase 2	16	6-month PFS: 6% Median OS: 7 months
Trabectedin [71]	Randomized phase 2 (EORTC-1320-BTG)	90	No improvement of median PFS or median OS
Interferon-α [73]	Phase 2	35	6-month PFS: 54% Median OS: 8 months
Interferon-α [74]	Retrospective series	35	6-month PFS: 17% Median OS: 8 months
Pasireotide [75]	Phase 2	34	Grade 1: 6-month PFS: 50%: median OS: 104 weeks Grade 2–3: 6-month-PFS: 17%; median OS: 26 weeks
Octreotide [76]	Phase 2	16	6-month PFS: 44% Median OS: 7.5 months
Octreotide [77]	Phase 2	9	6-month PFS: 44% Median OS: 18.7 months
Bevacizumab [80]	Retrospective series	14	6-month PFS: 86% Median OS: not reached
Bevacizumab [81]	Retrospective series	15	6-month PFS: 44% Median OS: 15 months
Bevacizumab plus everolimus [79]	Phase 2	17	Stable disease: 88% 6-month PFS: 69% Median OS: 23.8 months
Everolimus plus octreotide [85]	Phase 2 (CEVOREM trial)	20	6-month PFS: 55% 6-month OS: 90% 12-month OS: 75% Partial response in 78% of patients
Erlotinib or gefitinib [82]	Phase 2	25	Grade 1: 6-month PFS: 25%; 12-month OS: 50% Grade 2–3: 6-month PFS: 29%; 12-month OS: 65%
Imatinib [83]	Phase 2	23	Grade 1: 6-month PFS: 45% Grade 2–3: 6-month PFS: 0%
Sunitinib [78]	Phase 2	36	6-month PFS: 42% Median PFS: 5.2 months Median OS: 24.6 months
Mifepristone [84]	Randomized phase 3 (SWOG-S9005)	164	No statistical difference between mifepristone and placebo in terms of PFS and OS

Pellerino et al, 2022

Neuro-Oncology 2014; **0**, 1–6, doi:10.1093/neuonc/nou148

Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma

Thomas J. Kaley, Patrick Wen, David Schiff, Keith Ligon, Sam Haidar, Sasan Karimi, Andrew B. Lassman*, Craig P. Nolan, Lisa M. DeAngelis, Igor Gavrilovic, Andrew Norden, Jan Drappatz, Eudocia Quant Lee, Benjamin Purow, Scott R. Plotkin, Tracy Batchelor, Lauren E. Abrey, and Antonio Omuro

Table 1. Patient characteristics

	Aggressive Meningioma ($n = 36$)	Exploratory ($n = 13$)
Gender		
Male	14 (39%)	5 (38%)
Female	22 (61%)	8 (62%)
Median age (range)	61 (27–85)	48 (32–79)
Median KPS (range)	80 (60–100)	90 (60–100)
Histology		
Anaplastic (WHO grade III) meningioma	6	
Atypical (WHO grade II) meningioma	30	
Benign (WHO grade I) meningioma		4
Hemangiopericytoma		6
Hemangioblastoma		3
Number of prior therapies		
Median	5	5
Range	2–10	3–11
Mean	4.7	5.2
Location		
Frontal	14 (39%)	8 (62%)
Parietal	8 (22%)	0
Temporal	5 (14%)	2 (15%)
Occipital	3 (8%)	0
Infratentorial/spine	4 (11%)	2 (15%)
Extracranial	1 (3%)	0
Unknown	1 (3%)	1 (8%)

