TARGETED TREATMENTS FOR BRAIN TUMORS

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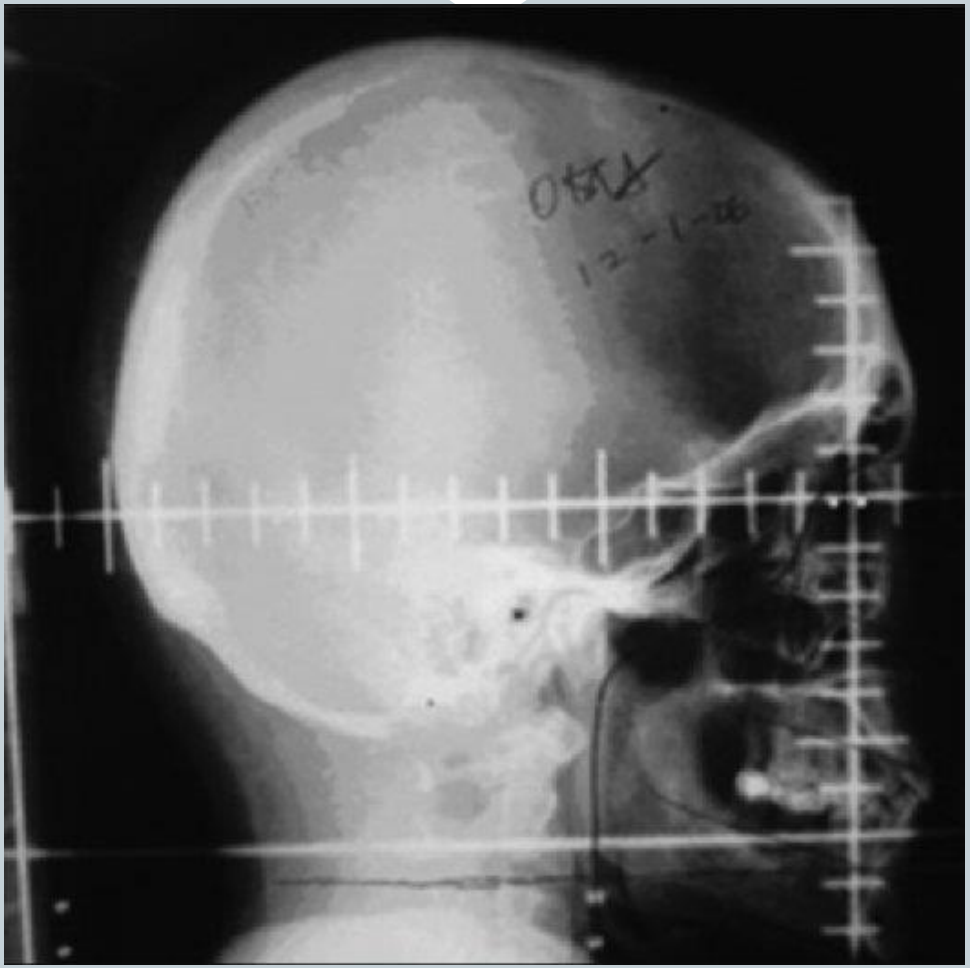
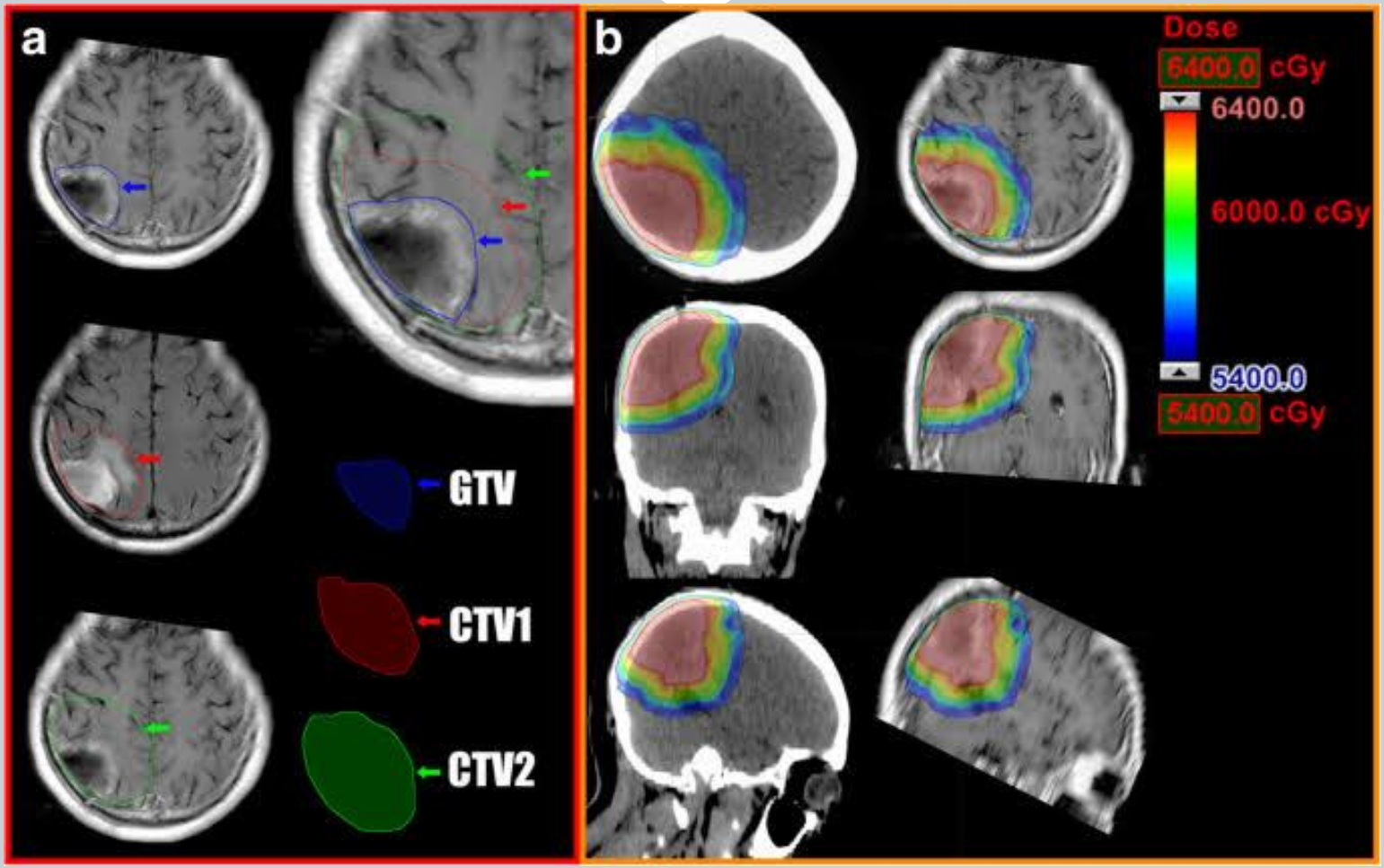
WHOLE BRAIN RADIATION THERAPY



