



June Parker. *Late February*. Pastel. From the collection of Mr. and Mrs. George Blanco, N. Egremont, Mass.

*Several new drugs are being investigated, many that interfere with oncogenic and tumor survival pathways, to downregulate growth and invasion of malignant gliomas.*

# Advances in Molecular Therapies in Patients With Brain Tumors

*Ivo W. Tremont-Lukats, MD, and Mark R. Gilbert, MD*

**Background:** We are witnessing the development of new treatment modalities for primary brain tumors. An area under intense investigation is the use of small molecules targeting intracellular signaling pathways that interfere with growth, invasion, and metastasis of high-grade gliomas.

**Methods:** We review clinical trials of small molecules in adults with brain tumors. This search included electronic databases, specialty journals, textbooks, proceedings, and Web sites of the National Cancer Institute and other cooperative brain tumor groups in Europe and the United States.

**Results:** Several drugs with the ability to down-regulate the growth and invasion of malignant gliomas are at various stages of testing. Most of these focus on interfering with oncogenic and tumor survival pathways. Examples include inhibitors of tyrosine kinases, farnesyltransferases, and matrix metalloproteinases. These molecules are at different stages of testing, and a conclusive picture of which drug is most effective, either alone or in combination, needs better definition. The metalloproteinase inhibitor marimastat with temozolomide has given the best results to date in phase II trials, increasing the rate of 6-month progression-free survival for recurrent glioblastoma multiforme and anaplastic gliomas.

**Conclusions:** As our understanding of the biology of gliomas increases and new drugs targeting specific molecular pathways enter well-designed cooperative trials, the control and prognosis of these tumors should improve.

## Introduction

The treatment of cancer is evolving, propelled by advances in the molecular biology of tumors and the unraveling of the cellular machinery that accounts for the malignant phenotype. The search continues for new therapies to target specific steps in the pathogenesis of high-grade gliomas. Investigators are concentrating efforts on this area of brain tumor research because treatment with conventional cytotoxic agents has shown little progress.<sup>1</sup>

*From the Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas. Submitted November 5, 2002; accepted December 26, 2002.*

*Address reprint requests to Mark R. Gilbert, MD, Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 431, Houston, TX 77030. E-mail: mrgilbert@mdanderson.org*

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The molecular pharmacotherapeutic approaches to brain tumors can be broadly divided into gene therapy, antisense oligonucleotides, immunotherapy, and small molecules with inhibitory activity on tyrosine kinases, farnesyltransferase, and matrix metalloproteinases. In this article we do not address gene therapy, antisense oligonucleotides, or immunotherapy since each of these topics warrants separate reviews. We focus on agents designed to interfere with intracellular signal transduction by inhibiting one or several steps in the cell cycle, blocking angiogenic signals, or interfering with the ability of glioma cells to invade and spread.

This article reviews the status of interventions using agents that modify the intracellular transduction pathways in glioma cells.

## Gliomagenesis: A Primer

Abnormalities in receptor tyrosine kinase pathways and loss of tumor suppressor genes are critical in the transformation and growth of malignant gliomas. Several papers have reviewed in detail the molecular pathogenesis of gliomas.<sup>2,4</sup> We present a summary of this knowledge as a framework to understand the mechanism of action of targeted therapies. Although still incompletely understood, astrocytes undergo trans-

formation with the loss of tumor suppressor genes critical for cell growth, differentiation, and function. These genes are TP53, the retinoblastoma (Rb) gene, the INK4a (inhibitor of cyclin-dependent kinase 4) gene, and the PTEN gene. In low-grade astrocytomas, TP53 is inactive by mutation or gene deletion. The progression into anaplastic astrocytoma and glioblastoma multiforme (here, *secondary* GBM) is accompanied by Rb and PTEN mutations with cell aneuploidy and overexpression of cyclin-dependent kinase 4. Generally, secondary GBMs predominate in younger patients and represent 40% of all glioblastomas.

In de novo GBMs (*primary* GBM), the sequence of genetic changes is different with a final, identical phenotype (Fig 1). Primary GBMs tend to show amplification of the epidermal growth factor receptor (EGFR), deletions in the INK4a gene with loss of p14 and p16, and diploid cells. The protein encoded by the Rb gene (pRb) regulates the cell cycle by inhibiting progression beyond the G<sub>1</sub>/S restriction point. Mitogenic signals activate a molecular cascade known as Ras-mitogen activated protein kinase (Ras/MAPK). MAPK inhibits pRb and activates the transcriptional factor E2F and cells enter the S phase. The INK4a gene converges on the Rb pathway by activating three cyclin kinase inhibitors: p15, p16, and p19. They inhibit a family of kinases known as cyclin-dependent kinases 2, 4, and 6, triggering cell-cycle progression by inhibiting pRb. Thus, the Rb pathway plays a major role in the phenotype of anaplastic astrocytoma and GBM.