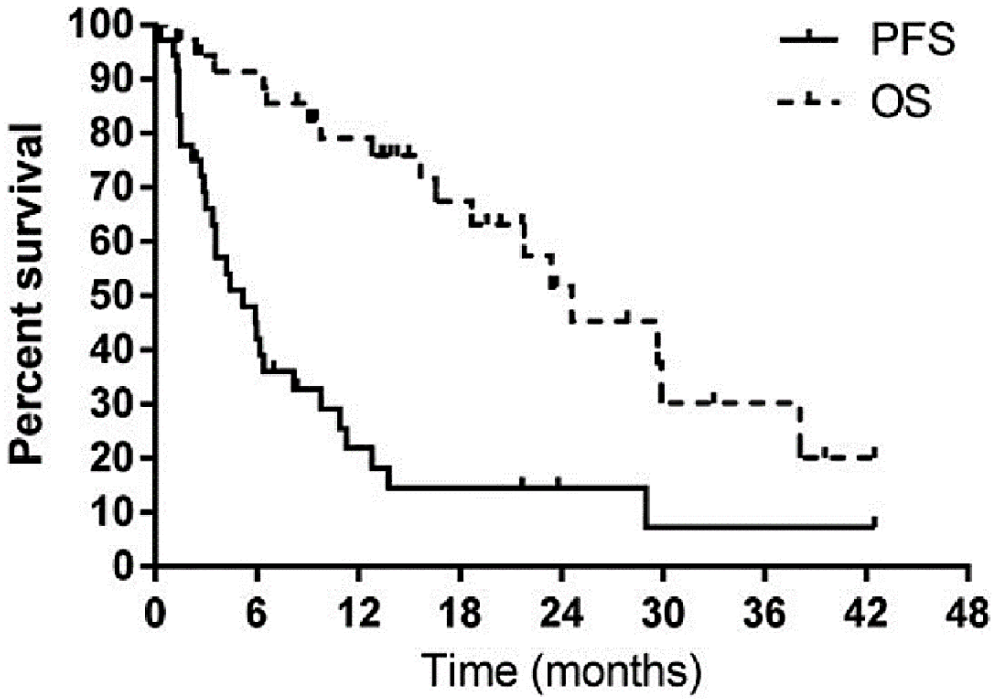
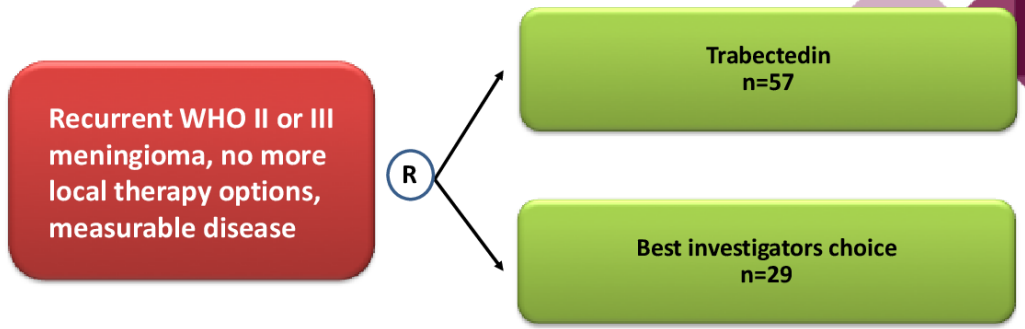
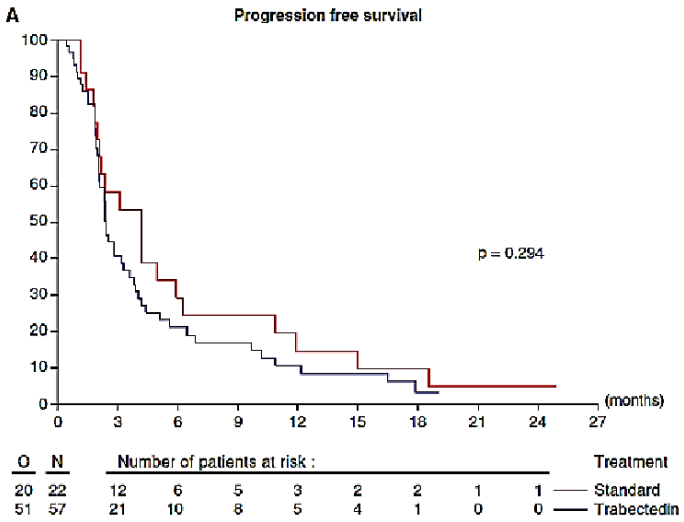


