Targeted Therapies

2

Manfred Westphal and Katrin Lamszus

Contents

M. Westphal (✉)
Department of Neurosurgery, U. K. Eppendorf, Martinistr. 52, 20246 Hamburg, Germany
e-mail: westphal@uke.uni-hamburg.de

2.1 Definition

The concept of targeted therapies has been developed in general oncology and describes the treatment of cancers according to markers or pathways that have been identified in the tumor tissue after biopsy or resection. Many of these targets have been identified by correlative studies of subgroups of patients from large cohorts of clinical trials who were segregated on the basis clinical characteristics, and there is a demand that future trials or therapies should be stratified or administered accordingly [22]. Also, targets from general oncology were extrapolated to neuro-oncology.

Other approaches apply gene expression analyses to come up with molecules that are consistently active in gliomas, glioma stem cells or subgroups of clinical trials [26, 29, 42, 44]. Recently more stringent approaches geared towards the discovery of specific glioma-associated pathways have been used that (assuringly) confirmed the prior key suspects governing glioma biology, which are the receptor tyrosine kinases and disruptions of the p53 and RB pathways [10].

2.2 The Basis of Targeting

Targeting treatment has to be based on the proof of target presence and activation. The first analysis is either genetic or immunohistochemical, but recent developments indicate that more complex but technologically increasingly feasible methods need to be included. Whereas for example the presence of VEGF in glioblastoma can be taken for granted, the presence of EGF-R needs to be verified and quantified, as well as the presence of the important vIII

J.-C. Tonn et al. (eds.), *Oncology of CNS Tumors*,
DOI: 10.1007/978-3-642-02874-8_2, © Springer-Verlag Berlin Heidelberg 2010

variant. Activation of the subsequent downstream pathways is not consistent and may be assessed by array-based analysis of the phosphorylation patterns. Genetic information needs to be qualified by additional analysis of the "methylome" because epigenetics modify the results of simple genetic analysis. Currently gene expression array technology is becoming easier and cheaper and will find its way into personalized treatment, which is only another way of looking at targeted therapies.

In the evolution of targeted therapies, prototypically distinct receptor tyrosine kinase has been targeted with antibodies or small molecule inhibitors. Many other target categories have been identified, and the common theme is the selective presence or overexpression or overactivation in a tumor.

In the context of neuro-oncology, targeting has gained a second meaning by including the concept of delivering (targeting) a drug to its desired site of action by local application, which could involve direct local injection, stereotactic placements of delivery catheters or even delivery via motile stem cells as specified further below. In general, despite a wealth of promising agents and concepts, the experience with targeted small molecule therapies in glioma is disappointing [40]. Because of the dual nature of targeting in neuro-oncology, molecular and spatial, progress will be slower than in other areas.

2.3 Targeted Molecules: Growth Factor Systems/Angiogenesis

Due to the discovery that many of the molecular alterations in glioma affect the expression of growth factors and the corresponding growth factor receptors, these as well as their intracellular signaling pathways have become the focus of specific drug development or extrapolation from general oncology. Without trying to give a complete account of all targeted therapy developments, some overview is given in Table 2.1, illustrating the broad biological diversity of targets, the prevalence of growth factor-related targets and the current clinical status.

The receptor for epidermal growth factor (EGF-R) was identified very early as a molecular target for glioma [6]. Agents interfering with the EGF-receptor on the intracellular as well as extracellular level have been the most numerous in development [60]. Erlotinib (Tarceva®) and gefitinib (Iressa®), both small ATP mimetic agents interfering intracellularly with receptor phosphorylation, being as such prototypic small molecule RTK-inhibitors, seem to be ideal candidates for successful glioma therapy. They have been evaluated in several clinical trials, but have shown only limited activity and did not become established in standard therapy [9] as single agents. Of particular disappointment, it was noted

Table 2.1 Clinical developments for targeted therapies for Glioblastoma

Target	Reagent class	Reagent	Clinical phase
EGF receptor	Antibodies	Cetuximab	I
		Nimotuzumab	III
	Small molecule RTK	Erlotinib	I
		Gefitinib	I
	Vaccine	Unique vIII EGFR peptide sequence	III
	Targeted toxin	TGF-α Pseudomonas exotoxin chimeric protein	I/II
PDGF + VEGF receptor	Small molecule RTK	Sunitinib	II
VEGF	Antibody	Bevazizumab	II
VEGF-R	Small molecule RTK	Cediranib	II
IL-13 receptor	Targeted toxin	Engineered IL13 pseudomonas exotoxin chimeric protein	III
IL-4 receptor	Targeted toxin	IL4 PSET chimeric protein	I/II
Transferrin receptor	Targeted toxin	Transferrin diphtheria toxin	III
Matrix metalloproteases	Enzyme inhibitor	Marimastat	III
Integrin receptors	Peptide analogue (avβ3)	Cilengitide	III
TGF-β immunosuppression	Anti-sense oligonucleotide	AP12009	II
mTOR	RNA-translation inhibitor	Temsirolimus	II

that the expected molecular predictors appear to be only of limited value [50] or need to be interpreted in a complex context [41].