IMRT/VMAT


a
GTV
CTV1
CTV2
b
Dose
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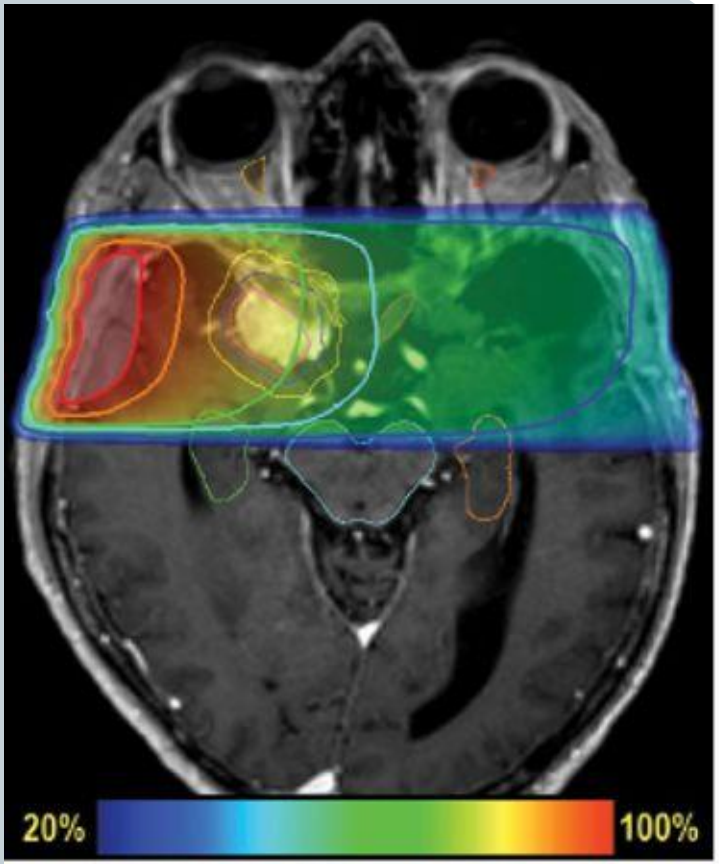
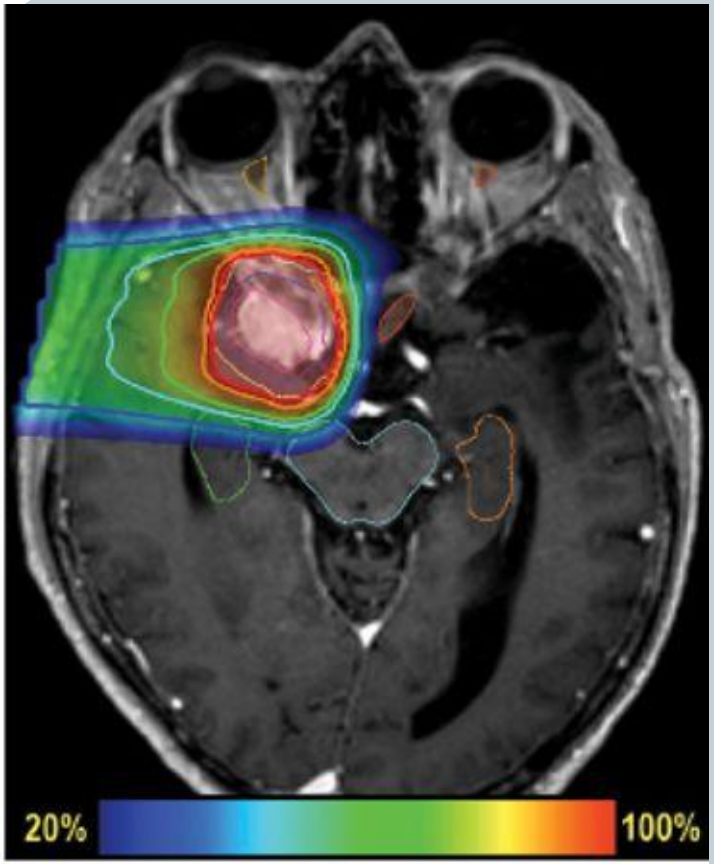
6400.0
6000.0 cGy
5400.0
5400.0 cGy