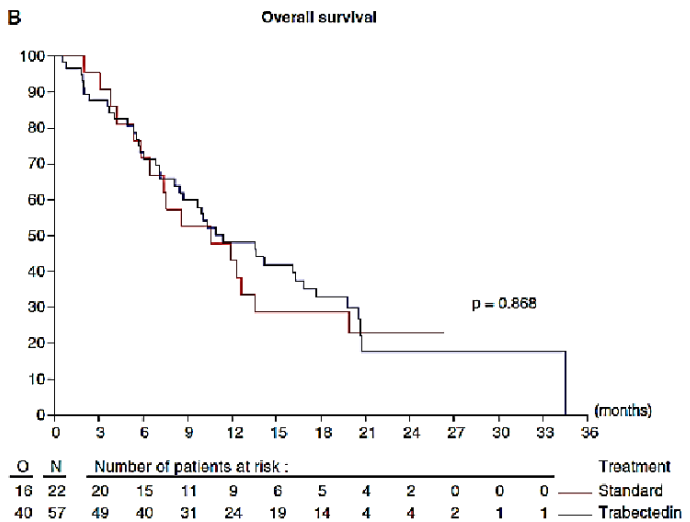
Fig. 1. Kaplan–Meier curves for PFS and OS: PFS6 = 44% (95% CI: 27.0–59.7); median PFS = 5.2 mo (95% CI: 2.8–8.3 mo); median OS = 24.6 mo (95% CI: 16.5–38.4 mo); 1-year OS = 79.2% (95% CI: 61.1–89.7); 2-year OS = 51.7% (95% CI: 29.4–70.4).

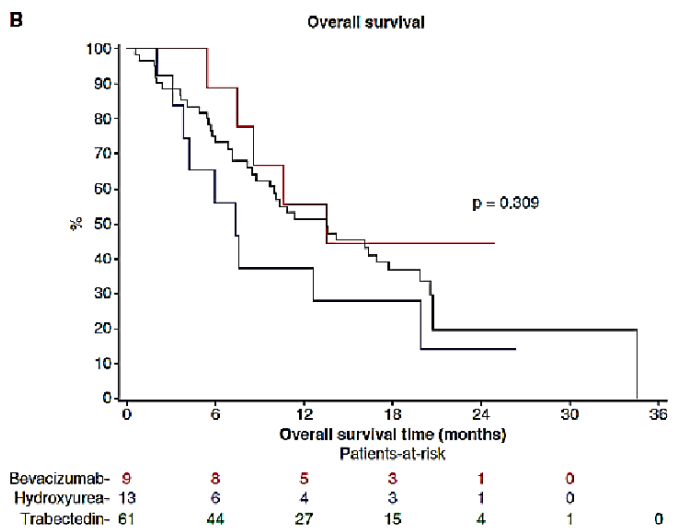
Neuro-Oncology
24(5), 755–767, 2022 | https://doi.org/10.1093/neuonc/noab243 | Advance Access date 21 October 2021

Trabectedin for recurrent WHO grade 2 or 3 meningioma: A randomized phase II study of the EORTC Brain Tumor Group (EORTC-1320-BTG)

