Neuro-Oncology 12(3):304–316, 2010.
doi:10.1093/neuonc/nop068

Small molecule kinase inhibitors in glioblastoma: a systematic review of clinical studies

Philip C. De Witt Hamer

Neuro-oncology Research Group, Cancer Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands; Neurosurgical Center Amsterdam, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Neurosurgical Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

The efficacy of small-molecule kinase inhibitors has recently changed standard clinical practice for several solid cancers. Glioblastoma is a solid cancer that universally recurs and unrelentingly results in death despite maximal surgery and radiotherapy with concomitant and adjuvant temozolomide. Several clinical studies using kinase inhibitors in glioblastoma have been reported. The present study systematically reviews the efficacy, toxicity, and tissue analysis of small-molecule kinase inhibitors in adult patients with glioblastoma as reported in published clinical studies and determines which kinases have been targeted by the inhibitors used in these studies. Publications were retrieved using a MEDLINE search and by screening meeting abstracts. A total of 60 studies qualified for inclusion, of which 25 were original reports. A total of 2385 glioblastoma patients receiving kinase inhibitors could be evaluated. The study designs included 2 phase III studies and 37 phase II studies. Extracted data included radiological response, progression-free survival, overall survival, toxicity, and biomarker analysis. The main findings were that (i) efficacy of small-molecule kinase inhibitors in clinical studies with glioblastoma patients does not yet warrant a change in standard clinical practice and (ii) 6 main kinase targets for inhibitors have been evaluated in these studies: EGFR, mTOR, KDR, FLT1, PKCβ, and PDGFR.

Keywords: clinical trial, glioblastoma, kinases, review, small-molecule inhibitors.

Received June 5, 2009; accepted September 29, 2009.

Corresponding Author: Philip C. De Witt Hamer, MD, Neurosurgical Center Amsterdam, VU University Medical Center, De Boelelaan 1117, Amsterdam, The Netherlands (p.dewitthamer@vumc.nl).

Small-molecule compounds that inhibit the kinase domain of specific kinase targets have recently changed clinical practice for several advanced solid cancers, such as lapatinib, which inhibits HER2 and EGFR in HER2-positive metastatic breast cancer;[1] sunitinib, which inhibits VEGFR and PDGFR in metastatic renal-cell carcinoma;[2] and sorafenib, which inhibits RAF, PDGFR, VEGFR, and KIT in advanced hepatocellular carcinoma[3] and also in advanced renal-cell carcinoma.[4] These advances followed the seminal contribution to cancer therapy by gefitinib for chronic myeloid leukemia by inhibiting the ABL/CBR fusion protein[5] and for gastrointestinal stroma tumor by inhibition of the activating KIT mutation.[6]

Glioblastoma is one of the most aggressive solid cancers and the most common primary brain tumor. Because this tumor is inherently resistant to conventional therapy, the median patient survival is approximately 14 months. Although standard treatment with surgery, irradiation, and temozolomide postpones progression and extends survival to some extent, these tumors universally recur and unrelentingly result in death.[7] Therefore, improvement of treatment options for patients with glioblastoma is imperative. For this purpose, inhibition of kinase targets that drive glioblastoma growth seems a reasonable treatment strategy to be further explored.

Several clinical studies have reported the efficacy of kinase inhibitors in glioblastoma. The outcome of these clinical studies has not been systematically reviewed, although a number of reviews highlight in their discussions a selection of studies using kinase inhibitors for glioblastoma.[8–15] The aim of the present study was to review the efficacy of small-molecule kinase inhibitors in adult patients with glioblastoma based on published clinical study results and to determine which kinases are targeted by the inhibitors used in these clinical studies.

Search Strategy and Data Extraction

Results of clinical studies were obtained from 2 sources. A systematic search was performed in PubMed MEDLINE with the MeSH term "glioma" limited by publication type "clinical trial" and "adults", with publication after January 1, 2002. Furthermore, the abstracts of the annual meetings of the American Society for Clinical Oncology from 2002 to 2008, of the European Association of Neuro-Oncology from 2005 to 2008, of the Society for Neuro-Oncology from 2003 to 2008, and of the World Federation of Neuro-Oncology in 2001 and 2005 were systematically searched for preliminary outcome data of clinical studies.

To compare the data obtained from studies without control patient groups, the results from published studies in patients with newly diagnosed and progressive glioblastoma receiving conventional therapy were included as historical controls.

The data extracted from these sources were the total number of patients in the study, the number of evaluated patients in the population used for data extraction, histopathological diagnosis, study design, type of inhibitor and dosage, inhibitor target, percentage of radiologically complete responses and partial responses, median progression-free survival (mPFS), PFS at 6 months (PFS6), median overall survival (mOS), OS at 12 months (OS12), the number of adverse events of grade 3, 4, or 5 according to the National Cancer Institute Common Toxicity Criteria, and the tissue analysis in relation to response. Data on the effect of kinase inhibitors on the functional status of patients were unavailable from the vast majority of evaluable studies. As far as possible, the data were extracted for the glioblastoma subgroup. When exact percentages and survival times were not provided, these were estimated from the time to progression and survival curves.

Publications and abstracts were screened for efficacy data. Audiovisual material at the ASCO website (http://www.asco.org/ASCOv2/Meetings/Abstracts) was available for some of the meeting presentations and was scanned for additional data not included in the meeting abstract. If no outcome data (ie, radiological response, PFS, or OS) were provided, the publication or abstract was excluded from the analysis.

Meta-analysis of the efficacy data was not performed because of the small sample sizes and the highly selected populations with inhomogeneity of inclusion criteria, histopathological diagnosis, stages of disease, drug schedules, and definitions of outcome and efficacy. Therefore, analysis of data is descriptive and qualitative.

Results

A total of 60 studies qualified for inclusion, of which 25 were published as original reports in peer-reviewed journals and 35 as meeting abstracts. Study designs included 2 phase III studies, 1 randomized phase II study, 28 single-arm phase II studies, 8 single-arm phase I/II studies, 16 phase I studies, 4 retrospective observational series, and 1 pharmacodynamic study. The sum of evaluated patients receiving kinase inhibitors was 2385. The average number of evaluable patients per study was 40, ranging from 6 to 178.

The efficacy, toxicity, and tissue analysis results are listed in Table 1.

Radiological Response

Radiological response rates (ORs) were evaluable in 51 studies.

The reported objective radiological ORs were approximately double the baseline rates after inhibition of EGFR using erlotinib or gefitinib in 6 of 12 evaluable single-inhibitor studies, in 2 of 7 studies combining inhibition of EGFR and mTOR, and in none of 4 evaluable studies combining EGFR inhibition with conventional therapy. In 1 study combining EGFR inhibition by erlotinib with VEGF inhibition by bevacizumab, an OR of 48% was observed,[16] which was comparable with the results for pan-VEGFR inhibition with cediranib.[17] The ORs after inhibition of mTOR were comparable with the baseline results in 4 single-agent studies. Inhibition of PKCβ by enzastaurin increased the OR compared with baseline in 1 of 3 studies. Two of 6 single-agent studies using PDGFR/KIT/ABL inhibition by imatinib and 3 of 5 combination therapy studies with imatinib and hydroxyurea showed an increased OR. The combination of imatinib, hydroxyurea, and KDR inhibition by vatalanib resulted in increased ORs in 2 of 2 studies.

Progression-Free Survival

The PFS was evaluable as mPFS in 36 studies and as PFS6 in 34 studies.