PROTON BEAM THERAPY

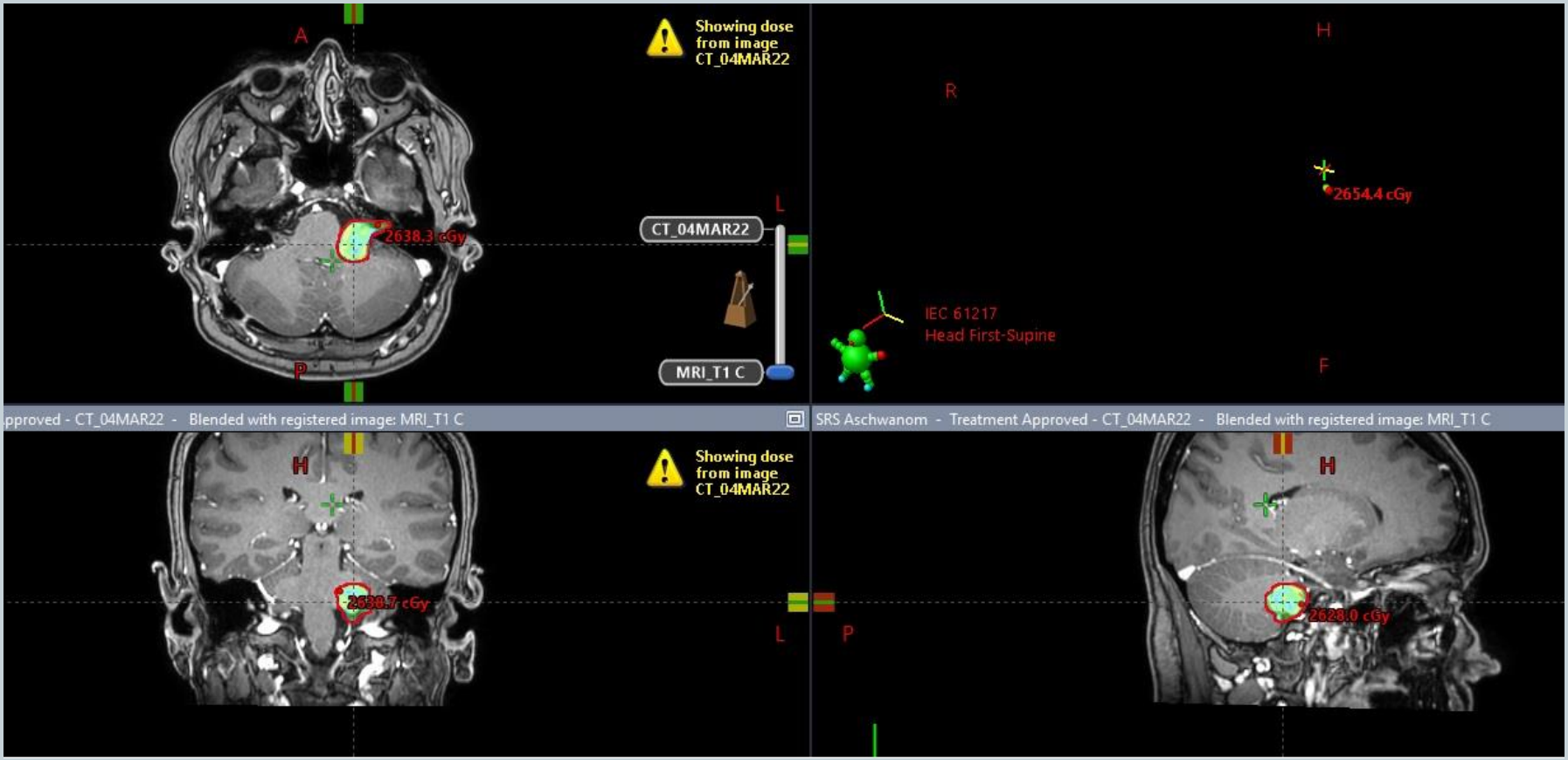


X-ray (traditional) radiation beam



Proton radiation beam

SRS/SRT


A
P
2638.3 cGy
Showing dose from image CT_04MAR22
L
CT_04MAR22
MRI_T1 C
H
R
2654.4 cGy
IEC 61217
Head First-Supine
F
pproved - CT_04MAR22 - Blended with registered image: MRI_T1 C
SRS Aschwanom - Treatment Approved - CT_04MAR22 - Blended with registered image: MRI_T1 C
H
2638.7 cGy
Showing dose from image CT_04MAR22
L
P
H
2628.0 cGy

EVOLUTION OF CHEMOTHERAPY

Historically – post op Radiation +/- CCNU/BCNU

- Development of cancer genomics revolutionizing the diagnostic criteria
- Fifth edition of the World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5) in 2021
- Advancement in the role of molecular diagnostics in CNS tumor classification discovery of impactful and experimental molecular-targeted therapies provides new insights for current management and prognosis

Roger Stupp, 2005

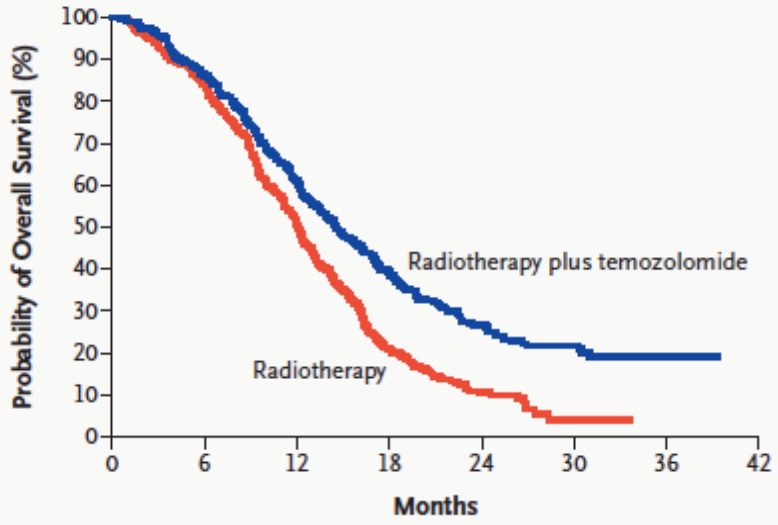
The NEW ENGLAND JOURNAL of MEDICINE

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*

STANDARD OF CARE



No. at Risk							
Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

The two-year survival rate was 26.5 percent with radiotherapy plus temozolomide and 10.4 percent with radiotherapy alone

2018

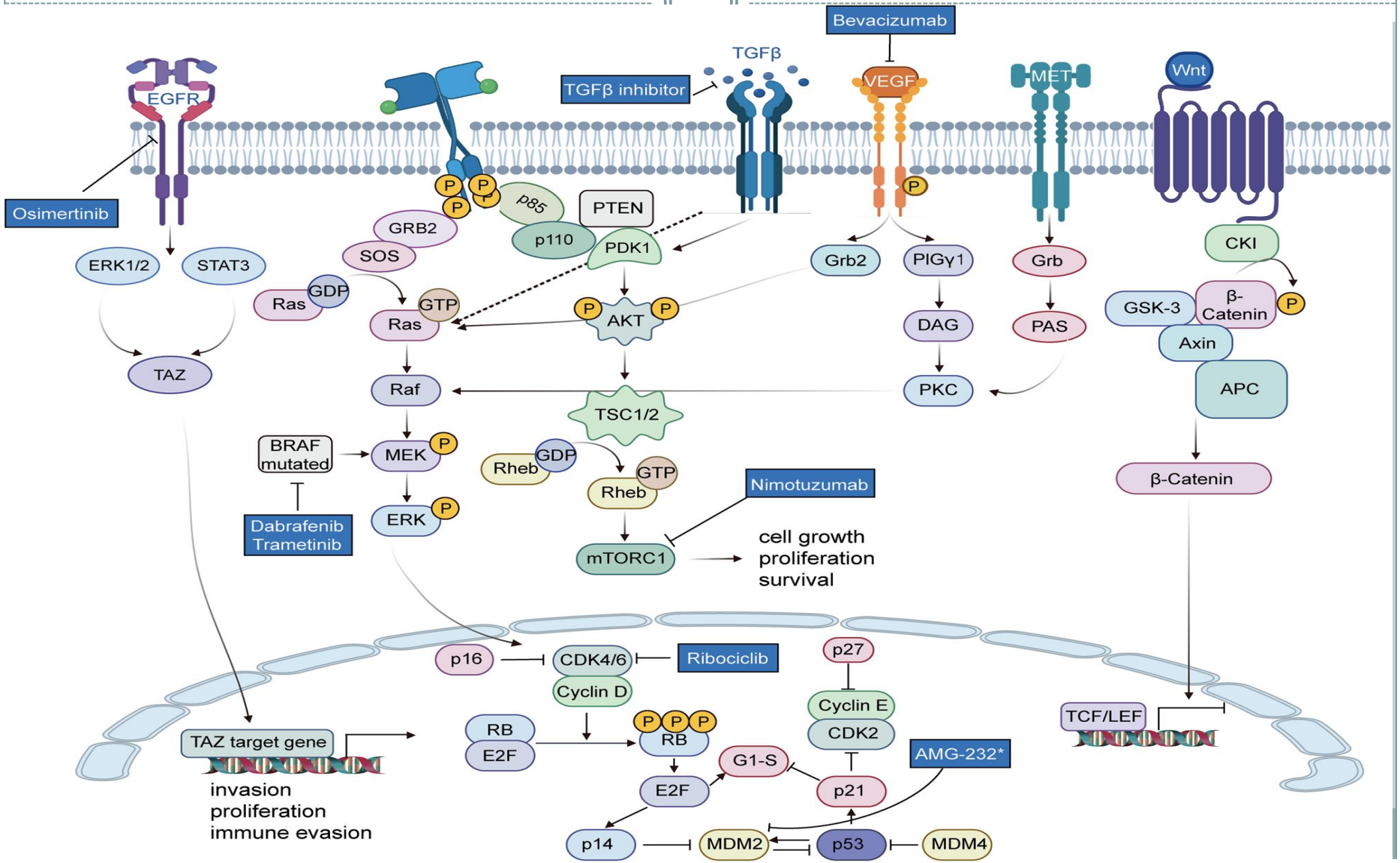
CCR Translations

Clinical Cancer Research

Targeted Therapies for Brain Tumors: Will They Ever Deliver?