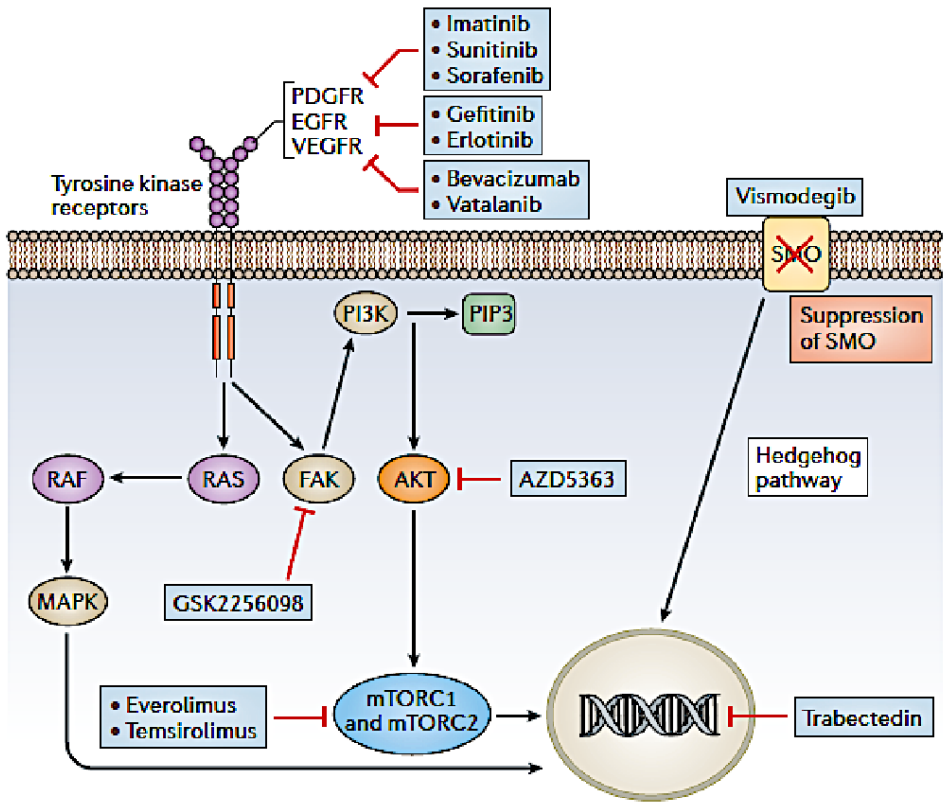








POSSIBLE TARGETS FOR FUTURE THERAPIES



Preusser et al, Nature Rev Neurol 2018

Table 2 Molecular Targets

Drug Class	Molecular Target/Biomarker
AKT inhibitor	AKT1 (pGlu17Lys) mutation[24,25]
Hedgehog inhibitor	SMO (pTrp535Leu) mutation[24,25]
FAK inhibitor	NF2 (merlin) loss[43,44]
Immune checkpoint inhibitor	PD-L1, PD-L2, B7-H3, and CTLA-4[45–47]
VEGF or VEGFR inhibitor	VEGF or VEGFR2[48–50]
PI3K inhibitor	PI3K[29]
mTOR inhibitor	mTOR[51,52]
Somatostatin analog	Somatostatin receptors[51]
Gemcitabine	Cytidin[53]

Abbreviation: AKT, gene coding for protein kinase B; FAK, focal adhesion kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositol-3-kinase; VEGF, vascular endothelial growth factor.