Similar cascades exist for other signal transduction molecules. Many factors such as the epidermal growth factor (EGF) and the vascular endothelial growth factor (VEGF) bind to specific tyrosine kinase receptors with downstream effects resulting in typical final tumor behavior or proliferation, invasion, and angiogenesis. The enhancement in signal transduction pathways can result from overexpression of growth factors, their receptors, or mutations in downstream signaling proteins leading to constitutive activation or inactivation of negative regulators of the pathway. Examples of each type of abnormality that contributes to malignant phenotype are found in glial tumors. Overexpression in the EGFR is common in GBM (up to 70% of specimens) and is a hallmark of primary glioblastomas.<sup>4</sup>

The loss of heterozygosity in chromosome 10q causes inactivation of PTEN, a gene downstream of focal adhesion kinase (Fak), which controls cell migration and invasiveness. This effect is mediated by activating Akt, a serine/threonine (ser/thr) kinase involved in cell proliferation and survival.<sup>4,5</sup> Although primary mutations in Ras are less common or absent in glial tumors compared with other cancers, there is

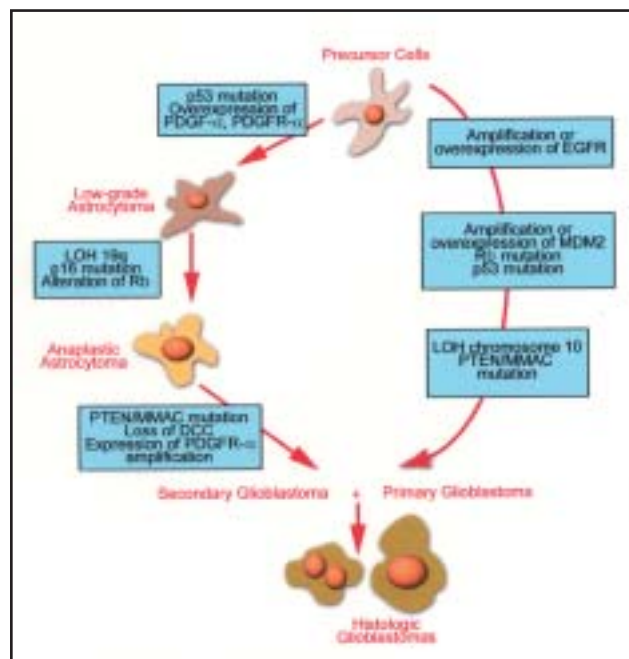


Fig 1. — Genetic pathways leading to primary and secondary gliomas. Arrows indicate increase, upregulation, and overexpression or amplification (EGFR = epidermal growth factor receptor, PTEN = phosphatase tensin homology gene on chromosome 10, PDGF = platelet-derived growth factor, FGF2 = fibroblast growth factor 2, Rb = retinoblastoma gene, CDK4 = cyclin-dependent kinase 4, GBM = glioblastoma multiforme). MMAC = mutated in multiple advanced cancers, DCC = deleted in colorectal carcinoma, LOH = loss of heterozygosity).

overexpression or constitutive activation of other receptor tyrosine kinases as well as autocrine loop that in turn activate Ras, spawning interest in the modulation of Ras signal transduction cascade as a therapeutic approach.<sup>6,7</sup>

Agents are available that selectively block steps in the Ras/MAPK/CDK/Rb cascade and that act on the PI3K/Akt pathway (Fig 2). In theory, every step could be inhibited, but in reality, the development of tyrosine kinase inhibitors has been most successful.<sup>8</sup> Albeit a rapidly evolving field, this review summarizes the status of targeted therapies.

## EGFR Tyrosine Kinase Inhibitors

### STI571

**Drug Overview<sup>9-12</sup>:** STI571 (imatinib mesylate, Gleevec) is an oral phenylaminopyrimidine with inhibitory activity against the platelet-derived growth factor receptor (PDGFR), c-kit, and the abl receptor tyrosine kinases. STI571 inhibited the growth of U343 and U87 GBM (which contains a PDGF/PDGFR autocrine loop) cell lines in vitro and when implanted into the brains of nude mice.<sup>13</sup> Absorption after an oral dose is good, with a half-life of 13 to 16 hours. The drug is given as 400 mg orally once a day and is metabolized

in the liver by CYP3A4 enzymes. Although well tolerated, even with prolonged dosing in patients with chronic myelogenous leukemia, STI571 can cause thrombocytopenia, neutropenia, nausea, myalgias, edema, diarrhea, fatigue, skin rash, and arthralgias.

**Clinical Trials:** The North American Brain Tumor Consortium (NABTC) is testing STI571 in a phase III trial (NABTC 99-08) in patients with recurrent malignant gliomas.<sup>14</sup> The objectives of this trial are to find the maximum tolerated dose (MTD) in patients with malignant gliomas with or without enzyme-inducing antiepileptic drugs (EIAEDs), to define its safety profile, and to determine efficacy as measured by response rates and 6-month progression-free survival (PFS). The European Organization for the Research and Treatment of Cancer (EORTC) Brain Tumor Group has two ongoing studies, EORTC-16011 and EORTC-26013,<sup>15</sup> in which STI571 is given to patients with low- and high-grade gliomas in relapse after radiation therapy or chemotherapy. The objectives are similar to those of NABTC 99-08 and include a pharmacokinetic analysis. Patients are stratified according to histology, receiving oral STI571 once or twice daily. One cycle is defined as 4 weeks, and treatment continues for up to 9 courses in the absence of disease progression or unacceptable toxicity.