To interfere with ligand binding, two antibodies against the regular receptor have been developed, which differ in affinity. Cetuximab (Erbitux®) has been extrapolated from the treatment of colon cancer with as of yet limited experience [4]. Nimotuzumab (Theraloc®) has a lower affinity and therefore binds preferentially to overexpressing cells with fewer side effects. It has been in clinical trials in adult supratentorial malignant glioma [45] and pediatric patients with brain stem gliomas where efficacy was seen (Bode et al., unpublished observation). Currently nimotuzumab is being tested in newly diagnosed glioblastoma in a phase III trial in addition to the Stupp regimen.

Of great interest are reagents specifically directed against the vIII variant of the EGF receptor, which are used for radioimmunotherapy (see below) or vaccination. As the vIII variant provides a unique site of antigenicity, any such reagents should be highly selective [32].

The EGF-R is also used as a target for a targeted toxin delivered by convection (TP38, a construct of TGFα-coupled to the toxin domain of pseudomonas exotoxin) and has been shown to be safely administered via direct intraparenchymal delivery [52], but the development is currently stalled in phase II.

The PDGF receptor has long been an intriguing target in glioma biology because the PDGF receptor was and still is suspected to be a crucially involved transforming oncogene in glioma development, and upon this experimental models are built [15, 56]. There are only few reagents available for this pathway, the earliest being suramin, which consequently was tried in the experimental setting [5] and early clinical trials, but showed very limited, insignificant efficacy [37]. Revived interest came with the development of a tyrosine kinase inhibitor with a very selective activity against c-kit overexpressing tumors, of which the gastrointestinal stromal tumor (GIST) was the prime example. Because of its relatedness/partial homology with c-sis, it was hoped that imatinib (Glivec®) would also be effective in gliomas, but a large phase III trial combining imatinib and hydroxyurea failed to show convincing efficacy (EORTC, unpublished results). Currently, there are no other reagents in evaluation. Also, because of the crucial relevance of this system, it is unlikely that a reagent of such selectivity can be found that will target tumoral PDGF receptor pathways and not have a limiting bone marrow toxicity [7].

VEGF and the corresponding receptor became of interest as a prime target also in neuro-oncology [48] because angiogenesis is one of the key events in the transition from low-grade to high-grade glioma, and overexpression/upregulation of vascular endothelial growth factor (VEGF) is one of the key events leading to the angiogenic phenotype of glioblastoma [54]. Reagents targeting free VEGF, the receptor and the signaling pathway have been developed and extensively tested. For free VEGF, a neutralizing antibody, bevazuzumab (Avastin®), and a receptor fragment (VEGF-trap) are under investigation with promising early phase results [28, 61].

After initial hesitation to use Avastin® for intracranial lesions because of fear of hemorrhages, it has been used in combination with Irinotecan and shown dramatic radiological responses, although the translation into overall survival is still awaited, so a phase III trial is under development. Coherent with animal experiments [33], application of Avastin leads to rapid shrinking of tumors and foremost disappearance of contrast enhancement, but also to accelerated diffusely infiltrative growth (Fig. 2.1).

As for small anti-angiogenic molecules, tyrosine kinase inhibitors have been developed, one of which has been found effective in renal cancer and is now extrapolated to glioblastoma.

Sunitinib (Sutent®), another inhibitor of the tyrosine kinases VEGF-R and PDGF-R, has shown promising activity experimentally [17], seems to affect the distribution of temozolamide [63] and is in phase II clinical trial for recurrent glioblastoma.

A broad and irreversible inhibitor of VEGF, cediranib has been found to lead to vessel normalization within 4 weeks of daily oral administration [3] and also the alleviation of edema in patients with recurrent glioblastoma. This molecule awaits further testing in trials beginning in 2009.

In the context of growth factor-driven biological systems relevant for tumor homoestasis, there is also the HGF/Met system, being the hepatocyte growth factor (HGF)/scatter factor and its cognate receptor MET, the product of the c-met protooncogene. This system is relevant for several aspects in angiogensis, being active as mitogen, motogen and morphogen [36]. With MET consistently part of the list of overexpressed genes in gliomas in gene expression studies, it has moved into the focus of therapeutic efforts [35], but has been