Goldbrummer et al, EANO Guidelines, Lancet Oncol 2016; Neuro-Oncol 2021

Clinical trials of systemic treatment for meningioma

Treatment	Study type	Setting	N of patients	Results
Hydroxyurea	retrospective case series	recurrent WHO grade 1 meningioma	60	Duration of stable disease: 3–12 months (median 4.0 months)[286]
Hydroxyurea	retrospective case series	recurrent WHO grade 2/3 meningioma	35	6-month PFS: 3.0% (median PFS 2.0 months)[428]
Interferon-α	Phase 2	Recurrent grade 1	35	6-month and 12-month PFS: 54%, 31%; mOS: 8 months[429]
Interferon-α	Retrospective case series	Recurrent WHO grade 2/3	35	6-month PFS: 17%[430]
Bevacizumab	retrospective review	recurrent meningioma	14	6-month PFS: 86%[431]
Bevacizumab	retrospectively study	Atypical and anaplastic meningiomas	15	mPFS: 26 weeks. 6-month PFS: 43.8 %[290]
Mifepristone	Phase III	unresectable meningioma	164	Failure-free and OS were no statistical difference between mifepristone and placebo[288]
Pasireotide LAR	phase II	recurrent or progressive meningioma	34	It has limited efficacy in recurrent meningiomas[244]
Octreotide	phase II	recurrent high-grade meningioma	9	6-month PFS: 44.4 %, mPFS: 4.23 months[432]
Sandostatin LAR	prospective pilot trial	recurrent meningiomas	16	6-month PFS: 44%, mOS: 7.5 months[433]
Temozolomide	Phase II	refractory meningioma	16	Time to tumor progression: 2.5–5.0 months (median 5.0 months); OS: 4–9 months (median 7.5 months)[434]
Trabectedin	phase II	recurrent WHO grade 2 or 3 meningioma	90	not improve PFS and OS[435]
Octreotide and everolimus	phase II CEVOREM trial	recurrent meningiomas	20	6-month PFS: 55%, and OS 6- and 12-month were 90 and 75%, respectively[308]
Everolimus and bevacizumab	phase II	recurrent meningioma	18	median duration of disease stabilization: 10 months[436]
Sunitinib	phase II	recurrent WHO grades 2–3 meningioma	36	mPFS: 5.2 months, and mOS: 24.6 months[307]
Nivolumab	phase II	recurrent atypical/ anaplastic meningioma	25	6-month PFS: 42.4%; mOS: 30.9 months; One patient achieved radiographic response (ongoing at 4.5 years).[293]

PFS progression-free survival, *OS* overall survival; progression-free survival, *mPFS* median progression-free survival, *mOS* median overall survival, *N* number

Li S, et al. Signal Transduction and Targeted Therapy. 2023 Jan 4;8(1):8.

SYSTEMIC TREATMENT FOR GRADE 2,3 MENINGIOMAS: DO WE HAVE A STANDARD?

Ongoing trials

ClinicalTrials.gov

Trial ID	Type of Study	Arm of Treatment	n	Endpoints
NCT02648997	Phase 2	Nivolumab alone (Cohort 1) or in combination with ipilimumab (Cohort 2)	50	Primary: 6-month PFS Secondary: median PFS, median OS, ORR, safety
NCT03631953	Phase 1	Alpelisib in combination with trametinib	25	Primary: DLT
NCT04728568	Prospective	Sintilimab	15	Primary: PFS Secondary: OS
NCT04501705	Prospective	Apatinib	29	Primary: 6-month PFS Secondary: ORR, OS
NCT03604978	Phase 1–2	Nivolumab alone or plus ipilimumab in combination with fractionated SRS	15	Primary: DLT, safety, ORR Secondary: median PFS, median OS, changes in peripheral T-cells
NCT02933736	Early phase 1	Ribociclib	48	Primary: plasma exposure, CSF penetration, brain accumulation of ribociclib
NCT02523014	Phase 2	Vismodegib or FAK inhibitor, or GSK2256098 or capivasertib, or abemaciclib based on molecular screening	124	Primary: 6-month PFS, ORR Secondary: median PFS, median OS, safety
NCT04659811	Phase 2	Pembrolizumab plus SRS	90	Primary: 12-month PFS Secondary: median PFS, median OS
NCT04374305	Phase 2	Brigatinib	80	Primary: radiological response rate Secondary: safety
NCT03095248	Phase 2	Selumetinib	34	Primary: change in hearing response, response rate of other NF2-related tumors (including meningiomas)
NCT04541082	Phase 1	ONC206	102	Primary: MTD