The mPFS approximately doubled in progressive glioblastoma compared with baseline in 1 of 8 evaluable studies with EGFR inhibition by gefitinib or erlotinib[18] and in 1 of 6 evaluable studies with combined EGFR and mTOR inhibition using gefitinib at high dose.[19] Seven evaluable studies combining EGFR inhibition with conventional therapy had PFS comparable with baseline values. The mPFS was comparable with baseline in 3 evaluable studies with single-agent mTOR inhibition. The remarkable OR of VEGFR inhibition by cediranib was substantiated by a slightly increased mPFS of 4 months.[17] The mPFS was increased in 2 of 4 evaluable studies with imatinib as single-agent therapy, although a relevant number of anaplastic gliomas were included in these 2 studies.[20,21] One of 3 evaluable studies using combined imatinib and hydroxyurea showed a small increase in mPFS of 3.6 months compared with baseline.[22]

The PFS6 was comparable with baseline in all 8 evaluable studies with EGFR inhibitors as single-agent therapy, was possibly increased in 2 of 5 evaluable studies with combined EGFR and mTOR inhibition including 1 study with a number of anaplastic

Table 1. A summary of efficacy, toxicity, and tissue analysis in clinical studies with small molecule kinase inhibitors in adult patients with newly diagnosed and progressive glioblastoma.

Kinase target	First author	Year	Reference(s)	Total no. of patients in the study	No. of patients in evaluated population				Study design	Therapy	CR (%)	PR (%)	OR (%)	mPFS	PFS6 (%)	mOS	OS12 (%)	Toxicity as no. of grade 3, 4, or 5 events in no. of evaluable patients	Tissue analysis to predict response[e]
					Newly diagnosed		Progressive												
					GB	AG	GB	AG											
Baseline studies																			
	Stupp	2005	7	573	286				III	rth	—	—	—	5	9	12.1	51	—	NA
	Stupp	2005	7	573	287				III	rth + tmz	—	—	—	6.9	27	14.6	61	75 in 284	NA
	Athanassiou	2005	60	130	57				r II	rth	—	—	—	5.2	45	7.7	16	—	NA
	Athanassiou	2005	60	130	53				r II	rth + tmz	—	—	—	10.8	67	13.4	56	6 in 110	NA
	Brada	2001	61	138			138		II	tmz	2	6	8	2.1	18	5.4	15	60 in 138	NA
	Yung	2000	62	225			112		r II	tmz	0	5	5	3	21	7.1	22	26 in 110	NA
	Yung	2000	62	225			113		r II	Procarbazine	0	5	5	2.1	8	5.6	18	26 in 110	NA
	Wong	1999	63	375			225		[d]	Various salvage treatments without tmz, without kinase inhibitors	—	—	6	2.3	15	6.3	21	—	NA
Single target small molecule inhibitors																			
EGFR																			
	Van den Bent	2009	45,64,65	54			54		r II	Erlotinib 150–500 mg pod vs tmz or carmustine	0	4	4	1.8	11	7.7	22	13 in 54	ihc: EGFR EGFRvIII* PTEN pAKT; fish: EGFR; mut: EGFR
	Preusser	2008	44	21			14	7	RObs	Erlotinib 100–150 mg pod or Gefitinib 250 mg pod	0	14	14	3.1	19	5.1	5	1 in 21	ihc: EGFR EGFRvIII PTEN pAKT
	Franceschi	2007	42	16			16		II	Gefitinib 250 mg pod	0	0	0	2.1	13	6.2	14	5 in 28	ihc: EGFR pAKT; fish: EGFR
	Buie	2007	66	6			6		I	Erlotinib 450–900 mg every 3 days	0	17	17	—	—	—	—	0 in 6	None
	Mellinghoff	2006	46	49			49		II	Erlotinib 150–500 mg pod or Gefitinib 250–1000 mg pod	0	18[a]	18	—	—	—	—	—	ihc: EGFRvIII* PTEN*; fish: EGFR; mut: EGFR, HER2, PTEN; pcr: EGFR EGFRvIII
	Haas-Kogan	2005	43	52			29		I	Erlotinib dosage unavailable	0	17	17	—	—	—	—	—	ihc: EGFR* EGFRvIII pAKT*; fish: EGFR*; mut: EGFR PTEN
	Cloughesy	2005	67,68	48			48		II	Erlotinib 150–300 mg pod	2	6	8	—	17	—	—	—	ihc: EGFR EGFRvIII PTEN; fish: EGFR
	Rich	2004	31,69	57			57		II	Gefitinib 500–1000 mg pod	0	0	0	2	13	9.9	36	27 in 55	ihc: EGFR EHGRvIII; pcr: EGFR
	Uhm	2004	70	96	96				II	Gefitinib 500–1000 mg pod	—	—	—	6.8	62	12.8	54	21 in 63	ihc: EGFR EGFRvIII; fish: EGFR
	Raizer	2004	71	45			31		II	Erlotinib 150 mg pod	0	0	0	2.3	0	—	—	—	None
	Lieberman	2004	72	65			38		I/II	Gefitinib 250–1000 mg pod	0	13	13	2	9	—	—	—	None
	Vogelbaum	2004	18,73,74	31			16		II	Erlotinib 150 mg pod	0	25	25	5.2	—	—	—	—	fish: EGFR
	Peery	2003	75	57			52		II	Gefitinib 500–1000 mg pod	0	2	2	—	—	—	—	10 in 52	ihc: EGFR EGFRvIII; pcr: EGFR
mTOR																			
	Cloughesy	2008	39	15			15		I	Rapamycin 2–10 mg pod	0	7	7	3.6	—	—	—	7 in 15	ihc: pS6K pAKT pPRAS40*
	Galanis	2005	27	65			65		II	Temsirolimus 250 mg ivw	0	0	0	2.3	8	4.4	—	40 in 65	ihc: PTEN S6K pS6K* AKT pAKT; fish: EGFR PTEN; act: S6K

	Chang	2005	26,76	43			43		II	Temsirolimus 170–250 mg ivw	0	5	5	2.3	2	—	—	49 in 43	None
	Chang	2004	77	12			9		I	Temsirolimus 250–330 mg ivw	0	0	0	—	—	—	—	4 in 12	None
VEGFR																			
FLT1/KDR	Batchelor	2007	17	16			16		II	Cediranib 45 mg pod	0	56	56	4	30	7.5	—	9 in 16	ihc: VEGFR1 VEGFR2 VEGFR3 PDGFRα PDGFRβ; plasma: VEGF PIGF* sVEGFR2* bFGF* SDF1α*
KDR	Conrad	2004	28,78–80	55			55		I/II	Vatalanib 150–2000 mg pod	0	4	4	2.5	25	—	—	10 in 45	None
PKCβ																			
	Kreisl	2009	81	26			17	9	I	Enzastaurine 500–1000 mg pod	4	4	8	1.4	—	5.7	—	9 in 22	Plasma: Pgsk3β
	Fine	2008	34,82–84	266			174		III	Enzastaurine 500 mg pod vs lomustine	0	3	3	1.5	11	6.6	15	14 in 167	None
	Fine	2005	85,86	85			57		II	Enzastaurine 500 mg pod	0	18	18	—	—	—	—	3 in 85	None
Multitarget small molecule inhibitors																			
PDGFR/KIT/ABL																			
	Raymond	2008	87–89	112			51		II	Imatinib 600–1000 mg pod	0	6	6	1.8	16	5.9	—	34 in 112	mut: KIT PDGFRα PDGFRβ ABCG2
	Razis	2007	90	20	19	1			PD	Imatinib 800 mg pod	0	0	0	—	—	6.2	—	—	ihc: AKT MAPK p27 EGFR PDGFR
	Viola	2007	21	20			18	2	II	Imatinib 800 mg pod	0	0	0	7.8	52	—	—	0 in 20	ihc: PDGFRα PDGFRβ
	Wen	2006	41,91,92	55			34		I/II	Imatinib 800 mg pod	0	6	6	—	3	—	—	35 in 55	pcr: EGFR EGFRvIII; mut: PTEN PDGFRα PDGFRβ
	Marosi	2006	20	34			23	11	II	Imatinib 400 mg pod	0	18	18	9.5	33	12.3	45	0 in 34	ihc: PDGFRα PDGFRβ KIT ABL
	Franceschi	2005	93	28			16		II	Imatinib 250 mg pod	0	0	0	2	13	6.1	14	5 in 28	None
KIT/PDGFR/KDR/FLT3/RET																			
	Chaskis	2008	94	12			7	5[b]	II	Sunitinib 37.5 mg pod	0	8	8	—	—	—	—	5 in 12	None
EGFR/VEGFR																			
	Kreisl	2008	95	32			32		II	Vandetanib 300 mg pod	0	16	16	—	—	—	—	11 in 32	None
KDR/FLT1/PDGFR/FLT3/RET/KIT																			
	Reardon	2008	96	16			16		II	Sorafenib 400 mg pod + tmz	0	0	0	—	—	—	—	7 in 16	None
Combination therapy																			
EGFR + mTOR																			
	Kreisl	2009	36	22			22		I/II	Gefitinib 250 mg pod + everolimus 70 mg ivw	0	14	14	2.6	5	—	—	21 in 22	ihc: EGFR PTEN pAKT pS6K EGFRvIII
	Friedman	2008	97	27			27		II	Erlotinib 150–500 mg pod + Rapamycin 5–10 mg pod	0	0	0	—	—	—	—	6 in 27	None
	Phuphanich	2008	19	18			18		I	Gefitinib 250–1000 mg pod + rapamycin 2–6 mg pod	0	0	0	5	—	9.4	—	6 in 18	None
	Reardon	2006	24	34			29	5	I	Gefitinib 500–750 mg pod + rapamycin 5–10 mg pod	0	6	6	2.1	24	—	—	36 in 32	ihc: pMAPK pS6K pAKT PTEN EGFR; fish: EGFR PTEN