### ZD1839

**Drug Overview<sup>16-29</sup>:** ZD1839 (Iressa) is an anilinoquinazoline with a selective inhibitory action on the EGFR tyrosine kinase activity. Pharmacodynamic studies in patients with cancer showed that ZD1839 suppressed EGFR tyrosine phosphorylation in all EGFR-expressing cells and inhibited MAPK activation and cell proliferation. Moreover, ZD1839 increased apoptosis and the expression of the cyclin kinase inhibitor p27.<sup>30</sup> Activation of the pro-apoptotic protein Bad may trigger the apoptosis program in cells exposed to ZD1839.<sup>31</sup>

ZD1839 is an oral drug with 50% bioavailability. A recent report demonstrated peak plasma drug concentrations ( $C_{max}$ ) occurred between 3 and 7 hours after administration.<sup>18</sup>  $C_{max}$  and the area under the concentration-time curve (AUC) were dose-proportional from 10 to 100 mg, with a half-life of 28 hours (range 12 to 51 hours). Food reduces drug absorption, as  $C_{max}$  is 34% lower. The drug is most likely metabolized in the liver since urinary recovery of ZD1839 was <0.5%.<sup>18</sup> This tyrosine kinase inhibitor is given in doses ranging from 50 to 700 mg once a day either intermittently (14 of 28 days) or continuously. In another phase I trial, the MTD was 800 mg per day.<sup>32</sup> Diarrhea, elevation of liver enzymes, acneiform rash (in more than 50% of treated patients), and nausea/vomiting were the most common

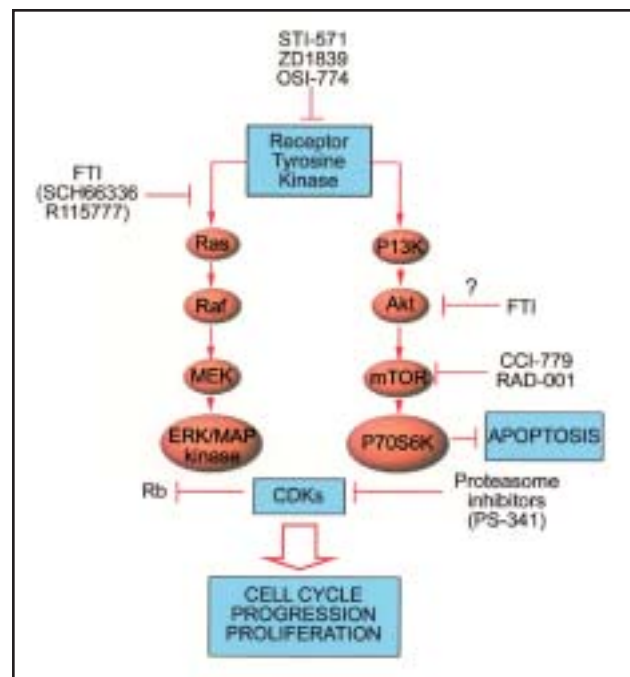


Fig 2. — Tyrosine receptor kinase-mediated cell signaling pathways and therapeutic targets of small inhibitory molecules in clinical trials against gliomas. Arrows indicate stimulation, and T lines indicate suppression or inhibition (ERK = extracellular-related kinase, mTOR = mammalian target of rapamycin, PI3K = phosphatidylinositol-3-OH-kinase, p70/S6 kinase, FTI = farnesyl transferase inhibitor).

toxicities. Preliminary data in vitro and in vivo reveal synergism between ZD1839 and radiation treatment, cisplatin, carboplatin, paclitaxel, and docetaxel, even in EGFR-negative tumors, raising the possibility of molecular targets other than EGFR.<sup>27-29</sup>

**Clinical Trials:** Since overexpression of EGFR has been reported in 41% of GBM and is a probable negative prognostic factor in patients under 60 years of age,<sup>33</sup> ZD1839 is currently being investigated against malignant gliomas in four clinical trials. The National Cancer Institute and Duke University conducted a phase II trial (NCI-1253) using ZD1839 as a single agent for GBM at first relapse.<sup>34</sup> The North Central Cancer Treatment Group (NCCTG) has a phase II trial testing radiotherapy (NCCTG-N0074) with ZD1839 for newly diagnosed GBM.<sup>35</sup> The NABTC is testing ZD1839 alone (NABTC 00-01)<sup>36</sup> or combined with temozolomide (NABTC 01-02)<sup>37</sup> for recurrent GBM.

## OSI-774

**Drug Overview**<sup>7,38-41</sup>: OSI-774 (CP-358,774, erlotinib, Tarceva), another inhibitor of EGFR tyrosine kinase active at nanomolar concentrations as an ATP-mimic, blocks the cell cycle at G<sub>1</sub>. Levels of p27 and pRb accumulate, and apoptosis is induced. Combining OSI-774 with cisplatin, doxorubicin, or gemcitabine increases cytotoxicity.<sup>7</sup> At a dose of 150 mg per day orally, the average half-life was 24 ± 16 hours with a volume of distribution of 136 ± 93 L. The median C<sub>max</sub> was 3 hours. The metabolism of OSI-774 is in the liver by the CYP-3A4 enzyme system. Reported side effects include diarrhea, fatigue, headache, mucositis, nausea, a transient elevation of liver enzymes, and an acneiform rash that can be severe. The rash, distributed preferentially in face and trunk, can be present in up to 78% of patients.