Michael A. Vogelbaum

GLIOMAS


Bevacizumab
TGFβ
TGFβ inhibitor
VEGF
MET
Wnt
EGFR
Osimertinib
P
p85
p110
PTEN
PDK1
GRB2
SOS
Ras
GDP
GTP
AKT
ERK1/2
STAT3
TAZ
Grb2
PIGγ1
DAG
PKC
Grb
PAS
CKI
GSK-3
β-Catenin
Axin
APC
β-Catenin
Raf
TSC1/2
BRAF mutated
MEK
ERK
Dabrafenib
Trametinib
Rheb
GDP
GTP
Nimotuzumab
mTORC1
cell growth
proliferation
survival
p16
CDK4/6
Ribociclib
Cyclin D
p27
Cyclin E
CDK2
RB
E2F
G1-S
p21
AMG-232*
p14
MDM2
p53
MDM4
TAZ target gene
invasion
proliferation
immune evasion
TCF/LEF

GBM

Alkylating agent and MGMT promoter methylation

- TMZ might lead to recurrence of GBM with high expression of MGMT (Neuropathol Appl Neurobiol. 2015;41(6):694–720)
- Resistance to TMZ was presumed related to MGMT gene fusion or rearrangement mutation (Nature Communications. 2020;11(1):1–10)
- Animal models present that Bortezomib could increase the sensitivity of GBM to temozolomide by reducing MGMT mRNA and protein (Br J Cancer. 2019;121(7):545–55)
- Newly discovered enhancer, namely K-M enhancer, increases MGMT expression thus inducing TMZ resistance despite of the hypermethylated MRMT promoter. Nature Communications. 2018;9(1):1–14.

- Frenel et al. proved that the combination of folic acid, TMZ and radiotherapy in the treatment of unmethylated MGMT patients was feasible, suggesting the prospect of inducing MGMT methylation in GBM therapy (NCT01700569) Ann Oncol. 2020;31:S400–S400.

TYROSINE KINASE RECEPTORS

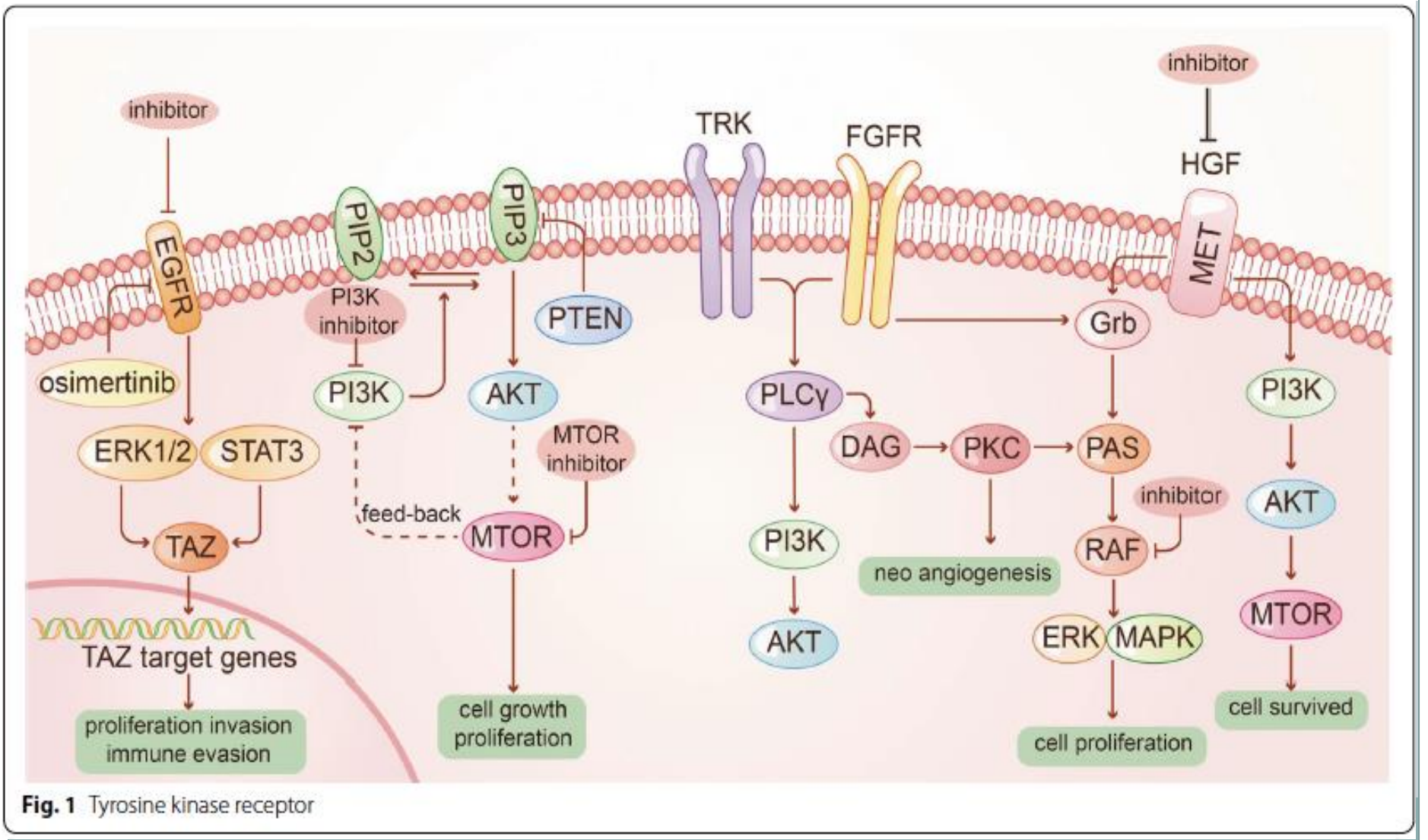


Fig. 1 Tyrosine kinase receptor

Tyrosine kinase receptor

Epidermal growth factor receptor (EGFR)

- EGFR inhibitors
- Antibodies, vaccines, CAR-T and other therapies to limit the content of EGFR
- EGFR mutations occur in about 50% of all GBM samples, of which more than 40% are gene amplification, and the rest include gene mutations, rearrangements, splicing site changes, etc.
- The most common gene mutation of EGFR is EGFRvIII (deletion of exons 2–7) as a potential marker of treatment for GBM.