Pellerino et al, 2022

Clinical trials on CAR T-based management of brain cancer

S no.	Targets	Phases	Status	Indications	CAR designs	Administration routes	Comments	Identifiers
1	IL3Rα2	I	Completed	Recurrent/refractory malignant glioma	IL13-CD3ζ CD8+ cytotoxic T-lymphocyte clones	Intracranial	Transient inflammatory response, necrosis at tumor site, antigen loss	NCT00730613 [79]
2	IL3Rα2	I	Completed	Recurrent/refractory malignant glioma	IL-13 zetakine	Intratumoral infusion	No dose-limiting toxicity	NCT01082926 [80]
3	IL3Rα2	I	Ongoing	Recurrent/refractory malignant glioma	IL-13–4-1BBζ memory-derived T cells	Intracranial, intraventricular	Complete clinical response up to 7.5 months, antigen loss	NCT02208362 [82]
4	IL3Rα2	I	Ongoing	Leptomeningeal glioblastoma, ependymoma, or medulloblastoma	IL3Rα2-specific CAR with 4-1BB co-stimulation	Intraventricular	Evaluation of safety, feasibility, persistence, expansion	NCT04661384 [83]
5	IL3Rα2	I	Ongoing	Recurrent/refractory pediatric brain tumors	IL3Rα2-specific CAR	Intraventricular	Assessment of side effects, after lymphodepletion	NCT04510051 [84]
6	IL3Rα2	I	Ongoing	Glioblastoma	IL3Rα2-targeted CAR	Intraventricular, intratumoral	Trial for combination therapy with checkpoint inhibitor	NCT04003649 [134]
7	EGFRvIII	I, II	Completed	Malignant glioma	EGFRvIII-CD28–4-1BBζ Bulk T cells	Intravenous	Progression-free survival uup to12.5 months, dose-limiting toxicity at higher doses	NCT01454596 [86]
8	EGFRvIII	I	Terminated	Glioblastoma	EGFRVIII-4-1BBζ CAR	Intravenous	Increased IDO, FOXP3, IL-10, PD-L1 and TGFβ, antigen loss	NCT02209376 [90]
9	EGFRvIII	I	Completed	Glioblastoma	EGFrvIII-specific CAR T expressing 4-1BB and TCRζ	Intravenous	Result has not yet been published	NCT03726515 [92]
10	EGFRvIII	I	Terminated	Glioma grade IV	EGFRvIII CAR	Systemic	Radiolabelling of CAR T cells	NCT02664363 [136]
11	EGFRvIII	I	Terminated	Recurrent glioblastoma	EGFRvIII-targeted CAR	Intracerebral	Recruitment halted	NCT03283631 [174]
12	EGFR806	I	Ongoing	Recurrent/refractory EGFR+ pediatric CNS tumors	EGFR806-specific CAR	Delivered into tumor cavity or ventricular system	Evaluation of safety, efficacy, tolerability, distribution, tumor response	NCT03638167 [94]
13	EGFR806	I	Ongoing	Solid tumors including neuroblastoma	EGFR806-specific CAR	Systemic	Assessment of on target off tumor toxicity	NCT03618381 [95]
14	HER2	I	Completed	Glioblastoma	HER2-CD28ζ virus-specific T cells	Intravenous	No dose limiting toxicity	NCT01109095 [100]
15	HER2	I	Ongoing	Recurrent/refractory glioblastoma grade III/IV	HER2-specific, hinge-optimized, 4-1BB-co-stimulatory chimeric receptor	Intracerebral	Investigation on side effects and best suit dose	NCT03389230 [102]
16	HER2	I	Ongoing	Metastatic meningeal neoplasm	HER2-specific CAR	Intraventricular	Evaluation of side effects, best dose	NCT03696030 [103]
17	HER2	I	Ongoing	Recurrent/refractory HER2+ pediatric CNS tumors	HER2-specific CAR	Intracerebral	Evaluation of safety, efficacy, distribution	NCT03500991 [105]
18	HER2	I	Ongoing	HER2+ CNS tumors	HER2-specific CAR	Intracranial	Evaluation of efficacy, side effects, largest safe dose	NCT02442297 [106]

Huang Z, et al. Molecular Cancer. 2023 Dec;22(1):1-27.