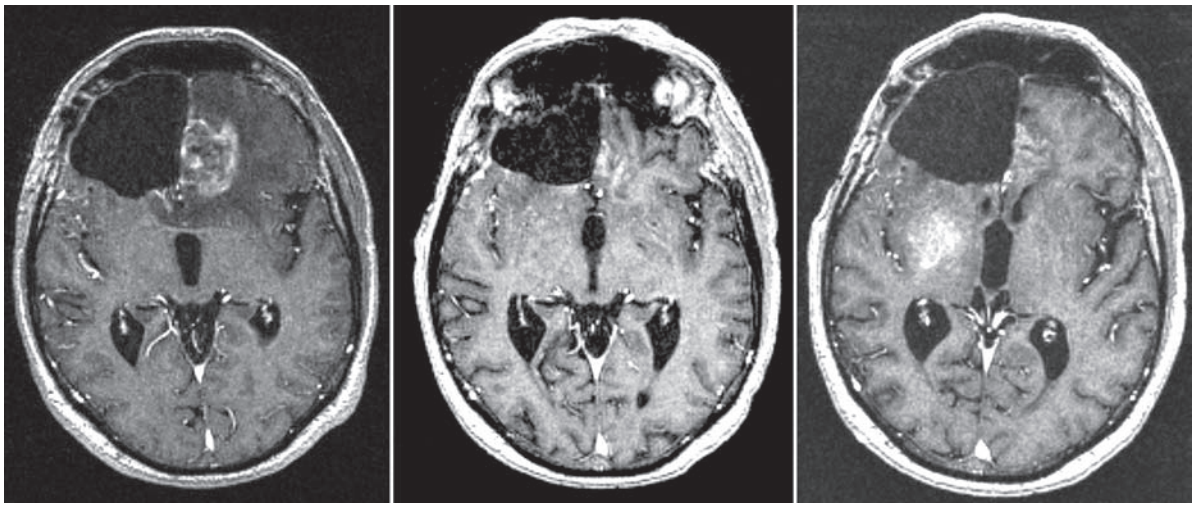

Fig. 2.1 Three stages of a patient with second recurrence of glioblastoma (*left*) treated with bevazizumab plus irinotecan for 8 weeks (*middle*) and 14 weeks (*right panel*)

hampered by the long absence of suitable reagents, which became available only recently [35, 39].

2.4 Targeted Molecules: Signal Transduction

Antibodies bind only extracellular domains of receptors and are problematic in their delivery to tumors. To circumvent that problem, the small molecule tyrosine kinase inhibitors described above were developed, basically targeting the same molecule but from the other side of the membrane. In the search for further intracellular targets, all parts of the signaling cascades have been evaluated, and in the context of glioblastoma where frequently there is a dysfunction of the PTEN molecule, mammalian target of rapamycin (mTOR) has been identified as a potentially very effective target [19]. Rapamycin, a long-known drug used for post-transplant immunosuppression, is in clinical trials for glioblastoma [13] and may be further evaluated with special respect to the individual genetic tumor signatures related to that pathway, which includes PI3 kinase and AKT signaling. Another molecule in clinical evaluation is the RNA-translation inhibitor temsirolimus (CCI-779), which was tested with marginal activity in phase II [11] and is now most often used in combination with other small molecule receptor tyrosine kinase inhibitors.

2.5 Targeted Molecules: Invasion

Single cell invasion as a unique trait of glial neoplasms and the single most important factor for treatment failure [25] has long been a target for specific therapies. The enzymes involved in degradation of the extracellular matrix as well as cellular adhesion molecules mediating cell motility have been the targets for drug development.

Centrally involved in matrix degradation are the matrix metalloproteases (MMPs). There is a wealth of information and in vitro studies on the various MMP inhibitors, but only one reagent inhibiting MMP activity has been tested in a clinical trial without showing efficacy [38]. Despite the negative result of this marimastat trial, some efficacy may have been seen in combination with chemotherapy, and further confirmation from a clinical trial is awaited. The inhibition of MMPs is still of major research interest, and possibly more efficacy can be seen with other reagents such as siRNA [31].

Centrally involved with cell adhesion and motility are the integrins [14], which have a dual role not only in invasion but also in angiogenesis. One of the key integrin receptors in neuro-oncology is $a_v\beta_3$, which has long been investigated [55], but only recently have reagents become available that selectively block that receptor and are considered promising [47]. After mixed results from a phase II trial in which the patients were also treated with temozolamide, the subsequent analysis suggested that a phase III study with Cilengitide® for

patients with glioblastoma in whom the MGMT-gene is not methylated is warranted and is currently being initiated with the results expected by 2011.

2.6 Targeted Molecules: The Immune System

Immunosuppression is a long-proven mechanism by which glioblastoma escapes the natural surveillance and has been identified as a major target in glioma therapy [59]. TGF-β2 appears to be the major immunosuppressive factor, although recently a very complex system of other immunomodulatory systems interacting with lymphocytic activators and inhibitors has been receiving more attention.

TGF-β2 has been targeted with an antisense molecule called AP12009 that is a phosphothyroate heptamer. It is applied by stereotactic intraparenchymal infusion. So far, it has gone through a phase II trial in which it appeared to have some activity in anaplastic astrocytomas and is awaiting a confirmatory trial [30].

A direct immunization strategy became an obvious approach when the vIIIEGF-R was discovered with a unique peptide sequence in it that allows for very specific immunization. Using a synthetic peptide with that sequence as an immunogen, a large vaccination phase III trial is currently in progress [53].

Many other molecules have been found relevant in the mediation of the cellular immune responses or their repression (such as Annexin, Decorin, CRXC4, Fas-ligand, TRAIL, STAT3 and many others), but none of them have yet matured to the stage of clinical trials [16]. Apart from the AP12009 trial, the most advanced activity is currently seen in the area of dendritic cell vaccination where clinical trials are ongoing [18].