**Clinical Trials:** An active phase I trial at the University of California San Francisco (UCSF 01104) is using OSI-774 alone or combined with temozolomide to treat high-grade gliomas with recurrent or stable disease, with or without EIAEDs.<sup>42</sup>

## Phosphoinositide 3-Kinase (Pi3k) Inhibitors

### CCI-779 (Rapamycin Analog Drug)

**Drug Overview**<sup>43-51</sup>: Rapamycin is a macrolide produced by *Streptomyces hygroscopicus*, structurally related to cyclosporine and tacrolimus. Rapamycin and its analog CCI-779 inhibit a kinase known as mTOR (mammalian target of rapamycin), an enzyme activated

through the PI3K/Akt cascade. This blockade leads to cell arrest in G<sub>1</sub>. Rapamycin and its analogs are cytostatic against xenografts of glioblastoma, medulloblastoma, breast cancer, and prostate cancer.<sup>47,52</sup> PTEN-negative tumors seem to be more sensitive to inhibition than PTEN-positive tumors with reduction of proliferation, tumor size, and p70/S6 kinase activity.<sup>53,54</sup> Rapamycin is also a radiosensitizer in xenografts and spheroids with the U87 cell line.<sup>55</sup>

The dosing schedules for CCI-779 include a daily intravenous dose for 5 days every 2 weeks or a single weekly infusion, with a half-life of approximately 17 hours. Phase I trials in other cancers have determined that the MTD for heavily pretreated and minimally pretreated patients is 15 and 19.3 mg/m<sup>2</sup> per day, respectively. The most frequent toxicity symptoms are mucositis, skin rash, neutropenia, and thrombocytopenia.

**Clinical Trials:** NABTC 01-01 is a phase I/II trial using CCI-779 to determine MTD, pharmacokinetics, and tumor activity in patients with recurrent gliomas with or without EIAEDs. The dosing schedule of CCI-779 is a single weekly intravenous infusion starting at 250 mg and escalating to 780 mg.<sup>56</sup> Results for patients on EIAEDs were published in abstract form, reporting the MTD as 250 mg intravenously, with 1 of 6 participants having grade III hypertriglyceridemia.<sup>57</sup> The NCCTG has a phase II trial (N997B) testing CCI-779 in patients with recurrent GBM.<sup>58</sup> CCI-779 is given at 250 mg intravenously over 1 hour once a week until tumor progression or unacceptable toxicity. Four weeks of treatment defines one cycle. Although listed as a phase II trial, this study includes a dose-seeking phase for patients on EIAEDs.

Buckner et al<sup>59</sup> published a phase I dose-calculation study on safety and tolerability of CCI-779 in 22 patients with tumors of the central nervous system on EIAEDs. Eligible patients received CCI-779 as a 30-minute intravenous infusion daily for 5 days every 2 weeks, starting at 15 mg/m<sup>2</sup>. The MTD was not reached, but the highest dose was 37 mg/m<sup>2</sup>, with side effects similar to those reported in other trials using lower doses in patients not taking EIAEDs. More than 50% of patients had stable disease and 38% (8 of 22 patients) received more than 9 courses.

### RAD-001 (Rapamycin Analog Drug)

**Drug Overview**<sup>60-64</sup>: RAD-001 (SDZ-RAD, everolimus) is another drug used after organ transplantation with the same molecular and cellular mode of action as CCI-779. However, it is physicochemically different from rapamycin with a different pharmacokinetic profile. RAD-001 inhibits the growth-factor-driven

Table 1. — Toxicity of Farnesyl Transferase Inhibitors in Glioma Clinical Trials

| Drug     | Neutrophils | Platelets | Fatigue | Nausea/Vomiting | Diarrhea | Neuropathy | Confusion |
|----------|-------------|-----------|---------|-----------------|----------|------------|-----------|
| SCH66336 | +           | +         | +       | +               | +        | +          | –         |
| R115777  | +           | +         | +       | +               | –        | +          | +         |

proliferation of hematopoietic and nonhematopoietic cells in vitro with a 50% inhibitory concentration ( $IC_{50}$ ) of 0.2 to 1.6 nM, approximately 2 to 3 times less potent than rapamycin. Interestingly, it has the same efficacy as rapamycin when given orally to rat and monkey models of transplantation.

**Clinical Trials:** Currently, RAD-001 is undergoing evaluation in laboratory models of malignant gliomas and is expected to be in clinical trials in the near future.