Continued

Table 1. *Continued*

Kinase target	First author	Year	Reference(s)	Total no. of patients in the study	No. of patients in evaluated population				Study design	Therapy	CR (%)	PR (%)	OR (%)	mPFS	PFS6 (%)	mOS	OS12 (%)	Toxicity as no. of grade 3, 4, or 5 events in no. of evaluable patients	Tissue analysis to predict response[e]
					Newly diagnosed		Progressive												
					GB	AG	GB	AG											
	Doherty	2006	23	28			22		RObs	Gefitinib 500 mg pod + rapamycin 4 mg pod	0	18	18	3	25	—	—	3 in 28	None
	Badruddoja	2006	98	21			18		I/II	Gefitinib 500–1500 mg pod + rapamycin 2 mg pod	0	0	0	3	17	—	—	8 in 18	None
	Nguyen	2006	99	19			19		I/II	Gefitinib 250 mg pod + everolimus 30–70 mg ivw	0	11	11	2.6	5	6.5	—	—	None
EGFR + conventional therapy																			
	Prados	2009	32,100	65	65				II	Erlotinib 100–300 mg pod + tmz	—	—	—	8.2	72	19.3	68	48 in 65	ihc: EGFR EGFRvIII PTEN*; fish: EGFR; pcr: MGMT*
	Schwer	2009	25	15			11	4	I	Gefitinib 250 mg pod + radiosurgery	—	—	—	—	53	10	—	—	None
	Brown	2008	101	97	97				II	Erlotinib 150 mg pod+ tmz + rth	—	—	—	7.2	—	15.3	61	—	ihc: EGFR EGFRvIII PTEN p53; fish: EGFR
	De Groot	2008	37,102	44			43		II	Erlotinib 150–200 mg pod + carboplatin	0	2	2	2	13	7.5	—	82 in 43	ihc: EGFR EGFRvIII pAKT PTEN
	Chakravarti	2006	103–106	178	178				I/II	Gefitinib 500 mg pod + rth	—	—	—	5.1	—	11	—	—	ihc: EGFRvIII PTEN
	Prados	2006	107,108	83			60		I	Erlotinib 100–500 mg pod + tmz	0	8	8	2	7	—	—	36 in 83	None
	Krishnan	2006	109	19	19				I	Erlotinib 100–200 mg pod + rth	0	0	0	6	—	13.8	—	5 in 20	None
	Brewer	2006	33,38,110	28	28				II	Erlotinib 50–150 mg pod + tmz + rth	0	0	0	3.6	—	—	—	40 in 27	Fish: EGFR
PDGFR/KIT/ABL + hydroxyurea																			
	Shah	2007	33	16			11	5	RObs	Imatinib 400–500 mg pod + hydroxyurea	0	21	21	—	—	10	—	8 in 16	None
	Dresemann	2008	111,112	240			120		III	Imatinib 600 mg pod + hydroxyurea vs hydroxyurea	0	2	2	1.6	5	—	—	—	None
	Dresemann	2008	35,113	30	30				II	Imatinib 600 mg pod + hydroxyurea	0	13	13	—	60	—	67	4 in 30	None
	Dresemann	2006	29	30			30		RObs	Imatinib 400–600 mg pod + hydroxyurea	3	17	20	2.5	32	4.8	25	0 in 30	None
	Reardon	2005	22,114–116	33			33		II	Imatinib 400–500 mg pod + hydroxyurea	3	6	9	3.6	27	12.2	—	14 in 33	None

Others																				
KDR + PDGFR/KIT/ABL	Kirkpatrick	2008	30	37			34	3	I	Vatalanib 2000 mg pod + imatinib 'standard dose' + hydroxyurea	0	22	22	—	27	—	—	—	None
EGFR + VEGF	Sathornsumetee	2008	16,117,118	25			25		II	Erlotinib 200–650 mg pod + bevacizumab	—	—	48	—	24	—	—	—	None
EGFR + SRC	Reardon	2008	119	15			13	2	I	Erlotinib 150–450 mg pod + dasatinib 100 mg pod	0	0	0	—	—	—	—	1 in 15	None
KIT/PDGFR/KDR/FLT/RET	Wuthrick	2008	120	10			10		I	Sunitinib 37.5 mg pod + rth	0	10	10	—	—	—	—	1 in 10	None
KDR + PDGFR/KIT/ABL	Sathornsumetee	2007	121	35			35		I	Vatalanib 500–1000 mg pod + imatinib 400–500 mg pod + hydroxyurea	0	29	29	—	—	—	—	4 in 35	None
KDR/FLT1/PDGFR + EGFR/HER2	Reardon	2007	122	32			32		II	Pazopanib 400 mg pod + lapatinib 1000 mg pod	0	0	0	—	—	—	—	10 in 75	ihc: PTEN EGFRvIII
PDGFR/KIT/ABL	Sathornsumetee	2006	123	56	46	10[c]			I	Imatinib unavailable dose + tmz	0	7	7	—	—	—	—	5 in 56	None
PDGFR/KIT/ABL + mTOR	Desjardins	2006	124	28			28		I	Imatinib 400 mg pod + hydroxyurea + everolimus 2.5 mg ivd	0	4	4	—	—	—	—	1 in 5	None
KDR	Reardon	2004	125,126	60			60		I/II	Vatalanib 500–1500 mg pod + tmz or lomustine	0	7	7	3.5	15	—	—	3 in 60	None

Abbreviations: rII, randomized phase II study; Robs, retrospective observational study; PD:, pharmacodynamic study; tmz, temozolomide 150–200 mg/m^2 po 5 days/28 days; rth, radiotherapy; pod, per os daily; ivw, intravenous weekly; ivd, intravenous daily; CR, complete response; PR, partial response; mPFS, median progression-free survival; PFS6: progression-free survival at 6 months; mOS, median overall survival; OS12, overall survival at 12 months; ihc, immunohistochemistry to determine protein expression; fish, fluorescence in situ hybridization to determine gene amplification; mut, sequencing analysis to determine gene mutation; pcr, PCR to determine gene copy number or gene expression; act, kinase activity assay to determine protein activity; plasma, plasma protein concentration analysis; na, not applicable. For comparison, baseline studies with conventional therapies are listed. Studies are categorized by single-target inhibitors, multitarget inhibitors, and combination therapies; subcategorized by kinase drug target; and sorted by year of publication and number of patients.

[a]Partial response defined as $>25\%$ decrease of bidirectional area.

[b]Including 4 progressive low-grade gliomas.

[c]Including 1 pleiomorph xanthoastrocytoma.

[d]Prognosis study with data from 8 phase II trials.