2.7 Targeted Molecules: Genetic Targeting of Oncolytic Viruses

In addition to molecules expressed specifically on the cell surface or secreted by glioma cells, characteristic genetic aberrations irrelevant to any signaling also lend themselves to targeting. Foremost, p53 and RB gene mutations have been characterized over almost 20 years [2], but no obvious therapeutic intervention has become apparent from the frequent mutations as such. As these two tumor suppressor genes are also relevant for viral replication, a logical development has been the development of a whole family of selective oncolytic viruses that can be targeted to glioma cells because they conditionally replicate in characteristic genetic contexts such as the mutation or deletion of p53 [24], a disrupted RB pathway [23] or homozygous deletions of p16. Early clinical trials of these replication-competent adenoviruses have been completed and found to be safe [12, 58], but further advanced clinical testing is still awaited.

2.8 Targeted Molecules: Radioimmunotherapy with Specific Ligands for "Oncoproteins"

Part of the glioma cell lineage is a "mesenchymal" phenotype [44] that expresses molecules used for the interaction of the cells with the extracellular matrix of the environment. One of these molecules is tenascin, which has been found to be overexpressed in many analyses. Antibodies to tenascin were developed long ago and have been used for radioimmunotherapy via direct intraparenchymal application with proof of principle and acceptable safety, but outstanding randomized phase III tirals to determine the efficacy are still awaited [27, 46, 49]. Basically, any molecule that is specifically overexpressed in gliomas lends itself to such radioimmunotherapy, but compared to tenascin, all other developments are quite delayed, with the farthest away probably being the anti-EGF-R vIII project.

2.9 Targeted Delivery: Intraparenchymal Delivery

The blood–brain barrier impedes the delivery of many small molecules with the wrong biophysical properties and of almost all large molecules that need to get into not only the vascular tree, but also the tumor. Therefore, a direct intraparenchymal drug delivery modality was developed that uses stereotactically placed catheters and a constant low pressure infusion [8]. Delivering large molecules reverses the deterring

properties of the blood–brain barrier because after delivery beyond the blood brain barrier, the large molecules cannot escape [20]. Prototypically for the use of that technique in neuro-oncology, targeted toxins were generated; these are chimeric molecules that bind to a selectively overexpressed cell surface molecule and by virtue of receptor internalization deliver the toxin part into the cell. TGF-α binding to the EGF-R, interleukin-4 and interleukin-13 has been linked with the pseudomonas exotoxin (PSET) and has been tested in phase I/II, TGF-α-PSET, also know as TP38 [51] and IL-4-PSET [62], or phase III (IL-13-PSET) [34, 43]. Both phase I/II reagents hold promise, especially for improving convection techniques [21], and also the IL-13 reagent (cintredekin besudotox), which was used for perilesional multiple site convection in the post-resection period for newly diagnosed patients with glioblastoma, showed efficacy slightly above Gliadel® wafers, which were the comparator in the open label phase III trial, but this failed to reach statistical significance (S. Chang, in preparation). Another agent, a transferrin linked to diptheria-toxin that was used for intratumoral delivery in non-resectable recurrent patients in phase III, was prematurely closed with only very limited signs of efficacy in this difficult disease stage (Laske et al., unpublished results).

2.10 Targeting Through Motile Delivery Systems

As invasiveness of single cells over large distances from the tumors leads inadvertently to treatment failure, thought has been given to the development of disseminated drug delivery or motile therapy targeting this invasive population, and this has led to the evaluation of neural stem cells as a delivery vehicle [1]. This methodology is very complex, especially the production of such cells as a stable and easily handled reagent, but after many years, it appears as if early clinical trials will begin in the year 2009. The cells are still artificially immortalized, and the reagent delivered will be HSV-Tk as the paradigmatic pro-drug-converting enzyme that converts gancyclovir. The reagent is rather non-specific, but the targeting of the delivery is even more so because theoretically even single cells can be traced and destroyed.

2.11 Targeting Other Intracranial Tumors

With a focus on astrocytic and oligodendrocytic gliomas, this chapter cannot give enough consideration to other tumor entities in neuro-oncology for which, however, the development of targeted therapies is not nearly as advanced, and when tested, they have been very disappointing.

2.12 Targeted Therapies for Meningioma

Meningiomas are usually treated by resection, and if this is incomplete or impossible, by adjuvant stereotactic radiation. A number of intriguing molecules associated with meningiomas, such as the progesterone receptor, dopamine receptors and receptors for somatostatin, have been found successively. None of these have led to the establishment of a medical approach to non-resectable meningiomas, although all agents have shown activity in some selected cases, albeit without any clues as to what the basis of such efficacy was. In desperate cases therefore antiprogesterones, dopamin-agonists and inhibitors of somatostatin receptors are still applied to attempt stabilization when surgical and radiotherapeutic options are exhausted.

2.13 Targeted Therapies for Ependymoma

Identifying a molecular target suitable for the specific therapy of ependymoma has continued to elude all attempts. Surgery is still the paramount element in the treatment, which in cases of dissemination, non-resectability or recurrence is complemented by radiation and/or chemotherapy. No cell surface markers or specific signaling pathways have been identified.

2.14 Targeted Therapies for Medulloblastoma

Medulloblastoma is becoming an increasingly complex disease with molecular subtypes in the pediatric and the adult subgroups. Signaling pathways around

the sonic hedgehog/patched pathway are being identified, and specific reagents are available and are in clinical testing for the appropriate subtype.