## Inhibition of Ras: Farnesyl Transferase Inhibitors

Ras, an abbreviation that originated from rat sarcoma, is a low-molecular-weight GDP/GTP-binding guanine triphosphatase (GTPase) with a determinant role in malignant transformation, invasion, and spread of gliomas. Ras mutations or constitutive activation have been described in gliomas,<sup>3</sup> although controversy surrounds the observation of a mutated ras gene.<sup>6</sup> Ras undergoes a series of posttranslational modifications, starting with a lipid modification called farnesylation. Farnesylation is catalyzed by farnesyltransferase (FTase) and depends on the enzymatic recognition of a specific carboxyl terminal sequence known as CAAX where C is cysteine, AA is aliphatic amino acids, and X is any amino acid, preferably methionine or serine. This process anchors Ras to the cell membrane, a required step of the cancer-causing activity of Ras.

### SCH66336

**Drug Overview**<sup>32,49,65-67</sup>: SCH66336 (lonafarnib, Sarasar) is an 11-piperidinyl trihalogenated analog with better pharmacokinetics and potency than its prototype SCH44342. It is an oral nonpeptidomimetic inhibitor of FTase and is active against tumors with wild-type mutant Ras proteins. Potential FTase substrates that can serve as farnesyl transferase inhibitor targets may include other G proteins that can be farnesylated, such as Rheb, Rho, and CENP-E,F proteins.<sup>67</sup> Cells exposed to SCH66336 can arrest in  $G_1$  or in  $G_2/M$ . SCH66336 inhibited viability and growth of glioblastoma cell lines U-251 MG, U-251/E4 MG, and U-87 MG in a time- and dose-dependent manner.<sup>68</sup> It also has a synergistic effect with STI571, the taxanes, cisplatin, cyclophosphamide, 5-fluorouracil, and vincristine.<sup>69-71</sup>

SCH66336 is absorbed slowly, with a  $C_{max}$  of 1.5 to 12.3 hours and a half-life between 5 and 16 hours. Phase I trials have tested SCH66336 given twice a day for 7 days every 3 weeks or as twice daily continuous treatment. The common toxicities are noted in Table 1. An interesting effect of SCH66336 is its ability to inhibit MDR1 product P-glycoprotein, a protein with a major role in the development of resistance to chemotherapy by cancer cells.<sup>72</sup>

**Clinical Trials:** The M. D. Anderson Cancer Center launched a phase II trial (DM 01-258) evaluating temozolomide plus SCH66336 for recurrent GBM.<sup>73</sup> The temozolomide dose is 150 mg/m<sup>2</sup> daily  $\times$  5 days every 28 days, and the SCH66336 dose is 150 mg orally twice a day from days 8 to 28 of each cycle. Results are not yet available.

### R115777

**Drug Overview**<sup>32,65-67</sup>: R115777 (tipifarnib) is a nonpeptidomimetic methyl-quinolone initially developed as an antifungal agent. Like SCH66336, R115777 (Zarnestra) is a selective nonpeptidomimetic inhibitor of FTase. It is a radiosensitizer, inducing postmitotic necrotic cell death of radioresistant glioma cell lines in vitro.<sup>74</sup> Because of these findings, it seems reasonable to test R115777 concurrently with radiation therapy in the future. R115777 has a rapid absorption in the gastrointestinal tract, with a  $C_{max}$  of 0.5 to 4 hours, a half-life of 5 hours, and a plasma steady state within 2 to 3 days after the first dose.<sup>75</sup> In a phase I trial, the recommended dose orally was 300 mg twice a day,<sup>76</sup> but initial studies recommended 500 mg twice a day for 5 consecutive days with 9 days of rest.<sup>75</sup>

**Clinical Trials:** To determine the MTD, drug activity, and toxicity of R115777, the NABTC conducted a phase I/II trial (NABTC 99-01) using R115777 in patients with recurrent or progressive malignant glioma taking or not taking EIAEDs.<sup>77</sup> All patients without EIAEDs received R115777 at 300 mg orally twice daily for 21 days, with 7 days of rest. Among 33 enrolled patients who had GBM, 3 had a partial response, 2 had stable disease for more than 6 months, and 15% had been progression-free at 6 months.<sup>78</sup> Patients on EIAEDs had dose escalation beginning at 300 mg orally once a day on day 1, up to a maximum of 600 mg orally twice a day. The dose escalation was still ongoing.

## Inhibitors of VEGF Tyrosine Kinase

The growth of a glial tumor depends variably on angiogenesis, defined as the induction of new capillary blood vessels necessary to support a developing mass. Diffusible molecules (angiogenic factors) that recognize and bind to endothelial receptors trigger angiogenesis (Fig 3). This ligand-receptor coupling generates endothelial proliferation and migration. Of these angiogenic factors, VEGF is the best known, showing overexpression in brain tumors, especially in GBM. At least two structurally related tyrosine kinase receptors for VEGF are expressed in the endothelial cells of anaplastic astrocytoma and GBM: flt-1 (VEGF receptor-1) and flk-1 (VEGF receptor 2), each encoded by a different gene.

### SU5416

**Drug Overview**<sup>79,84</sup>: SU5416 (semaxanib), a quinolone derivative, is a synthetic reversible inhibitor of VEGF receptor-2 and PDGF receptors. SU5416 inhibited the growth of glioma xenografts and significantly prolonged median survival in rats transplanted with GS-9L glioma cells.<sup>83,84</sup> The dose-limiting toxicities were nausea, headache, and an increased risk of thromboembolic complications.