[e]Tissue analysis results that are significantly correlated with efficacy are marked with an asterisk.

gliomas,[23,24] and was increased in 1 of 4 evaluable studies with EGFR inhibition combined with conventional therapy, which included a relevant number of anaplastic gliomas.[25] When EGFR inhibition was combined with VEGFR ligand binding by bevacuzimab, the PFS6 was 24%.[16] The PFS6 was comparable with baseline using both evaluable single-agent mTOR inhibitors.[26,27] In both studies with single-agent VEGFR inhibitors, the PFS6 was increased, including a PFS6 of 30% after cediranib in concordance with the increased OR and mPFS.[17,28] The PFS6 was comparable with baseline in 1 evaluable study with PKCβ inhibition. The same 2 studies with single-agent imatinib that had an increased mPFS also had an increase in PFS6.[20,21] Again, the number of anaplastic gliomas included in the study populations likely contributed to this finding. A slight increase in PFS6 was observed in 2 of 4 evaluable studies with combination therapy using imatinib and hydroxyurea, while 1 of these 2 studies was a retrospective observational series.[22,29] Furthermore, the study with combined imatinib, hydroxyurea, and KDR inhibition by vatalanib had a PFS6 of 27%, although a number of anaplastic gliomas were included.[30]

Overall Survival

The OS was evaluable as mOS in 23 studies and as OS12 in 12 studies.

The mOS increased to 9.9 months in 1 of 5 evaluable studies with single-agent EGFR inhibition.[31] In the 1 evaluable study with combined EGFR and mTOR inhibition, the mOS was also increased.[19] The mOS was remarkably increased to 19.3 months in 1 of 6 evaluable studies with the combination of EGFR inhibition and conventional therapy, erlotinib, and temozolomide in this study with newly diagnosed glioblastomas.[32] Another study with combination therapy using EGFR inhibition by gefitinib and radiosurgery showed an increased mOS; however, anaplastic gliomas were included.[25] The one evaluable study with single-agent mTOR inhibition had an mOS comparable with baseline. The 1 evaluable study with VEGFR inhibition by cediranib, with encouraging OR, mPFS, and PFS6, barely presented an increase in mOS.[17] The mOS was comparable with baseline in 2 evaluable studies with PKCβ inhibition by enzastaurin. In 1 of 4 evaluable studies with imatinib as single-agent therapy, the mOS was increased, although a substantial number of anaplastic gliomas were included.[20] The mOS was increased in 2 of 3 evaluable studies with imatinib in combination with hydroxyurea; of these 2 studies, 1 included a number of anaplastic gliomas[33] and the other showed an mOS of 12.2 months in progressive glioblastoma.[22]

The OS12 was increased to 36% in 1 of 5 evaluable studies with EGFR inhibition.[26] In 1 of 2 evaluable studies with EGFR inhibition by erlotinib combined with temozolomide, the OS12 was increased to 68%.[32] In 1 evaluable study with PKCβ inhibition by enzastaurin, the OS12 was comparable with baseline.[34] The OS12 was increased to 45% in 1 of 2 evaluable studies with imatinib as single-agent therapy, which included a large number of anaplastic gliomas. Combination therapy using imatinib and hydroxyurea increased the OS12 in both evaluable studies.[29,35]

Toxicity

Toxicity data were evaluable in 26 studies.

The toxicity increased to 27 events in 55 patients in 1 of 7 evaluable studies with EGFR inhibition by gefitinib compared with baseline.[31] The toxicity of therapy combining EGFR and mTOR inhibition was increased up to 36 events in 32 patients in 2 of 6 evaluable studies.[24,36] Toxic events associated with therapy combining EGFR inhibition by erlotinib with conventional therapy, such as temozolomide,[32] carboplatin,[37] or temozolomide, and radiotherapy[38] were considerably increased, with 48 events in 65 patients, 82 in 43 patients, and 40 in 27 patients, respectively. In 3 of 4 evaluable studies with mTOR inhibition by rapamycin or temsirolimus, toxicity was increased up to 49 events in 43 patients.[26,27,39] The toxicity was increased in 1 of 2 studies with VEGFR inhibition by cediranib[17] and was not increased with PKCβ inhibition. Imatinib was associated with increased toxicity (35 events in 55 patients) in 1 of 5 evaluable studies.[40] The combination therapy of imatinib and hydroxyurea showed increased toxicity (up to 8 events in 16 patients) in 2 of 4 evaluable studies.[22,41]

Tissue Analysis

Patient tissue was analyzed in relation to response in 27 studies. The activation status of a substrate downstream of the kinase target was verified in 4 studies after EGFR inhibition[42–45] and in 2 studies after mTOR inhibition,[27,39] of which 3 provided an indication of target inactivation after kinase inhibition.[27,39,43] Several molecular markers have been found to predict response, sometimes with conflicting results.

An association between tissue analysis and response to EGFR inhibition was identified in 3 of 10 studies that analyzed tissue. In one of these studies, the presence of the EGFRvIII mutant correlated with poor PFS after erlotinib.[45] In the second study, the presence of the EGFRvIII mutant coinciding with PTEN protein expression was associated with radiological response after erlotinib or gefitinib.[46] In the third study, high EGFR protein expression, EGFR amplification, and low phosphorylated AKT protein expression, as a downstream target of EGFR, each correlated with radiological response, and in addition, high phosphorylated AKT protein expression was associated with poor PFS.[43]

A response correlation was found in 2 studies describing tissue analysis after mTOR inhibition. In one study, high protein expression of phosphorylated PRAS40, as a downstream target of AKT, correlated with poor PFS after rapamycin.[39] In the other study, high protein expression of phosphorylated S6K, as a downstream

target of mTOR, was associated with radiological response after temsirolimus.[27]

After VEGFR inhibition by cediranib, radiological tumor progression was associated with a decrease in the plasma protein level of PIGF and an increase in plasma protein levels of sVEGFR2, bFGF, and SDF1α.[17]

A survival benefit was identified in patients with both a methylated MGMT promotor status and positive PTEN protein expression after combination therapy of EGFR inhibition by erlotinib and temozolomide during and after radiotherapy.[32]

Kinase Drug Targets

The targets of small-molecule kinase inhibitors in clinical studies with glioblastoma patients have mainly been 6 kinases: EGFR, mTOR, KDR, FLT1, PKCβ, and PDGFR. In addition, 3 evaluated multitargeted agents also inactivate other kinase targets nonspecifically: imatinib also inhibits KIT and ABL, sunitinib also inhibits FLT3 and RET, and lapatinib also inhibits HER2.

Discussion

The main findings of the present study are that (i) the efficacy of small-molecule kinase inhibitors in clinical studies with adult glioblastoma patients does not yet warrant a change in standard clinical practice, and (ii) the main kinase targets of the inhibitors evaluated in these studies are EGFR, mTOR, KDR, FLT1, PKCβ, and PDGFR.

The evaluated studies have several limitations that should be considered in interpreting these results. First, many of the studies were not designed to determine the efficacy of therapy and consequently no control group was included for comparison of results in the intervention group. Included in this analysis were outcome results from 4 retrospective observational, 1 pharmacodynamic, 16 phase I, and 8 phase I/II studies. Control group data were available from 1 randomized phase II and 2 phase III studies. Second, sample sizes were small. For instance, the average number of patients in the phase II studies was 39 (range: 12–65). Third, the study populations predominantly consisted of patients with progressive glioblastoma or anaplastic glioma, except for 9 studies of patients with newly diagnosed glioblastoma. Fourth, drug activity was usually unknown, as the inactivation of downstream targets was seldom verified in tissue samples. Fifth, the classical study endpoints of radiological response, PFS, and OS were evaluated, each with their limitations. Beneficial effects for individual patients, for instance in terms of improved quality of life or alleviation of symptoms, cannot be excluded by evaluation of these classical endpoints. As an example of the limitations of the classical endpoints, the radiological response criteria rely on enhancement due to blood-brain barrier disruption. Causes other than tumor progression can induce enhancement, such as postoperative gliosis, infection, or radiation necrosis, and enhancement can be reduced by stabilization of the blood-brain barrier rather than by a decrease of the tumor burden. Furthermore, limitations to the PFS as an endpoint are inherent to the radiological definition of progression, its dependence on timing of radiological follow-up, and the fact that radiological progression is not necessarily equal to cessation of clinical benefit. Evaluation of the OS is hampered by bias from subsequent salvage therapies after the trial intervention and does not reflect the quality of the prolonged lifetime.