- Osimertinib could not only inhibit EGFRnegative glioblastoma patient-derived xenograft (PDX), possibly via regulation of MAPK pathway, but also inhibit transcription factor EGFR-TAZ, providing a novel insight for drug reuse of EGFR-targeted inhibitors. Can Res. 2021;81(13):3580–92.
- Nimotuzumab was more effective with patients carrying activated akt/mTOR
- Depatuxizumab mafodotin (formerly ABT- 414), an antibody–drug conjugate using EGFR antibody as receptor-direction, seemed to be effective in recurrent GBM (rGBM) after standard treatment of TMZ but ineffective in newly-diagnosed GBM (NCT02573324)

- Vaccination Rindopepimut combined with TMZ in rGBM patients carrying EGFR-VIII is relatively active (originally NCT00458601) but it failed to present effectiveness in a phase III trial (NCT01480479)
- CAR-T therapy is still under phase I trial and demonstrates expected effect (NCT02209376)

PI3K/AKT/mTOR pathway

Temsirolimus, Buparlisib, Everolimus

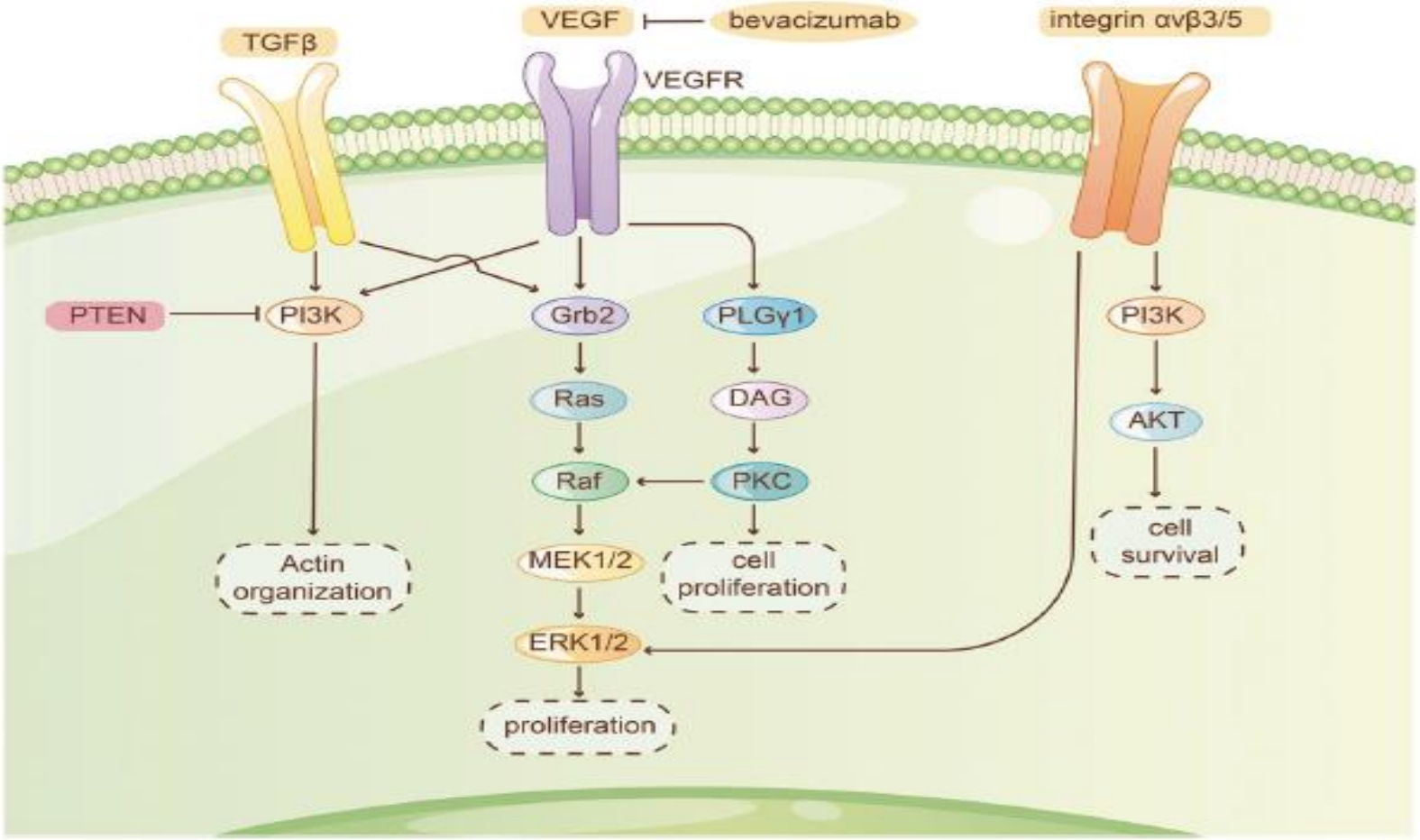
- PI3K pathway as a therapy target in GBM is often ineffective
- Combination strategies should be explored in the future
- Larotrectinib
- Entrectinib
- Tried in solid tumors, ph 1 trials for GBM

MET

- MET gene encodes hepatocyte growth factor receptor (also known as scatter factor), which is thought to play an important role in the migration, invasion, drug resistance and recurrence of glioma cells, especially in radiation resistance, inhibition of angiogenesis and hypoxia
- Since mutations in c-MET often lead to drug resistance in GBM patients, influencing the efficacy of PI3K targeted therapy, the combination of MET inhibitors and PI3K inhibitors can be considered in follow-up trials.

- Fibroblast growth factor receptor (FGFR)
- Neurotrophic tyrosine receptor kinases (NTRK)
- Cell cycle control and apoptosis regulating pathways The retinoblastoma (pRB) pathway (CDK4/6)
- BRAF mutation
- The p53 pathway
- TERT promoter mutation
- Proteasome

Micro environmental targets



Microenvironmental targets

Micro-environmental targets

Angiogenesis Vascular Endothelial Growth Factor (VEGF)

- Bevacizumab, a humanized monoclonal antibody against the VEGF-A ligand, binds to endothelial cells and inhibits angiogenesis
- Bevacizumab significantly improved PFS (NCT00884741).
- However, it did not improve OS even with the adjuvant chemoradiotherapy or lomustine and was reported with high frequency of adverse events (NCT00943826, NCT01290939)
- IDH1-wildtype GBM patients exhibited prolonged OS after receiving Bevacizumab therapy (NCT00943826)(J Clin Oncol. 2015;33(25):2735–44.)