**Clinical Trials**: NABTC 99-02 was a phase I/II trial to determine the MTD, toxicity, and efficacy of SU5416 in patients with recurrent or progressive supratentorial malignant gliomas.<sup>85</sup> Patients were stratified according to their use of EIAEDs. SU5416 was given intravenously on

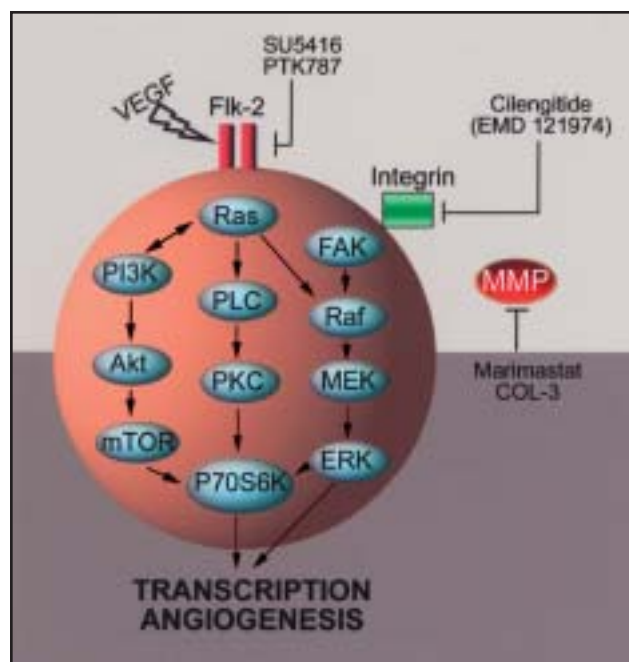


Fig 3. — Angiogenesis and matrix metalloproteinase inhibitors. Arrows indicate stimulation, and T lines indicate inhibition (PLC = phospholipase C, PKC = protein kinase C).

days 1 and 4 every week for 4 weeks. If no dose-limiting toxicity was present, patients were evaluated for response and continued with the same treatment schedule for 4 more weeks. At that point, response and toxicity were reevaluated before indefinite treatment until progression or dose-limiting toxicities occurred. The dose escalation ranged from 85 mg/m<sup>2</sup> to 340 mg/m<sup>2</sup>. This trial is now closed to accrual and results are expected soon.

### PTK787/ZK-222584

**Drug Overview**<sup>10,86-88</sup>: PTK787 (protein tyrosine kinase 787, formerly CGP-7978) is a newly synthesized compound belonging to the aminophthalazine class. It is a potent and selective inhibitor of VEGF receptor-2, with a weaker blocking effect on PDGF tyrosine kinase. Therefore, the drug interferes with VEGF- and PDGF-mediated angiogenesis in in vitro and in vivo models. When PTK787 is combined with irradiation, tumor growth of radiation-resistant p53-dysfunctional xenografts is significantly delayed.<sup>89</sup>

**Clinical Trials**: At the University of Texas M.D. Anderson Cancer Center and Duke University Medical Center, PTK787 is undergoing a phase IA trial (ID98-317) and a phase IB trial (DM01-401) using PTK787.<sup>90,91</sup> The aim of the phase IA trial is to determine the MTD and dose-limiting toxicity of continuous daily dosing of PTK787 in patients with recurrent or relapsing GBM. The drug starting dose is 500 mg once a day, with 500-mg escalations up to a maximum daily dose of 2000 mg. The investigators in this trial use dynamic MRI scans to determine vascular permeability and tumor blood flow before and during treatment. Preliminary results suggest that at doses of 500 to 1500 mg daily, PTK787 has antitumor activity, correlating with changes in the vascular permeability index as measured by dynamic MRI. Deep-vein thrombosis (DVT), pedal edema without DVT, and elevated liver enzymes were the principal adverse events.<sup>92</sup>

The IB phase will determine the MTD and dose-limiting toxicity of continuous once-daily dose of PTK787 plus temozolomide (arm 1) or PTK787 plus lomustine (arm 2). In both treatment arms, PTK787 is given once daily (except for day 1 of the first treatment cycle) at a starting dose of 500 mg with escalation up to 1500 mg daily. Preliminary results for arm 1 suggest good drug tolerance at 1000 mg daily, with antitumor activity noted (5 of 11 patients had stable disease).<sup>93</sup>

## Integrin Antagonists

Integrins are a family of transmembrane heterodimeric receptors that mediate cell adhesion with the extracellular matrix, cell migration, invasion, and neovas-

cularization.<sup>5,94</sup> Integrins form cytoplasmic complexes with Src family kinases, cytoskeletal proteins, growth factor receptors, MAPK, Ras, the nuclear factor of kappa light polypeptide gene enhancer in B cells (NF- $\kappa$ B), PIP3K, and protein kinase C.<sup>95-99</sup> Although the relationship between integrins and the extracellular matrix is complex and not completely understood, growing evidence points to a role of  $\alpha$ v $\beta$ 3 integrin receptors in growth regulation and antiapoptosis of tumor cells. The role of integrins in angiogenesis is also supported by the fact that integrins are active in angiogenic endothelium and dormant on quiescent endothelial cells and that blockade of  $\alpha$ v $\beta$ 3 receptors decreases angiogenesis, regresses tumors, and triggers endothelial apoptosis.<sup>100</sup> The efficacy of antagonizing integrins in glioma angiogenesis is uncertain, but evaluation of this strategy is underway.