2.15 Summary

While targeted therapy sounds like a buzzword, it describes a demand by the patients who increasingly question the concept of being unselectively poisoned. It also summarizes the attempt of basic and clinical researchers to dissect tumor-specific pathways that allow for a highly effective therapy for brain tumors. So far, the multitude of simultaneously activated pathways [57] and the single cell dissemination inherent to the invasive nature of glial tumors have precluded any successful targeting. Nevertheless, developments are being made in the right direction and with the growing awareness in the oncological community that *targeting* in neuro-oncology has a dual meaning: the parallel development of better molecular/pharmacological targeting as well as better local targeting in the sense of delivery to the target, which may be single infiltrating cells. Progress will be made in the field over the next years. Currently, antibody-based strategies, intraparenchymal administration and motile delivery seem to hold the most promise.

References

1. Aboody KS, Najbauer J, Danks MK. (2008) Stem and progenitor cell-mediated tumor selective gene therapy. Gene Ther 15:739–752
2. Anker L, Ohgaki H, Ludeke BI, Herrmann HD, Kleihues P, Westphal M. (1993) p53 protein accumulation and gene mutations in human glioma cell lines. Int J Cancer 55: 982–987
3. Batchelor TT, Sorensen AG, di Tomaso E, Zhang WT, Duda DG, Cohen KS, Kozak KR, Cahill DP, Chen PJ, Zhu M, Ancukiewicz M, Mrugala MM, Plotkin S, Drappatz J, Louis DN, Ivy P, Scadden DT, Benner T, Loeffler JS, Wen PY, Jain RK. (2007) AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell 11:83–95
4. Belda-Iniesta C, Carpeno Jde C, Saenz EC, Gutierrez M, Perona R, Baron MG. (2006) Long term responses with cetuximab therapy in glioblastoma multiforme. Cancer Biol Ther 5:912–914
5. Bellinzona M, Roser F, Matthies C, Samii M, Saini M. (2004) Biopolymer-mediated suramin chemotherapy in the treatment of experimental brain tumours. Acta Oncol 43:259–263
6. Bigner SH, Humphrey PA, Wong AJ, Vogelstein B, Mark J, Friedman HS, Bigner DD. (1990) Characterization of the epidermal growth factor receptor in human glioma cell lines and xenografts. Cancer Res 50:8017–8022
7. Board R, Jayson GC. (2005) Platelet-derived growth factor receptor (PDGFR): a target for anticancer therapeutics. Drug Resist Updat 8:75–83
8. Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH. (1994) Convection-enhanced delivery of macromolecules in the brain. Proc Natl Acad Sci USA 91: 2076–2080
9. Brandes AA, Franceschi E, Tosoni A, Hegi ME, Stupp R. (2008) Epidermal growth factor receptor inhibitors in neuro-oncology: hopes and disappointments. Clin Cancer Res 14:957–960
10. Cancer Genome Atlas Research Network. (2008) Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 455:1061–1068
11. Chang SM, Wen P, Cloughesy T, Greenberg H, Schiff D, Conrad C, Fink K, Robins HI, De Angelis L, Raizer J, Hess K, Aldape K, Lamborn KR, Kuhn J, Dancey J, Prados MD. (2005) Phase II study of CCI-779 in patients with recurrent glioblastoma multiforme. Invest New Drugs 23:357–361
12. Chiocca EA, Abbed KM, Tatter S, Louis DN, Hochberg FH, Barker F, Kracher J, Grossman SA, Fisher JD, Carson K, Rosenblum M, Mikkelsen T, Olson J, Markert J, Rosenfeld S, Nabors LB, Brem S, Phuphanich S, Freeman S, Kaplan R, Zwiebel J. (2004) A phase I open-label, dose-escalation, multi-institutional trial of injection with an E1B-attenuated adenovirus, ONYX-015, into the peritumoral region of recurrent malignant gliomas, in the adjuvant setting. Mol Ther 10:958–966
13. Cloughesy TF, Yoshimoto K, Nghiemphu P, Brown K, Dang J, Zhu S, Hsueh T, Chen Y, Wang W, Youngkin D, Liau L, Martin N, Becker D, Bergsneider M, Lai A, Green R, Oglesby T, Koleto M, Trent J, Horvath S, Mischel PS, Mellinghoff IK, Sawyers CL. (2008) Antitumor activity of rapamycin in a phase I trial for patients with recurrent PTEN-deficient glioblastoma. PLoS Med 5:e8
14. D'Abaco GM, Kaye AH. (2007) Integrins: molecular determinants of glioma invasion. J Clin Neurosci 14:1041–1048
15. Dai C, Lyustikman Y, Shih A, Hu X, Fuller GN, Rosenblum M, Holland EC. (2005) The characteristics of astrocytomas and oligodendrogliomas are caused by two distinct and interchangeable signaling formats. Neoplasia 7:397–406
16. Das S, Raizer JJ, Muro K. (2008) Immunotherapeutic treatment strategies for primary brain tumors. Curr Treat Options Oncol 9:32–40
17. de Bouard S, Herlin P, Christensen JG, Lemoisson E, Gauduchon P, Raymond E, Guillamo JS. (2007) Anti-angiogenic and anti-invasive effects of sunitinib on experimental human glioblastoma. Neuro Oncol 9:412–423
18. De Vleeschouwer S, Fieuws S, Rutkowski S, Van Calenbergh F, Van Loon J, Goffin J, Sciot R, Wilms G, Demaerel P, Warmuth-Metz M, Soerensen N, Wolff JE, Wagner S, Kaempgen E, Van Gool SW. (2008) Postoperative adjuvant dendritic cell-based immunotherapy in patients with relapsed glioblastoma multiforme. Clin Cancer Res 14:3098–3104
19. Ermoian RP, Kaprealian T, Lamborn KR, Yang X, Jelluma N, Arvold ND, Zeidman R, Berger MS, Stokoe D, Haas-Kogan DA.