Integrin

- Cilengitide is a selective integrin inhibitor targeting αvβ3 and αvβ5, which its combination with Cediranib had a great tolerance to rGBM patients in a phase I trial (NCT00979862)
- TMZ/RT-TMZ plus Cilengitide with great tolerance and efficacy could not improve invasiveness or recurrent rate of newly-diagnosed GBM (NCT00813943)
- In GBM patients with MGMT promoter methylation, Cilengitide had good performance as adjuvant administration with standard treatment (NCT00689221, NCT00689221)
- Although Cilengitide has not exhibited remarkable potential as monotherapy, integrins remain to be the important target.

Immunotherapy

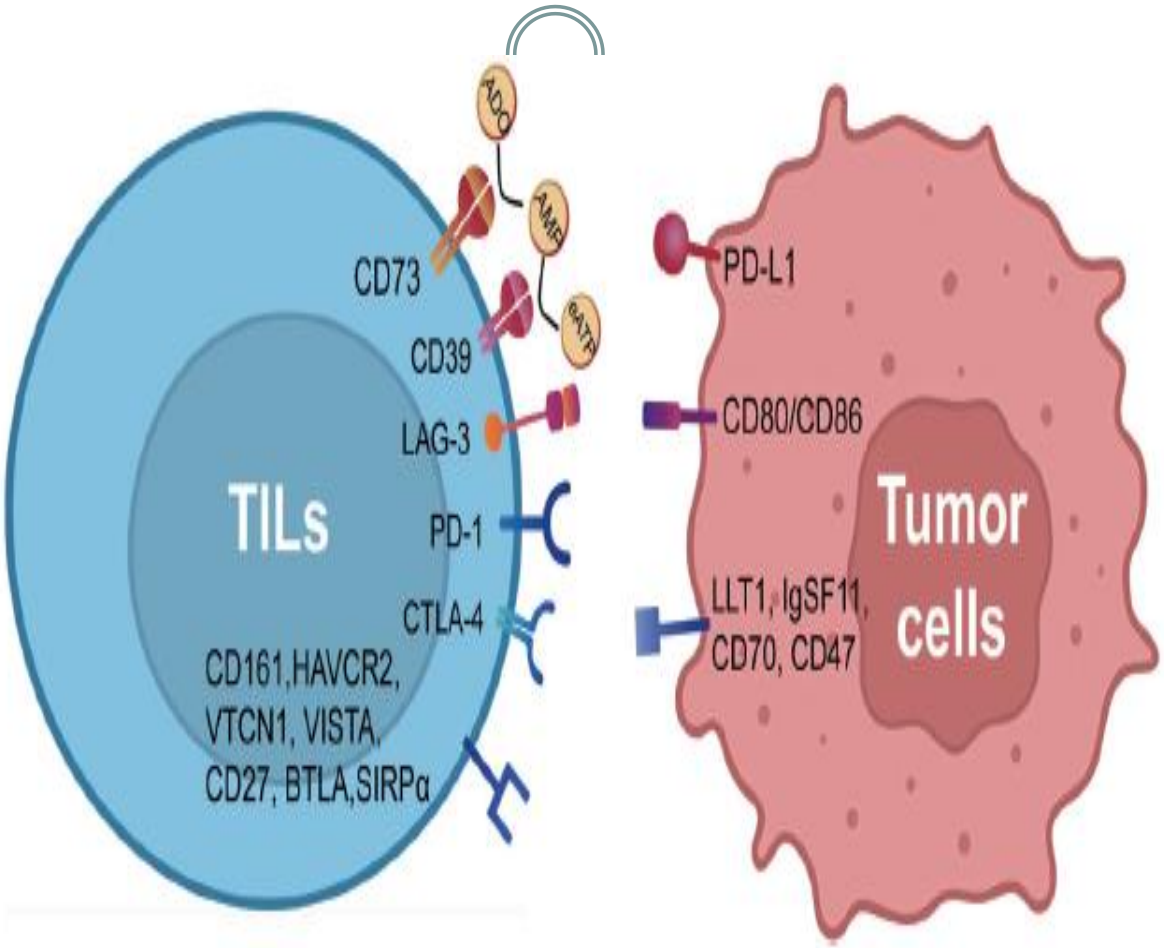


Fig. 3 Current immune checkpoint molecules. Given the complex relationship between tumor cells and tumor-infiltrating lymphocytes (TILs), various clinical trials have been implemented based on the immune checkpoint molecules (PD-1/PD-L1, CTLA4, LAG-3, and other classic immune checkpoint molecules). Created with BioRender.com (https://biorender.com) and Reactome pathway database (https://reactome.org/)

Table 2. The clinical trials of immune checkpoint inhibitors

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

- Tumor-specific antigen polypeptide vaccines - The vaccine peptide rindopepimut was synthesized according to the small amino acid sequence around the fusion site on EGFRvIII. Benefit could not be reproduced in phase III clinical trial
- Innate immune cell therapies and vaccines - tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and tumor-infiltrating dendritic cells (TIDCs). Although these studies have shown mixed outcomes, the ability of DC vaccines to a patient's tumor cannot be underestimated, and innate immune cell therapies are currently shown to have both the advantages of very low side effects and high specificity.

Adaptive immune cell therapy - CAR-T is a genetically engineered T cell with an artificial receptor directed against the selected antigen

- The most studied targets of CAR-T in GBM are HER2, EGFRvIII, as well as IL-13αR2
- O'Rourke, et al stated that EGFRvIII-directed CAR-T cells are effective and safe
- Brown, et al used CAR-T cells targeting IL-13Rα2 in recurrent GBM patients.
- The results were dramatic, with complete regression of all lesions and the effect maintained for 7.5 months.
- This clinical trial is still ongoing (NCT02208362)

- Oncolytic virotherapy - Oncolytic viruses utilize the natural capability of viruses to replicate and lyse cells in combination with the release of neoantigens and damage-associated molecular patterns following tumor cell lysis, thereby invoking a robust immune response in the cancer area that further kills the tumor
- The most common are herpesviruses, reoviruses, poxviruses, adenoviruses, or Zika virus

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CANCER THERAPY AND PREVENTION

Targeted therapies in patients with newly diagnosed glioblastoma—A systematic meta-analysis of randomized clinical trials

Angelika Scherm[1] | Franziska Maria Ippen[2] | Peter Hau[1] | Hansjörg Baurecht[3] | Wolfgang Wick[2,4] | Jens Gempt[5] | Helge Knüttel[6] | Michael F. Leitzmann[3] | Corinna Seliger[2]

Substance	Author	Year	Study name	Phase	Targets
Bevacizumab	Chauffert	2014	TEMAVIR	II	VEGF
Bevacizumab	Gilbert	2014	RTOG-0825	III	VEGF
Bevacizumab	Chinot	2014	AVAglio	III	VEGF
Bevacizumab	Herrlinger	2016	GLARIUS	II	VEGF
Bevacizumab	Balana	2016	GENOM 009	II	VEGF
Cilengitide	Stupp	2014	CENTRIC	II	αvβ3/αvβ5
Cilengitide	Nabors	2015	CORE	II	αvβ3/αvβ5
Everolimus	Chinnaiyan	2018	RTOG-0913	II	mTOR
Nimotuzumab	Westphal	2015	OSAG101-BSA-05	III	EGFR
Rindopepimut	Weller	2017	ACT IV	III	EGFRvIII
Temsirolimus	Wick	2016	EORTC 26082	II	mTOR
Veliparib	Sim	2021	VERTU	II	PARP