### Thalidomide

**Drug Overview**<sup>101-108</sup>: Thalidomide is a glutamic acid derivative chemically similar but functionally unrelated to bemegride and glutethimide. The mechanism of action of thalidomide is incompletely understood. A postulated antiangiogenic effect of thalidomide was based on its ability to inhibit or interfere with the expression of integrin receptors  $\alpha$ v $\beta$ 3 and  $\alpha$ v $\beta$ 5 as well as inhibit vascularization induced by basic fibroblastic growth factor (bFGF) and VEGF. This inhibition is due to intercalation of thalidomide into guanine-rich DNA promoter sites of bFGF and the  $\alpha$ v and  $\beta$ 3 integrin subunits.<sup>108-110</sup> Thalidomide is slowly absorbed, with a  $C_{\max}$  of 3 to 4 hours and large volume of distribution. The primary metabolic pathway is nonenzymatic hydrolysis in blood and tissue. The half-life of thalidomide is 5 to 8 hours. The most frequent side effects in glioma trials are fatigue, constipation, and neuropathy.

**Clinical Trials**: Several phase II trials with thalidomide as a single agent for malignant gliomas have been published.<sup>111-113</sup> The doses have ranged between 100 and 1200 mg per day. For this patient population, thalidomide is a safe drug with acceptable toxicity that appears to have little antitumor activity. We recently analyzed data from NABTC 99-04, a phase II trial with thalidomide plus temozolomide for recurrent GBM. Patients received thalidomide at 400 mg orally every 12 hours on a continuous dosing schedule. The best response rate (partial response plus stable disease rate) was 47%, with a median PFS of 13 weeks.<sup>114</sup> This outcome was not significantly different from the 6-month PFS in historical data from recurrent GBM. Recent data from a phase I trial suggest that the combination of temozolomide and thalidomide can be effective in the treatment of brain metastases from melanoma,<sup>115</sup> which raises the possibility that thalidomide is more effective for treating brain metastases than primary brain tumors.

### Cilengitide

**Drug Overview**<sup>116,117</sup>: Cilengitide (EMD 121974) is a potent selective inhibitor of the  $\alpha$ v $\beta$ 3 integrin receptor tested in phase I trials on renal cell and colon cancer.<sup>118</sup> The drug suppressed the growth of glioblastoma (U87MG) and medulloblastoma (DAOY) cell lines implanted orthotopically in nude mice.<sup>117</sup> Experimental evidence indicates that growth inhibition is through apoptosis in both brain capillary and brain tumor cells, by preventing their interaction with the matrix proteins vitronectin and tenascin.<sup>119</sup> Cilengitide has been given intravenously twice weekly at doses ranging from 30 to 1600 mg/m<sup>2</sup> per infusion.

**Clinical Trials**: The New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium opened a phase I trial (NABTT 9911) to find the MTD and assess tumor activity of cilengitide in recurrent or progressive malignant gliomas.<sup>120</sup> Patients are now at a dose level of 1200 mg/m<sup>2</sup>, and the dose-limiting toxicity at 480 mg/m<sup>2</sup> has been arthralgia.<sup>121</sup>

### Endothelin Receptor Antagonists

Endothelins (ET-1, ET-2, and ET-3) are 21-amino acid peptides with potent vasopressor and mitogenic activity whose role in cancer angiogenesis is under investigation. ET-1 receptors are expressed in several glioma cell lines, and ET binding to these receptors induces DNA synthesis and a potent proangiogenic factor. ET-1 is a survival/antiapoptotic factor produced by tumor vasculature involving protein kinase C and extracellular signal-regulated kinase pathways.<sup>122</sup> These biological effects are mediated by G-protein-linked receptors and depend on extracellular Ca<sup>2+</sup> influx. To date, two receptors with >50% homology have been cloned, ET<sub>A</sub> and ET<sub>B</sub>. A series of selective endothelin receptor antagonists have been introduced, focusing on the development of ET<sub>A</sub>-selective agents.

### Atrasentan

**Drug Overview**<sup>122-134</sup>: Atrasentan (ABT-627) is a pyrrolidine-3-carboxylic acid derivative with selectivity against the ET<sub>A</sub> receptor.<sup>135</sup> A phase I trial of atrasentan in refractory adenocarcinomas evaluated safety of the drug with dose escalation from 10 mg to 140 mg per day.<sup>126</sup> Absorption was rapid with a  $C_{\max}$  at 1.5 hours, a half-life of 24 hours, and steady-state concentrations in a week. The most common side effects were rhinitis, headache, fatigue, and edema. All symptoms were reversible after stopping the drug or treating symptomatically.