Clinical trials on CAR T-based management of brain cancer

S no.	Targets	Phases	Status	Indications	CAR designs	Administration routes	Comments	Identifiers
19	HER2	I	Ongoing	Pediatric recurrent/refractory ependymoma	HER2-specific CAR	Intravenous	Evaluation of safety and feasibility	NCT04903080 [107]
20	B7-H3	I, II	Ongoing	Recurrent/refractory glioblastoma	B7-H3-targeted CAR	Intratumoral, intraventricular	Concurrent therapy with temozolomide	NCT04077866 [111]
21	B7-H3	I	Ongoing	Diffuse intrinsic pontine glioma/diffuse midline glioma and recurrent or refractory pediatric central nervous system tumors	B7-H3-specific CAR	Delivered into tumor cavity or ventricular system	Assessment of safety, distribution, peripheral trafficking	NCT04185038 [112]
22	B7-H3	I	Unknown	Recurrent/refractory glioblastoma	B7-H3-targeted CAR	Intratumoral, intraventricular	Unknown status after May 2020	NCT04385173 [175]
23	CD147	I	Unknown	Malignant glioma	CD147 CAR T cells	Intracavity injection	Unknown status after May 2020	NCT04045847 [114]
24	GD2	I	Completed	Recurrent/refractory neuroblastoma	Anti-GD2 CAR	Systemic	No disease progression with detectable CAR levels upto 45 days	NCT02761915 [120]
25	GD2	I	Ongoing	GD2+ brain tumor	C7R-GD2.CAR T Cells	Intravenous	Ongoing safety and efficacy assessment	NCT04099797 [121]
26	GD2	I, II	Ongoing	Recurrent/refractory neuroblastoma	Anti-GD2 CAR T cells	Systemic	Dose escalation and expansion trial	NCT03373097 [122]
27	GD2	I	Ongoing	Intrinsic pontine glioma, spinal diffuse midline glioma	GD2-specific CAR	Intravenous	Assesment of safety, feasibility, recommendation of dose for phase II trial	NCT04196413 [123]
28	GD2	I	Ongoing	Pediatric neuroblastoma	GD2-specific CAR with autologous NKT cells expressing IL-15	Systemic	The first trial on GD2 expressing NKT cells	NCT03294954 [135]
29	EphA2	I, II	Withdrawn	Malignant glioma	EphA2-specific CAR	Systemic	Trial withdrawn	NCT02575261 [131]
30	CLTX	I	Ongoing	MMP2+ recurrent or progressive glioblastoma	CLTX (EQ)-CD28-CD3 zeta-CD19t-expressing CAR T lymphocytes	Intravenous	Tumor binding peptide used as targeting domain	NCT04214392 [127]
31	CD171	I	Ongoing	Neuroblastoma	CD171-specific CAR T cells expressing EGFR1	Systemic	Assessment for maximum tolerable dose	NCT02311621 [129]
32	NKG2D	I	Withdrawn	Solid tumors including glioblastoma	NKG2D-based CAR	Intravenous, intra-arterial	Trial withdrawn	NCT04270461 [142]
33	EGFRvIII, IL13Rα2, HER2, CD133, EphA2 or GD2	I	Ongoing	Recurrent malignant glioma	Biological, antigen-specific CAR T cells	Systemic delivery of lentiviral vector	Personalized CAR design based on tumor antigen expression	NCT03423992 [176]

Huang Z, et al. Molecular Cancer. 2023 Dec;22(1):1-27.

Summary

- The fifth edition of the WHO classification of CNS tumors in 2021 has incorporated many advanced molecular alterations into the diagnostic standards.
- Failure of several targeted agents, especially for GBM, illustrates that CNS tumors do not only rely on a single pathway driven targeted therapy.
- Future treatment may be improved in the following ways:

1)the combination strategies of multiple targeted drugs and immunotherapeutic approaches have been proven efficacy against brain tumors, especially for recurrent/ progressive patients, and could be the trend of treatment management in the future;

2) the limited scale of participation and specific patient groups indicates the necessity of performing more larger and multicenter clinical trials to assess efficacy and safety;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