CONCLUSIONS

- None of the investigated substances provided a significant improvement in OS, although a potentially clinically meaningful extension in PFS has been demonstrated with regard to VEGF/VEGFR blockade
- Personalized design of randomized trials, including a careful selection of patient populations that should focus on molecular markers that may predict the response to the specific agents used in the tria

LOW GRADE GLIOMAS

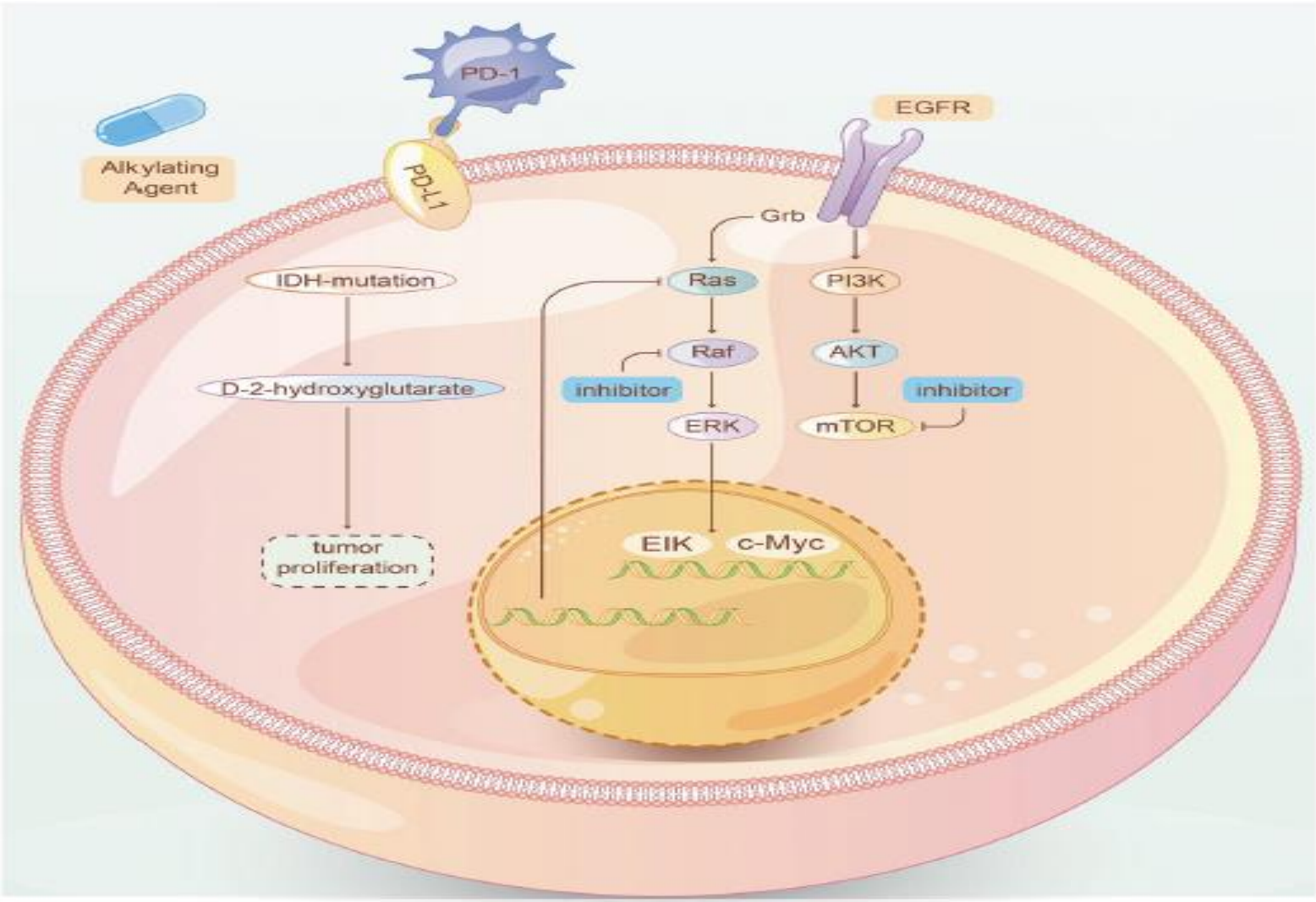

Fig. 5 Candidate molecular targets amenable to targeted interventions in LGG

FDA approves dabrafenib with trametinib for pediatric patients with low-grade glioma with a BRAF V600E mutation

On March 16, 2023, the Food and Drug Administration approved dabrafenib (Tafinlar, Novartis) with trametinib (Mekinist, Novartis) for pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. The FDA also approved new oral formulations of both drugs suitable for patients who cannot swallow pills.

This represents the first FDA approval of a systemic therapy for the first-line treatment of pediatric patients with LGG with a BRAF V600E mutation.

View full prescribing information for Tafinlar and Mekinist.

Efficacy was evaluated in Study CDRB436G2201 (NCT02684058), a multicenter, open-label trial in patients with LGG (WHO grades 1 and 2) requiring first systemic therapy.

ORIGINAL ARTICLE

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

I.K. Mellinghoff, M.J. van den Bent, D.T. Blumenthal, M. Touat, K.B. Peters, J. Clarke, J. Mendez, S. Yust-Katz, L. Welsh, W.P. Mason, F. Ducray, Y. Umemura, B. Nabors, M. Holdhoff, A.F. Hottinger, Y. Arakawa, J.M. Sepulveda, W. Wick, R. Soffietti, J.R. Perry, P. Giglio, M. de la Fuente, E.A. Maher, S. Schoenfeld, D. Zhao, S.S. Pandya, L. Steelman, I. Hassan, P.Y. Wen, and T.F. Cloughesy

CONCLUSIONS

In patients with grade 2 IDH-mutant glioma, vorasidenib significantly improved progression-free survival and delayed the time to the next intervention. (Funded by Servier; INDIGO ClinicalTrials.gov number, NCT04164901.)

median progression-free survival, 27.7 months vs. 11.1 months; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.27 to 0.56; P<0.001)