The lack of efficacy in these clinical studies can have several causes. First, results that have been obtained in preclinical glioma models and that have motivated further clinical evaluation may not adequately represent the pathobiology of glioblastoma in patients. Second, the inhibitor may have failed to inactivate the target in glioblastoma cells, for instance due to low concentrations in tumor tissue or agent inactivation mechanisms. Third, the pursued kinase target may be active only in a subpopulation of patients. The efficacy of kinase inhibition in this subpopulation may have been diluted by unselected glioblastoma patients. Fourth, alternative kinase signaling pathways may be active in parallel with the inhibited target, so that a single target's inactivation does not reduce downstream oncogenic signaling. Fifth, beneficial effects from these kinase inhibitors are perhaps not portrayed by the classical endpoints as evaluated.

Several strategies may help overcome these issues. First, the best kinase drug targets need to be identified for glioblastoma. Second, the preclinical efficacy from inhibition of these drug targets needs to be rigorously verified in several glioblastoma models to complement each single model's limitations. Third, kinase inhibitors need to be developed and optimized further, for instance by directing toward downstream targets or toward multiple kinase targets or by using a combination of inhibitors. However, the toxicity of the evaluated kinase inhibitors was significant, and hence improved safety of new inhibitors remains important. Fourth, the inactivation of the target and its downstream substrate should be verified in early studies with glioblastoma tissue obtained from patients. An elegant proof-of-concept of this biological activity endpoint was recently demonstrated.[39] Fifth, the study populations need to be enriched by including patients likely to respond, by determining the activation status of the aimed drug target. Sixth, other clinical trial endpoints, such as quality of life and cognitive status, can be considered in addition to the classical trial endpoints.[47,48] The radiological response is a useful surrogate endpoint for glioma therapy in general, because objective results are provided shortly after therapy. From the presented data, it is clear that reduction in enhancement can also be observed after kinase inhibition. The PFS6 suitably predicts OS and therefore is considered a meaningful endpoint for evaluation of progressive glioblastoma. Perhaps the ideal endpoint for assessment of clinical benefit by targeted therapy would be a multidimensional construct of imaging, symptoms, quality, progression, and survival.

A more fundamental question is whether glioblastoma is in fact a kinase-driven cancer. Undoubtedly, oncogenic kinase signaling is involved in glioblastoma, but whether kinases are crucial for the oncogenic signaling network of glioblastoma and are thereby amenable to therapeutic inhibition, remains to be determined. Kinase drug targets that have changed clinical practice in the treatment of solid cancers are dysregulated in 1 of 3 ways: by mutation, gene overexpression, or protein fusion.[49] All three relevant mechanisms of kinase dysregulation have been identified in glioblastoma, for example, mutation of PIK3CA lipid kinase,[50] overexpression of the AURKA gene,[51] and fusion of FIG to ROS kinase.[52] Details on kinase involvement in glioblastoma can be found in dedicated reviews.[9,10,14,53,54] The protein kinase gene family consists of 518 members.[55] The status of the vast majority of these kinases remains to be determined in glioblastoma, and it is unclear which kinases are best for targeting with small molecule inhibitors. Therefore, it may prove worthwhile to evaluate kinase targets other than those currently utilized for small molecule inhibition in glioblastoma.[56]

Another fundamental question, if glioblastoma turns out to be kinase driven, is which strategy is best for kinase inhibition. For example, one of the more favorable responses in the clinical studies reviewed here has been observed using the FLT1/KDR inhibitor cediranib.[17] A strategy alternative for inhibition of kinase signaling other than using a small-molecule inhibitor is binding of the ligand of receptor tyrosine kinases with monoclonal antibodies. This strategy has recently been shown to hold promise as a cancer therapy for glioblastoma.[57–59]

In conclusion, this review of published clinical studies demonstrates small-molecule kinase inhibitors for adult patients with glioblastoma to be not effective enough yet to warrant a change in clinical practice, whereas the evaluated drug targets have been generally limited to EGFR, mTOR, KDR, FLT1, PKCβ, and PDGFR.

Acknowledgments

We would like to thank Prof. Dr W.P. Vandertop and Prof. Dr C.J. Van Noorden, University of Amsterdam, for their constructive discussion of an early version of the manuscript.

Conflict of interest statement. None declared.

Funding

The support from an Accelerate Brain Cancer Cure award and a grant from the Dutch Cancer Society are greatly appreciated.

References

1. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006;355:2733–2743.
2. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007;356:115–124.
3. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359:378–390.
4. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007;356:125–134.
5. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med.* 2001;344:1038–1042.
6. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med.* 2002;347:472–480.
7. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009;10:459–466.
8. Chang SM, Lamborn KR, Kuhn JG, et al. Neurooncology clinical trial design for targeted therapies: lessons learned from the North American Brain Tumor Consortium. *Neuro-Oncology.* 2008;10:631–642.
9. Chi AS, Wen PY. Inhibiting kinases in malignant gliomas. *Expert Opin Ther Targets.* 2007;11:473–496.
10. De Groot JF, Gilbert MR. New molecular targets in malignant gliomas. *Curr Opin Neurol.* 2007;20:712–718.
11. Omuro AM. Exploring multi-targeting strategies for the treatment of gliomas. *Curr Opin Investig Drugs.* 2008;9:1287–1295.
12. Omuro AM, Faivre S, Raymond E. Lessons learned in the development of targeted therapy for malignant gliomas. *Mol Cancer Ther.* 2007;6:1909–1919.
13. Reardon DA, Wen PY. Therapeutic advances in the treatment of glioblastoma: rationale and potential role of targeted agents. *Oncologist.* 2006;11:152–164.
14. Sathornsumetee S, Reardon DA, Desjardins A, Quinn JA, Vredenburgh JJ, Rich JN. Molecularly targeted therapy for malignant glioma. *Cancer.* 2007;110:13–24.
15. Wong ML, Kaye AH, Hovens CM. Targeting malignant glioma survival signalling to improve clinical outcomes. *J Clin Neurosci.* 2007;14:301–308.
16. Sathornsumetee S, Vredenburgh JJ, Rich JN, et al. Phase II study of bevacizumab and erlotinib in patients with recurrent glioblastoma multiforme. *J Clin Oncol.* 2008;26(suppl):abstract 13008.
17. Batchelor TT, Sorensen AG, di Tomaso E, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell.* 2007;11:83–95.
18. Vogelbaum MA, Peereboom D, Stevens G, Barnett G, Brewer C. Phase II trial of the EGFR tyrosine kinase inhibitor erlotinib for single agent therapy of recurrent glioblastoma multiforme: interim results. *J Clin Oncol.* 2004;22(suppl):abstract 1558.