(2009) Signal transduction molecules in gliomas of all grades. J Neurooncol 91:19–26
20. Ferguson S, Lesniak MS. (2007) Convection enhanced drug delivery of novel therapeutic agents to malignant brain tumors. Curr Drug Deliv 4:169–180
21. Fiandaca MS, Forsayeth JR, Dickinson PJ, Bankiewicz KS. (2008) Image-guided convection-enhanced delivery platform in the treatment of neurological diseases. Neurotherapeutics 5:123–127
22. Fine HA. (2007) Promising new therapies for malignant gliomas. Cancer J 13:349–354
23. Fueyo J, Alemany R, Gomez-Manzano C, Fuller GN, Khan A, Conrad CA, Liu TJ, Jiang H, Lemoine MG, Suzuki K, Sawaya R, Curiel DT, Yung WK, Lang FF. (2003) Preclinical characterization of the antiglioma activity of a tropism-enhanced adenovirus targeted to the retinoblastoma pathway. J Natl Cancer Inst 95:652–660
24. Geoerger B, Grill J, Opolon P, Morizet J, Aubert G, Lecluse Y, van Beusechem VW, Gerritsen WR, Kirn DH, Vassal G. (2003) Potentiation of radiation therapy by the oncolytic adenovirus dl1520 (ONYX-015) in human malignant glioma xenografts. Br J Cancer 89:577–584
25. Giese A, Bjerkvig R, Berens ME, Westphal M. (2003) Cost of migration: invasion of malignant gliomas and implications for treatment. J Clin Oncol 21:1624–1636
26. Godard S, Getz G, Delorenzi M, Farmer P, Kobayashi H, Desbaillets I, Nozaki M, Diserens AC, Hamou MF, Dietrich PY, Regli L, Janzer RC, Bucher P, Stupp R, de Tribolet N, Domany E, Hegi ME. (2003) Classification of human astrocytic gliomas on the basis of gene expression: a correlated group of genes with angiogenic activity emerges as a strong predictor of subtypes. Cancer Res 63:6613–6625
27. Goetz CM, Rachinger W, Decker M, Gildehaus FJ, Stocker S, Jung G, Tatsch K, Tonn JC, Reulen HJ. (2005) Distribution of labelled anti-tenascin antibodies and fragments after injection into intact or partly resected C6-gliomas in rats. Cancer Immunol Immunother 54:337–344
28. Gomez-Manzano C, Holash J, Fueyo J, Xu J, Conrad CA, Aldape KD, de Groot JF, Bekele BN, Yung WK. (2008) VEGF Trap induces antiglioma effect at different stages of disease. Neuro Oncol 10(6):940–945
29. Gunther HS, Schmidt NO, Phillips HS, Kemming D, Kharbanda S, Soriano R, Modrusan Z, Meissner H, Westphal M, Lamszus K. (2008) Glioblastoma-derived stem cell-enriched cultures form distinct subgroups according to molecular and phenotypic criteria. Oncogene 27:2897–2909
30. Hau P, Jachimczak P, Schlingensiepen R, Schulmeyer F, Jauch T, Steinbrecher A, Brawanski A, Proescholdt M, Schlaier J, Buchroithner J, Pichler J, Wurm G, Mehdorn M, Strege R, Schuierer G, Villarrubia V, Fellner F, Jansen O, Straube T, Nohria V, Goldbrunner M, Kunst M, Schmaus S, Stauder G, Bogdahn U, Schlingensiepen KH. (2007) Inhibition of TGF-beta2 with AP 12009 in recurrent malignant gliomas: from preclinical to phase I/II studies. Oligonucleotides 17:201–212
31. Kargiotis O, Chetty C, Gondi CS, Tsung AJ, Dinh DH, Gujrati M, Lakka SS, Kyritsis AP, Rao JS. (2008) Adenovirus-mediated transfer of siRNA against MMP-2 mRNA results in impaired invasion and tumor-induced angiogenesis, induces apoptosis in vitro and inhibits tumor growth in vivo in glioblastoma. Oncogene 27:4830–4840