MENINGIOMA

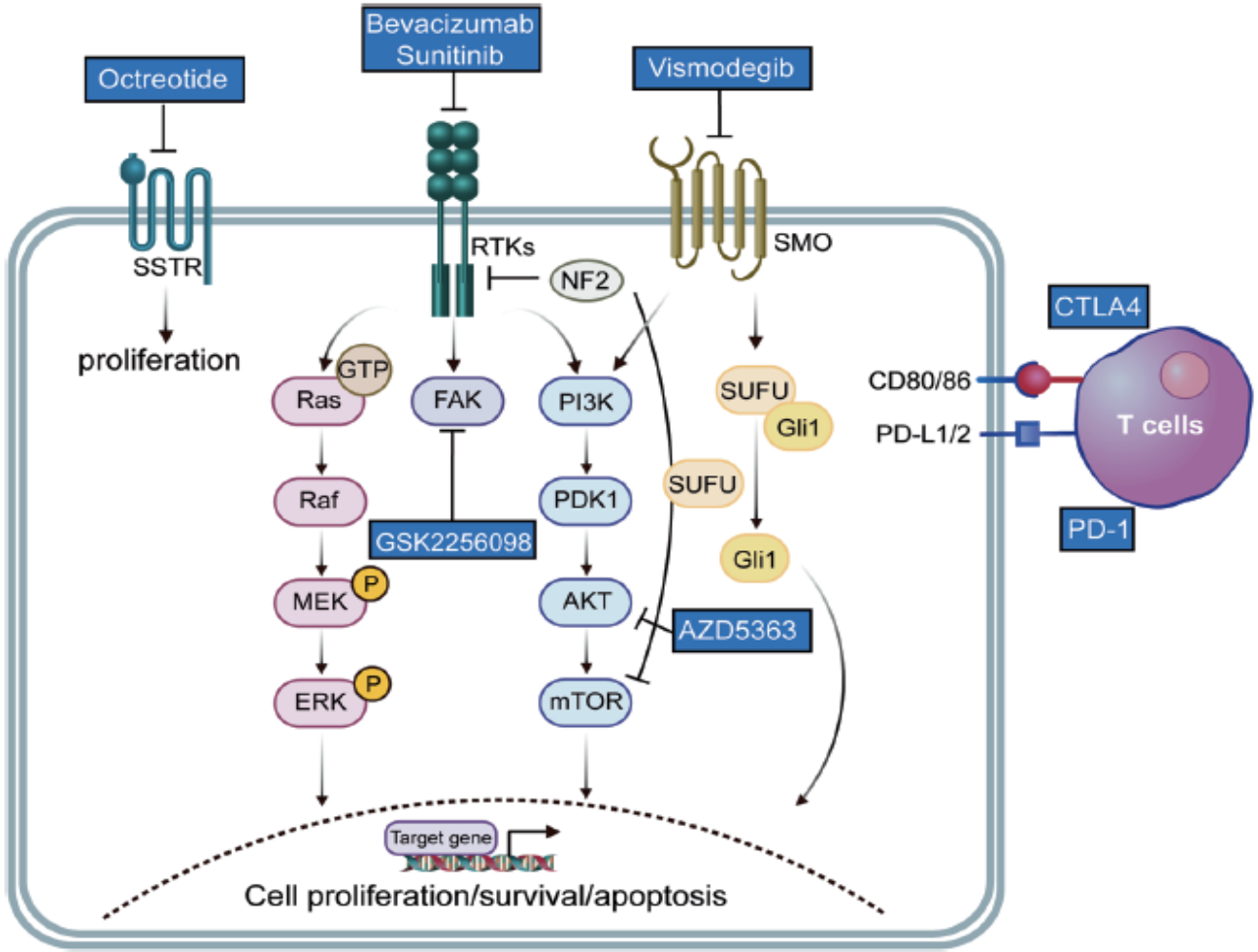

Fig. 4 Summary of the activated signaling pathways and drug targets in meningioma. There are many cellular processes involved in meningioma growth, such as the PI3K–AKT–mTORC pathway, MAPK (mitogen-activated protein kinase) pathway, as well as the Hedgehog pathway. The figure shows the current medical therapies for meningioma, which target diverse molecular targets. Created with BioRender.com (https://biorender.com) and Reactome pathway database (https://reactome.org/)

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

MEDULLOBLASTOMA

Table 1. Completed clinical trials exploring targeted therapies for SHH-MB patients.

Trial	Author	Drug	Study Phase	Number of Mb Patients	Endpoints	Results
Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors.	LoRusso 2011 [36]	Vismodegib	I	1	Safety and tumor responses	Acceptable safety profile. Antitumor activity was seen in 20/68 patients (19 with BCC and 1 MB).
Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a pediatric brain tumor consortium study.	Gajjar 2013 [37]	Vismodegib	I	33	Safety and tumor responses	Acceptable safety profile. Antitumor activity was seen in 1 of 3 patients with SHH-subtype disease.
Phase I, multicenter, open-label, first-in-human, dose-escalation study of the oral smoothened inhibitor sonidegib (LDE225) in patients with advanced solid tumors.	Rodon 2014 [35]	Sonidegib	I	9	Safety and tumor responses	Acceptable safety profile. Antitumor activity was seen in 6/16 patients with BCC and 3/9 patients with medulloblastoma (partial or complete response).
Phase II Clinical trial evaluating the efficacy and safety of GDC-II 0449 in adults with recurrent or refractory medulloblastoma.	Robinson 2015 [38]	Vismodegib	II	40	Safety and tumor responses	Acceptable safety profile. Antitumor activity was seen in 4/40 patients, all with SHH-subgroup MB.
Phase I study of oral sonidegib (LDE225) in pediatric brain and solid tumors and a phase II study in children and adults with relapsed medulloblastoma.	Kieran 2017 [39]	Sonidegib	I/II	55	Safety and tumor responses	Growth plate changes were observed in prepubertal pediatric patients. Antitumor activity was seen in 5 patients with SHH-subtype disease, 4 complete responders and 1 partial responder.
MEVITEM-a phase I/II trial of vismodegib + temozolomide vs. temozolomide in patients with recurrent/refractory medulloblastoma with Sonic Hedgehog pathway activation.	Frappaz 2021 [40]	Vismodegib + temozolo-mide	I/II	24	Safety and tumor responses	Terminated due to lack of success at the first stage of phase II.

- The SMO inhibitors vismodegib and sonidegib seem to be effective only in the subset of SHH-activated MB that harbors mutations upstream of SMO
- Furthermore, MB patients treated with SMO inhibitors exhibit treatment resistance and disease relapse over time, suggesting that therapy with the single agents alone may be inadequate, while combination therapies, especially with agents that are active downstream of SMO, might be an effective strategy to delay drug resistance and disease progression.

- GLI Inhibitors
- Indirect Inhibitors of the Transcriptional Factor GLI: Histone Deacetylases (HDACs) - Panobinostat is a synthetic non-selective pan-deacetylase inhibitor that is currently under investigation in a pilot phase I study (NCT04315064)
- CDK Inhibitors
- Bromodomain Proteins

CONCLUSIONS AND FUTURE DIRECTIONS

- 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;

3) Developing more effective drug delivery system to overcome the blood–brain barrier, such as nano-drug or extracellular vesicle-based drug delivery system;

4) performing a genetic/precision medical treatments based on the genomics technologies.

THANK YOU