19. Phuphanich S, Rudnick J, Chu R, Yu JS, Black KL. A phase I trial of gefitinib and sirolimus in adults with recurrent glioblastoma multiforme (GBM). *J Clin Oncol.* 2008;26(suppl):abstract 2088.
20. Marosi C, Vedadinejad M, Haberler C, et al. Imatinib mesylate in the treatment of patients with recurrent high grade gliomas expressing PDGF-R. *J Clin Oncol.* 2006;24(suppl):abstract 1526.
21. Viola FS, Katz A, Arantes A, et al. Phase II trial of high dose imatinib in recurrent glioblastoma multiforme (GBM) with platelet derived growth factor receptor (PDGFR) expression. *J Clin Oncol.* 2007;25(suppl):abstract 2056.
22. Reardon DA, Egorin MJ, Quinn JA, et al. Phase II study of imatinib mesylate plus hydroxyurea in adults with recurrent glioblastoma multiforme. *J Clin Oncol.* 2005;23:9359–9368.
23. Doherty L, Gigas DC, Kesari S, et al. Pilot study of the combination of EGFR and mTOR inhibitors in recurrent malignant gliomas. *Neurology.* 2006;67:156–158.
24. Reardon DA, Quinn JA, Vredenburgh JJ, et al. Phase 1 trial of gefitinib plus sirolimus in adults with recurrent malignant glioma. *Clin Cancer Res.* 2006;12:860–868.
25. Schwer AL, Kavanagh BD, McCammon R, et al. Radiographic and histopathologic observations after combined EGFR inhibition and hypofractionated stereotactic radiosurgery in patients with recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys.* 2009;73:1352–1357.
26. Chang S, Kuhn J, Wen P, et al. Phase II/pharmacokinetic study of CCI-779 in recurrent glioblastoma multiforme (GM). *Neuro-Oncology.* 2003;5:abstract TA-09.
27. Galanis E, Buckner JC, Maurer MJ, et al. Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group Study. *J Clin Oncol.* 2005;23:5294–5304.
28. Conrad C, Friedman H, Reardon DA, et al. A phase I/II trial of single-agent PTK 787/ZK 222584 (PTK/ZK), a novel, oral angiogenesis inhibitor, in patients with recurrent glioblastoma multiforme (GBM). *J Clin Oncol.* 2004;22(suppl):abstract 1512.
29. Dresemann G. Imatinib and hydroxyurea in pretreated progressive glioblastoma multiforme: a patient series. *Ann Oncol.* 2005;16:1702–1708.
30. Kirkpatrick JP, Rich JN, Vredenburgh JJ, et al. Final report: phase I trial of imatinib mesylate, hydroxyurea, and vatalanib for patients with recurrent malignant glioma (MG). *J Clin Oncol.* 2008;26(suppl):abstract 2057.
31. Rich JN, Reardon DA, Peery T, et al. Phase II trial of gefitinib in recurrent glioblastoma. *J Clin Oncol.* 2004;22:133–142.
32. Prados MD, Chang SM, Butowski N, et al. Phase II study of erlotinib plus temozolomide during and after radiation therapy in patients with newly diagnosed glioblastoma multiforme or gliosarcoma. *J Clin Oncol.* 2009;27:579–584.
33. Brewer C, Suh JH, Stevens GH, et al. Phase II trial of erlotinib with temozolomide and concurrent radiation therapy in patients with newly diagnosed glioblastoma multiforme. *J Clin Oncol.* 2005;23(suppl):abstract 1567.
34. Fine HA, Puduvalli VK, Chamberlain MC, et al. Enzastaurin (ENZ) versus lomustine (CCNU) in the treatment of recurrent, intracranial glioblastoma multiforme (GBM): a phase III study. *J Clin Oncol.* 2005;26(suppl):abstract 2005.
35. Dresemann G, Hosius C, Nikolova Z. Imatinib plus hydroxyurea as maintenance treatment in pre-treated non-progressive glioblastoma—a single-center phase II study. *Neuro-Oncology.* 2008;10:abstract MA-24.
36. Kreisl TN, Lassman AB, Mischel PS, et al. A pilot study of everolimus and gefitinib in the treatment of recurrent glioblastoma (GBM). *J Neurooncol.* 2009;92:99–105.
37. De Groot JF, Gilbert M, Hess K, et al. Phase II study of combination carboplatin and erlotinib in patients with recurrent glioblastoma multiforme. *J Clin Oncol.* 2007;25(suppl):abstract 2024.
38. Peereboom D, Brewer C, Suh JH, et al. Phase II trial of erlotinib with temozolomide and concurrent radiation therapy in patients with newly diagnosed glioblastoma multiforme: final results. *Neuro-Oncology.* 2006;8:abstract TA-41.
39. Cloughesy TF, Yoshimoto K, Nghiemphu P, et al. Antitumor activity of rapamycin in a phase I trial for patients with recurrent PTEN-deficient glioblastoma. *PLoS Med.* 2008;5:e8.
40. Wen P, Yung WK, Hess K, et al. Phase I study of STI571 for patients with recurrent malignant gliomas and meningiomas. *Neuro-Oncology.* 2001;3:abstract 407.
41. Shah GD, Silver JS, Rosenfeld SS, Gavrilovic IT, Abrey LE, Lassman AB. Myelosuppression in patients benefiting from imatinib with hydroxyurea for recurrent malignant gliomas. *J Neurooncol.* 2007;85:217–222.
42. Franceschi E, Cavallo G, Lonardi S, et al. Gefitinib in patients with progressive high-grade gliomas: a multicentre phase II study by Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). *Br J Cancer.* 2007;96:1047–1051.
43. Haas-Kogan DA, Prados MD, Tihan T, et al. Epidermal growth factor receptor, protein kinase B/Akt, and glioma response to erlotinib. *J Natl Cancer Inst.* 2005;97:880–887.
44. Preusser M, Gelpi E, Rottenfusser A, et al. Epithelial growth factor receptor inhibitors for treatment of recurrent or progressive high grade glioma: an exploratory study. *J Neurooncol.* 2008;89:211–218.
45. Van den Bent MJ, Brandes AA, Rampling R, et al. Randomized phase II trial of erlotinib (E) versus temozolomide (TMZ) or BCNU in recurrent glioblastoma multiforme (GBM): EORTC 26034. *Neuro-Oncology.* 2007;9:abstract MA-27.
46. Mellinghoff IK, Wang MY, Vivanco I, et al. Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. *N Engl J Med.* 2005;353:2012–2024.
47. Mauer ME, Bottomley A, Taphoorn MJ. Evaluating health-related quality of life and symptom burden in brain tumour patients: instruments for use in experimental trials and clinical practice. *Curr Opin Neurol.* 2008;21:745–753.
48. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol.* 2004;3:159–168.
49. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. *N Engl J Med.* 2005;353:172–187.
50. Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. *Science.* 2004;304:554.
51. Klein A, Reichardt W, Jung V, Zang KD, Meese E, Urbschat S. Overexpression and amplification of STK15 in human gliomas. *Int J Oncol.* 2004;25:1789–1794.
52. Charest A, Lane K, McMahon K, et al. Fusion of FIG to the receptor tyrosine kinase ROS in a glioblastoma with an interstitial del(6)(q21q21). *Genes Chromosomes Cancer.* 2003;37:58–71.
53. Newton HB. Molecular neuro-oncology and development of targeted therapeutic strategies for brain tumors. Part 1: growth factor and Ras signaling pathways. *Expert Rev Anticancer Ther.* 2003;3:595–614.
54. Newton HB. Molecular neuro-oncology and development of targeted therapeutic strategies for brain tumors. Part 2: PI3K/Akt/PTEN, mTOR, SHH/PTCH and angiogenesis. *Expert Rev Anticancer Ther.* 2004;4:105–128.

55. Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. *Science.* 2002;298:1912–1934.
56. Vieth M, Sutherland JJ, Robertson DH, Campbell RM. Kinomics: characterizing the therapeutically validated kinase space. *Drug Discov Today.* 2005;10:839–846.
57. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol.* 2009;27:740–745.
58. Sathornsumetee S, Cao Y, Marcello JE, et al. Tumor angiogenic and hypoxic profiles predict radiographic response and survival in malignant astrocytoma patients treated with bevacizumab and irinotecan. *J Clin Oncol.* 2008;26:271–278.
59. Vredenburgh JJ, Desjardins A, Herndon JE, 2nd, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol.* 2007;25:4722–4729.
60. Athanassiou H, Synodinou M, Maragoudakis E, et al. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. *J Clin Oncol.* 2005;23:2372–2377.
61. Brada M, Hoang-Xuan K, Rampling R, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. *Ann Oncol.* 2001;12:259–266.
62. Yung WK, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer.* 2000;83:588–593.
63. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol.* 1999;17:2572–2578.
64. Van den Bent MJ, Brandes AA, Rampling R, et al. Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC Brain Tumor Group Study 26034. *J Clin Oncol.* 2009;27:1268–1274.
65. Van den Bent MJ, Brandes AA, Rampling R, et al. Randomized phase II trial of erlotinib (E) versus temozolomide (TMZ) or BCNU in recurrent glioblastoma multiforme (GBM): EORTC 26034. *J Clin Oncol.* 2007;25(suppl):abstract 2005.
66. Buie LW, Lindley C, Shih T, et al. Plasma pharmacokinetics and cerebrospinal fluid concentrations of erlotinib in high-grade gliomas: a novel, phase I, dose escalation study. *J Clin Oncol.* 2007;25(suppl):abstract 2054.
67. Cloughesy T, Yung WK, Vredenburgh JJ, et al. Phase II study of erlotinib in recurrent GBM: molecular predictors of outcome. *J Clin Oncol.* 2005;23(suppl):abstract 1507.
68. Yung WK, Vredenburgh JJ, Cloughesy T, et al. Erlotinib HCl for glioblastoma multiforme in first relapse, a phase II trial. *J Clin Oncol.* 2004;22(suppl):abstract 1555.
69. Rich JN, Peery T, Reardon DA, et al. Phase I/II trial of the epidermal growth factor receptor small molecule inhibitor ZD1839 (gefitinib) in patients with first relapse glioblastoma. *Neuro-Oncology.* 2003;5:abstract TA-34.
70. Uhm JH, Ballman K, Giannini C, et al. Phase II study of ZD1839 in patients with newly diagnosed grade 4 astrocytoma. *J Clin Oncol.* 2004;22(suppl):abstract 1505.
71. Raizer J, Abrey LE, Wen P, et al. A phase II trial of erlotinib (OSI-774) in patients (pts) with recurrent malignant gliomas (MG) not on EIAEDs. *J Clin Oncol.* 2004;22(suppl):abstract 1502.
72. Lieberman FS, Cloughesy T, Fine HA, et al. NABTC phase I/II trial of ZD-1839 for recurrent malignant gliomas and unresectable meningiomas. *J Clin Oncol.* 2004;22(suppl):abstract 1510.
73. Vogelbaum MA, Peereboom D, Stevens G, Barnett G, Brewer C. Response rate to single agent therapy with the EGFR tyrosine kinase inhibitor erlotinib in recurrent glioblastoma multiforme: results of a phase II study. *Neuro-Oncology.* 2004;6:abstract TA-59.
74. Vogelbaum MA, Peereboom D, Stevens G, Barnett G, Sakala P, Brewer C. Initial experience with the EGFR tyrosine kinase inhibitor Tarceva (OSI-774) for single-agent therapy of recurrent/progressive glioblastoma multiforme. *Neuro-Oncology.* 2003;5:abstract TA-37.
75. Peery T, Reardon DA, Quinn JA, et al. Phase II trial of ZD1839 for patients with first relapse glioblastoma. *Proc Am Soc Clin Oncol.* 2003;22:abstract 396.
76. Chang SM, Wen P, Cloughesy T, et al. Phase II study of CCI-779 in patients with recurrent glioblastoma multiforme. *Invest New Drugs.* 2005;23:357–361.
77. Chang SM, Kuhn J, Wen P, et al. Phase I/pharmacokinetic study of CCI-779 in patients with recurrent malignant glioma on enzyme-inducing antiepileptic drugs. *Invest New Drugs.* 2004;22:427–435.
78. Reardon DA, Friedman H, Yung WK, et al. Preliminary phase I trial results: PTK787/ZK 222584 (PTK/ZK), an oral VEGF tyrosine kinase inhibitor, in combination with either temozolomide or lomustine for patients with recurrent glioblastoma multiforme (GBM). *Neuro-Oncology.* 2003;5:abstract TA-33.
79. Yung WK, Friedman H, Conrad C, et al. A phase I trial of single-agent PTK 787/ZK 222584 (PTK/ZK), an oral VEGFR tyrosine kinase inhibitor, in patients with recurrent glioblastoma multiforme. *Proc Am Soc Clin Oncol.* 2003;22:abstract 395.
80. Yung WK, Friedman HS, Jackson E, et al. A phase I trial of PTK787/ZK 222584 (PTK/ZK), a novel oral VEGF-R TK inhibitor in patients with recurrent GBM. *Neuro-Oncology.* 2001;3:abstract 409.
81. Kreisl TN, Kim L, Moore K, et al. A phase I trial of enzastaurin in patients with recurrent gliomas. *Clin Cancer Res.* 2009;15:3617–3623.
82. Puduvalli VK, Wick W, Chamberlain MC, et al. Enzastaurin versus lomustine in the treatment of recurrent, intracranial glioblastoma: a phase III study. *Neuro-Oncology.* 2008;10:abstract MA-35.
83. Thornton D, Graff J. Enzastaurin: an introduction to a new, targeted agent for the treatment of glioblastoma multiforme. *Neuro-Oncology.* 2006;8:abstract P142.
84. Wick W, Puduvalli VK, Chamberlain MC, et al. Enzastaurin (ENZ) versus lomustine (CCNU) in the treatment of recurrent, intracranial glioblastoma (GBM): a phase III study. *Neuro-Oncology.* 2008;10:abstract O22.
85. Fine HA, Kim L, Royce C, et al. Results from phase II trial of enzastaurin (LY317615) in patients with recurrent high grade gliomas. *J Clin Oncol.* 2005;23(suppl):abstract 1504.
86. Fine HA, Kim L, Royce C, et al. A phase II trial of LY317615 in patients with recurrent high grade gliomas. *J Clin Oncol.* 2004;22(suppl):abstract 1511.
87. Raymond E, Brandes AA, Dittrich C, et al. Phase II study of imatinib in patients with recurrent gliomas of various histologies: a European Organisation for Research and Treatment of Cancer Brain Tumor Group Study. *J Clin Oncol.* 2008;26:4659–4665.
88. Raymond E, Brandes AA, Van Oosterom A, et al. Multicentre phase II study of imatinib mesylate in patients with recurrent glioblastoma: an EORTC: NDDG/BTG Intergroup Study. *J Clin Oncol.* 2004;22(suppl):abstract 1501.
89. Van den Bent MJ, Brandes AA, Van Oosterom A, et al. Multicentre phase II study of imatinib mesylate (Gleevec) in patients with recurrent glioblastoma: an EORTC NDDG/BTG Intergroup Study. *Neuro-Oncology.* 2004;6:abtrsact TA-57.