32. Kuan CT, Wikstrand CJ, Bigner DD. (2001) EGF mutant receptor vIII as a molecular target in cancer therapy. Endocr Relat Cancer 8:83–96
33. Kunkel P, Ulbricht U, Bohlen P, Brockmann MA, Fillbrandt R, Stavrou D, Westphal M, Lamszus K. (2001) Inhibition of glioma angiogenesis and growth in vivo by systemic treatment with a monoclonal antibody against vascular endothelial growth factor receptor-2. Cancer Res 61:6624–6628
34. Kunwar S, Prados MD, Chang SM, Berger MS, Lang FF, Piepmeier JM, Sampson JH, Ram Z, Gutin PH, Gibbons RD, Aldape KD, Croteau DJ, Sherman JW, Puri RK. (2007) Direct intracerebral delivery of cintredekin besudotox (IL13-PE38QQR) in recurrent malignant glioma: a report by the Cintredekin Besudotox Intraparenchymal Study Group. J Clin Oncol 25:837–844
35. Lal B, Xia S, Abounader R, Laterra J. (2005) Targeting the c-Met pathway potentiates glioblastoma responses to gamma-radiation. Clin Cancer Res 11:4479–4486
36. Lamszus K, Laterra J, Westphal M, Rosen EM. (1999) Scatter factor/hepatocyte growth factor (SF/HGF) content and function in human gliomas. Int J Dev Neurosci 17:517–530
37. Laterra JJ, Grossman SA, Carson KA, Lesser GJ, Hochberg FH, Gilbert MR. (2004) Suramin and radiotherapy in newly diagnosed glioblastoma: phase 2 NABTT CNS Consortium study. Neuro Oncol 6:15–20
38. Levin VA, Phuphanich S, Yung WK, Forsyth PA, Maestro RD, Perry JR, Fuller GN, Baillet M. (2006) Randomized, double-blind, placebo-controlled trial of marimastat in glioblastoma multiforme patients following surgery and irradiation. J Neurooncol 78:295–302
39. Martens T, Schmidt NO, Eckerich C, Fillbrandt R, Merchant M, Schwall R, Westphal M, Lamszus K. (2006) A novel one-armed anti-c-Met antibody inhibits glioblastoma growth in vivo. Clin Cancer Res 12:6144–6152
40. Mason WP. (2008) Emerging drugs for malignant glioma. Expert Opin Emerg Drugs 13:81–94
41. Mellinghoff IK, Wang MY, Vivanco I, Haas-Kogan DA, Zhu S, Dia EQ, Lu KV, Yoshimoto K, Huang JH, Chute DJ, Riggs BL, Horvath S, Liau LM, Cavenee WK, Rao PN, Beroukhim R, Peck TC, Lee JC, Sellers WR, Stokoe D, Prados M, Cloughesy TF, Sawyers CL, Mischel PS. (2005) Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. N Engl J Med 353:2012–2024
42. Murat A, Migliavacca E, Gorlia T, Lambiv WL, Shay T, Hamou MF, de Tribolet N, Regli L, Wick W, Kouwenhoven MC, Hainfellner JA, Heppner FL, Dietrich PY, Zimmer Y, Cairncross JG, Janzer RC, Domany E, Delorenzi M, Stupp R, Hegi ME. (2008) Stem cell-related "self-renewal" signature and high epidermal growth factor receptor expression associated with resistance to concomitant chemoradiotherapy in glioblastoma. J Clin Oncol 26:3015–3024
43. Mut M, Sherman JH, Shaffrey ME, Schiff D. (2008) Cintredekin besudotox in treatment of malignant glioma. Expert Opin Biol Ther 8:805–812
44. Phillips HS, Kharbanda S, Chen R, Forrest WF, Soriano RH, Wu TD, Misra A, Nigro JM, Colman H, Soroceanu L, Williams PM, Modrusan Z, Feuerstein BG, Aldape K. (2006) Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. Cancer Cell 9:157–173

45. Ramos TC, Figueredo J, Catala M, Gonzalez S, Selva JC, Cruz TM, Toledo C, Silva S, Pestano Y, Ramos M, Leonard I, Torres O, Marinello P, Perez R, Lage A. (2006) Treatment of high-grade glioma patients with the humanized anti-epidermal growth factor receptor (EGFR) antibody h-R3: report from a phase I/II trial. Cancer Biol Ther 5:375–379
46. Reardon DA, Akabani G, Coleman RE, Friedman AH, Friedman HS, Herndon JE, 2nd, Cokgor I, McLendon RE, Pegram CN, Provenzale JM, Quinn JA, Rich JN, Regalado LV, Sampson JH, Shafman TD, Wikstrand CJ, Wong TZ, Zhao XG, Zalutsky MR, Bigner DD. (2002) Phase II trial of murine (131) I-labeled antitenascin monoclonal antibody 81C6 administered into surgically created resection cavities of patients with newly diagnosed malignant gliomas. J Clin Oncol 20:1389–1397
47. Reardon DA, Nabors LB, Stupp R, Mikkelsen T. (2008) Cilengitide: an integrin-targeting arginine-glycine-aspartic acid peptide with promising activity for glioblastoma multiforme. Expert Opin Investig Drugs 17:1225–1235
48. Reardon DA, Wen PY, Desjardins A, Batchelor TT, Vredenburgh JJ. (2008) Glioblastoma multiforme: an emerging paradigm of anti-VEGF therapy. Expert Opin Biol Ther 8:541–553
49. Reardon DA, Zalutsky MR, Akabani G, Coleman RE, Friedman AH, Herndon JE, 2nd, McLendon RE, Pegram CN, Quinn JA, Rich JN, Vredenburgh JJ, Desjardins A, Guruangan S, Boulton S, Raynor RH, Dowell JM, Wong TZ, Zhao XG, Friedman HS, Bigner DD. (2008) A pilot study: 131I-antitenascin monoclonal antibody 81c6 to deliver a 44-Gy resection cavity boost. Neuro Oncol 10:182–189
50. Rich JN, Reardon DA, Peery T, Dowell JM, Quinn JA, Penne KL, Wikstrand CJ, Van Duyn LB, Dancey JE, McLendon RE, Kao JC, Stenzel TT, Ahmed Rasheed BK, Tourt-Uhlig SE, Herndon JE, 2nd, Vredenburgh JJ, Sampson JH, Friedman AH, Bigner DD, Friedman HS. (2004) Phase II trial of gefitinib in recurrent glioblastoma. J Clin Oncol 22:133–142
51. Sampson JH, Akabani G, Archer GE, Berger MS, Coleman RE, Friedman AH, Friedman HS, Greer K, Herndon JE, 2nd, Kunwar S, McLendon RE, Paolino A, Petry NA, Provenzale JM, Reardon DA, Wong TZ, Zalutsky MR, Pastan I, Bigner DD. (2008) Intracerebral infusion of an EGFR-targeted toxin in recurrent malignant brain tumors. Neuro Oncol 10: 320–329
52. Sampson JH, Akabani G, Archer GE, Bigner DD, Berger MS, Friedman AH, Friedman HS, Herndon JE, 2nd, Kunwar S, Marcus S, McLendon RE, Paolino A, Penne K, Provenzale J, Quinn J, Reardon DA, Rich J, Stenzel T, Tourt-Uhlig S, Wikstrand C, Wong T, Williams R, Yuan F, Zalutsky MR, Pastan I. (2003) Progress report of a Phase I study of the intracerebral microinfusion of a recombinant chimeric protein composed of transforming growth factor (TGF)-alpha and a mutated form of the Pseudomonas exotoxin termed PE-38 (TP-38) for the treatment of malignant brain tumors. J Neurooncol 65:27–35
53. Sampson JH, Archer GE, Mitchell DA, Heimberger AB, Bigner DD. (2008) Tumor-specific immunotherapy targeting the EGFRvIII mutation in patients with malignant glioma. Semin Immunol 20(5):267–275
54. Schmidt NO, Westphal M, Hagel C, Ergun S, Stavrou D, Rosen EM, Lamszus K. (1999) Levels of vascular endothelial growth factor, hepatocyte growth factor/scatter factor and basic fibroblast growth factor in human gliomas and their relation to angiogenesis. Int J Cancer 84:10–18
55. Schnell O, Krebs B, Wagner E, Romagna A, Beer AJ, Grau SJ, Thon N, Goetz C, Kretzschmar HA, Tonn JC, Goldbrunner RH. (2008) Expression of integrin alphavbeta3 in gliomas correlates with tumor grade and is not restricted to tumor vasculature. Brain Pathol 18:378–386
56. Shih AH, Dai C, Hu X, Rosenblum MK, Koutcher JA, Holland EC. (2004) Dose-dependent effects of platelet-derived growth factor-B on glial tumorigenesis. Cancer Res 64:4783–4789
57. Stommel JM, Kimmelman AC, Ying H, Nabioullin R, Ponugoti AH, Wiedemeyer R, Stegh AH, Bradner JE, Ligon KL, Brennan C, Chin L, DePinho RA. (2007) Coactivation of receptor tyrosine kinases affects the response of tumor cells to targeted therapies. Science 318:287–290
58. Vecil GG, Lang FF. Clinical trials of adenoviruses in brain tumors: a review of Ad-p53 and oncolytic adenoviruses. J Neurooncol 65:237–246, 2003
59. Vega EA, Graner MW, Sampson JH. (2008) Combating immunosuppression in glioma. Future Oncol 4:433–442
60. Voelzke WR, Petty WJ, Lesser GJ. (2008) Targeting the epidermal growth factor receptor in high-grade astrocytomas. Curr Treat Options Oncol 9:23–31
61. Vredenburgh JJ, Desjardins A, Herndon JE, 2nd, Marcello J, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Sampson J, Wagner M, Bailey L, Bigner DD, Friedman AH, Friedman HS. (2007) Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 25:4722–4729
62. Weber F, Asher A, Bucholz R, Berger M, Prados M, Chang S, Bruce J, Hall W, Rainov NG, Westphal M, Warnick RE, Rand RW, Floeth F, Rommel F, Pan H, Hingorani VN, Puri RK. (2003) Safety, tolerability, and tumor response of IL4-Pseudomonas exotoxin (NBI-3001) in patients with recurrent malignant glioma. J Neurooncol 64:125–137
63. Zhou Q, Guo P, Gallo JM. (2008) Impact of angiogenesis inhibition by sunitinib on tumor distribution of temozolomide. Clin Cancer Res 14:1540–1549