90. Razis E, Selviaridis P, Fletcher JA, et al. Biochemical evidence of tumor response and measurable levels of the drug in glioblastoma tissue from patients treated with imatinib. *J Clin Oncol.* 2007;25(suppl): abstract 2023.
91. Wen P, Yung WK, Lamborn KR, et al. Phase I/II study of imatinib mesylate (STI571) for patients with recurrent malignant gliomas (NABTC 99-08). *Neuro-Oncology.* 2004;6:abstract TA-63.
92. Wen PY, Yung WK, Lamborn KR, et al. Phase I/II study of imatinib mesylate for recurrent malignant gliomas: North American Brain Tumor Consortium Study 99-08. *Clin Cancer Res.* 2006;12:4899–4907.
93. Franceschi E, Lonardi S, Tosoni A, et al. ZD1839 (Iressa) treatment for adult patients with progressive high-grade gliomas (HGG): an open label, single-arm, phase II study of the Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). *J Clin Oncol.* 2005;23(suppl):abstract 1564.
94. Chaskis C, Sadones J, Michotte A, Dujardin M, Everaert H, Neyns B. A phase II trial of sunitinib in patients with recurrent high-grade glioma. *J Clin Oncol.* 2008;26(suppl):abstract 13001.
95. Kreisl TN, Butman JA, Albert PS, Kim L, Moore K, Fine HA. A phase II trial of vandetanib for patients with recurrent glioblastoma multiforme. *Neuro-Oncology.* 2008;10:abstract MA-40.
96. Reardon DA, Desjardins A, Vredenburgh JJ, et al. A phase II trial of sorafenib (Nexavar) and protracted temozolomide for patients with recurrent glioblastoma. *Neuro-Oncology.* 2008;10:abstract MA-82.
97. Friedman HS, Desjardins A, Vredenburgh JJ, et al. Phase II trial of erlotinib plus sirolimus for recurrent glioblastoma multiforme (GBM). *J Clin Oncol.* 2008;26(suppl):abstract 2062.
98. Badruddoja MA, Das RM, Gabyan E, et al. Gefitinib and rapamycin for adult patients with recurrent glioblastoma multiforme. *Neuro-Oncology.* 2006;8:abstract TA-02.
99. Nguyen TD, Lassman AB, Lis E, et al. A pilot study to assess the tolerability and efficacy of RAD-001 (everolimus) with gefitinib in patients with recurrent glioblastoma multiforme (GBM). *Neuro-Oncology.* 2006;8:abstract TA-39.
100. Prados M, DeBoer R, Chang S, et al. Phase II study of Tarceva plus Temodar during and following radiotherapy in patients newly diagnosed with glioblastoma or gliosarcoma. *Neuro-Oncology.* 2007;9:abstract MA-50.
101. Brown PD, Krishnan S, Sarkaria J, et al. A phase II trial (N0177) of erlotinib and temozolomide (TMZ) combined with radiation therapy (RT) in glioblastoma multiforme (GBM). *J Clin Oncol.* 2008;26(suppl):abstract 2016.
102. De Groot JF, Gilbert MR, Aldape K, et al. Phase II study of carboplatin and erlotinib (Tarceva, OSI-774) in patients with recurrent glioblastoma. *J Neurooncol.* 2008;90:89–97.
103. Chakravarti A, Berkey B, Robins HI, et al. An update of phase II results from RTOG 0211: a phase I /II study of gefitinib with radiotherapy in newly diagnosed glioblastoma multiforme. *Neuro-Oncology.* 2006;8:abstract TA-08.
104. Chakravarti A, Berkey B, Robins HI, et al. An update of phase II results from RTOG 0211: a phase I/II study of gefitinib with radiotherapy in newly diagnosed glioblastoma. *J Clin Oncol.* 2006;24(suppl):abstract 1527.
105. Chakravarti A, Seiferheld W, Robbins HI, et al. An update of phase I data from RTOG 0211: a phase I/II clinical study of gefitinib + radiation for newly-diagnosed glioblastoma (GBM) patients. *J Clin Oncol.* 2004;22(suppl):abstract 1571.
106. Chakravarti A, Seiferheld W, Robins HI, et al. An update of phase I data from RTOG 0211: a phase I/II clinical study of ZD 1839 (gefitinib) + radiation for newly diagnosed glioblastoma (GBM) patients. *Neuro-Oncology.* 2004;6:abstract TA-12.
107. Prados M, Chang S, Burton E, et al. Phase I study of OSI-774 alone or with temozolomide in patients with malignant glioma. *Proc Am Soc Clin Oncol.* 2003;22:abstract 394.
108. Prados MD, Lamborn KR, Chang S, et al. Phase 1 study of erlotinib HCl alone and combined with temozolomide in patients with stable or recurrent malignant glioma. *Neuro-Oncology.* 2006;8:67–78.
109. Krishnan S, Brown PD, Ballman KV, et al. Phase I trial of erlotinib with radiation therapy in patients with glioblastoma multiforme: results of North Central Cancer Treatment Group protocol N0177. *Int J Radiat Oncol Biol Phys.* 2006;65:1192–1199.
110. Peereboom D, Brewer C, Stevens G, et al. Phase II trial of erlotinib with temozolomide and concurrent radiation therapy post-operatively in patients with newly diagnosed glioblastoma multiforme. *Neuro-Oncology.* 2004;6:abstract TA-41.
111. Dresemann G, Rosenthal M, Hoffken K, et al. Imatinib plus hydroxyurea versus hydroxyurea monotherapy in progressive glioblastoma (GBM)-an international open label randomised phase III study (AMBROSIA-study). *Neuro-Oncology.* 2007;9:abstract MA-17.
112. Dresemann G, Weller M, Bogdahn U, et al. Imatinib plus hydroxyurea versus hydroxyurea monotherapy in progressive glioblastoma-an international multicenter, open-label, randomized phase III study (AMBROSIA-study). *Neuro-Oncology.* 2008;10:abstract MA-19.
113. Dresemann G, Hosius C, Nikolova Z, Letvak L. Single center phase II trial analysing the role of imatinib/hydroxyurea in patients (pts) with pretreated non-progressive glioblastoma (GBM) as maintenance treatment. *J Clin Oncol.* 2007;25(suppl):abstract 2055.
114. Friedman HS, Quinn JA, Rich JN, et al. Imatinib mesylate (Gleevec) plus hydroxyurea is an effective regimen in the treatment of recurrent malignant glioma. Phase 2 study results. *J Clin Oncol.* 2005;23(suppl): abstract 1515.
115. Reardon DA, Friedman AH, Herndon JE, 2nd, et al. Phase II trial of imatinib mesylate plus hydroxyurea in the treatment of patients with malignant glioma. *Neuro-Oncology.* 2004;6:abstract TA-47.
116. Reardon DA, Quinn JA, Rich JN, et al. Imatinib mesylate (Gleevec) plus hydroxyurea: an effective regimen in the treatment of recurrent malignant glioma: phase 2 study results. *Neuro-Oncology.* 2005;7:abstract 35.
117. Sathornsumetee S, Desjardins A, Vredenburgh JJ, et al. Safety and efficacy of bevacizumab and erlotinib for recurrent glioblastoma patients in a phase II study. *Neuro-Oncology.* 2008;10:abstract MA-41.
118. Sathornsumetee S, Vredenburgh JJ, Rich JN, et al. Phase II trial of bevacizumab and erlotinib in recurrent glioblastoma multiforme (GBM). *Neuro-Oncology.* 2007;9:abstract MA-06.
119. Reardon DA, Desjardins A, Vredenburgh JJ, et al. A phase I trial of dasatinib (Sprycel) and erlotinib (Tarceva) for patients with recurrent malignant glioma. *Neuro-Oncology.* 2008;10:abstract MA-85.
120. Wuthrick E, Curran W, Lin A, et al. A phase I trial of hypofractionated stereotactic radiation therapy with sunitinib in recurrent high-grade glioma. *Neuro-Oncology.* 2008;10:abstract RO-14.
121. Sathornsumetee S, Rich JN, Vredenburgh JJ, et al. Phase I trial of imatinib mesylate, hydroxyurea and vatalanib for patients with recurrent glioblastoma multiforme (GBM). *J Clin Oncol.* 2007;25(suppl):abstract 2027.

122. Reardon DA, Groves MD, Wen P, et al. A phase II trial of lapatinib and pazopanib for patients with recurrent glioblastoma multiforme (GBM). *Neuro-Oncology*. 2007;9:abstract MA-07.

123. Sathornsumetee S, Rich JN, Vredenburgh JJ, et al. Phase I trial of temozolomide plus dose-escalating imatinib mesylate for patients with malignant glioma. *Neuro-Oncology*. 2006;8:abstract TA-50.

124. Desjardins A, Quinn JA, Rich JN, et al. A phase I trial of imatinib (Gleevec), hydroxyurea and RAD001 for patients with recurrent malignant glioma. *Neuro-Oncology*. 2006;8:abstract TA-14.

125. Reardon DA, Friedman H, Yung WK, et al. A phase I/II trial of PTK787/ZK 222584 (PTK/ZK), a novel, oral angiogenesis inhibitor, in combination with either temozolomide or lomustine for patients with recurrent glioblastoma multiforme (GBM). *J Clin Oncol*. 2004;22(suppl):abstract 1513.

126. Reardon DA, Friedman HS, Brada M, et al. A phase I/II trial of PTK787/ZK 222584 (PTK/ZK), a multi-vegf receptor tyrosine kinase inhibitor, in combination with either temozolomide or lomustine for patients with recurrent glioblastoma multiforme (GBM). *Neuro-Oncology*. 2004;6:abstract TA-48.