Table 2. — Classification of the Human Matrix Metalloproteinases by Primary Structure and Substrate Specificity

| Compound             | Class                       | Substrate         |
|----------------------|-----------------------------|-------------------|
| Prinomastat (AG3340) | Nonpeptidomimetic inhibitor | MMP-2, -3         |
| BAY 12-9566          | Nonpeptidomimetic inhibitor | MMP-2, -3         |
| BMS-275291           | Nonpeptidomimetic inhibitor | MMP-2, -9         |
| COGS 27023A          | Nonpeptidomimetic inhibitor | Nonspecific       |
| Marimastat (BB-251)  | Peptidomimetic inhibitor    | MMP-1, -2, -7, -9 |
| Metastat (COL-3)     | Modified tetracycline       | MMP-2, -9         |

**Clinical Trials:** The NABTT CNS Consortium has a phase I trial of atrasentan in patients with progressive or recurrent malignant gliomas (NABTT-2008) to determine MTD, pharmacokinetics, and activity in this patient population.<sup>136</sup>

## Matrix Metalloproteinase Inhibitors

The matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that degrade some components of the extracellular matrix. The human MMP gene family is grouped into five classes by primary structure and substrate specificity (Table 2). A review on MMPs and the development of MMP inhibitors (MMPIs) can be found elsewhere.<sup>137</sup> MMPs degrade the basement membrane and the extracellular matrix, thus facilitating tumor growth, invasion, and spread. The expression of MMP is increased in most cancers, including gliomas. Of all known MMPIs in clinical development (Table 2), marimastat, metastat, and prinomastat have been or are being tested in trials against gliomas.

### Marimastat

**Drug Overview<sup>137-142</sup>:** Marimastat (BB-251) is a low molecular weight drug that chelates the Zn<sup>++</sup> ion at the active site of MMPs. It is 20% to 50% bioavailable after oral administration, with a linear pharmacokinetics and a C<sub>max</sub> of 1.5 to 3.0 hours. The half-life of marimastat is 8 to 10 hours, so the drug can be given twice a day.<sup>141</sup> The main side effect is a dose-related polyarthrititis manifested by arthralgias in large and small joints, sometimes with visible redness and swelling. Marimastat-related arthralgias are treated with nonsteroidal anti-inflammatory drugs and a 10% reduction of the previous dose until symptoms are mild enough to tolerate or disappear.

**Clinical Trials:** Two phase II trials of marimastat and temozolomide for recurrent GBM and anaplastic gliomas showed that this combination appears to be effective to increase PFS.<sup>143,144</sup> In both trials, patients had progression after surgery, radiation therapy, and

one, at most, previous treatment with chemotherapy. Patients received temozolomide at 150 to 200 mg/m<sup>2</sup> per day on days 1 to 5 and marimastat at 50 mg orally once a day on days 8 to 28. In the GBM study, 5 patients (11%) had severe arthralgias that prompted drug withdrawal. Seventeen patients in the group with anaplastic gliomas required dose reduction from toxicity, but none were withdrawn. At 6 months, PFS was 39% and 54% for recurrent GBM and anaplastic gliomas, respectively.

These figures represent a gain of 29% and 14% over the expected target PFS for recurrent GBM and anaplastic gliomas treated with temozolomide alone.

### Metastat

**Drug Overview<sup>137,140</sup>:** Metastat (CMT-3, COL-3, Collagenex) is a chemically modified tetracycline with potent inhibition of MMP-2 and MMP-9 in cancer cell lines. This drug has been tolerated in doses up to 70 mg/m<sup>2</sup> per day, with a prolonged half-life and steady-state levels above the concentrations required for in vitro activity.

**Clinical Trials:** NABTT 9809 is a phase I/II trial to evaluate safety and tolerability of COL-3 in recurrent high-grade gliomas, with escalating doses of 25 mg/m<sup>2</sup> up to a maximum dose of 100 mg/m<sup>2</sup> once a day for 28 days.<sup>145</sup> Patients with or without EIAEDs are included. The maximum dose has been well tolerated with no responses among 25 patients enrolled thus far.

### Prinomastat

**Drug Overview<sup>140,146-149</sup>:** Prinomastat (AG3340), a nonpeptidic MMPI, inhibits MMP-2, -3, -9, and -13 with an IC<sub>50</sub> value of 0.1 ng/mL. Its cytostatic activity was optimized by drug fractionation but not by total daily dose, AUC, or C<sub>max</sub>. Prinomastat inhibited tumor growth and induced apoptosis of U87 glioblastoma cell xenografts.<sup>146</sup> The drug is lipophilic and crosses the blood-brain barrier, which prompted the use of prinomastat in clinical trials against glioma. Prinomastat is also synergistic with carboplatin and paclitaxel in vitro.<sup>137</sup> The drug has been tested in doses ranging from 2 to 100 mg orally twice a day.

**Clinical Trials:** DM99-254 was a randomized, placebo-controlled phase II trial of prinomastat with temozolomide after radiation therapy in patients with newly diagnosed GBM.<sup>150</sup> Patients were randomized after surgery and radiation therapy to continuous prinomastat 25 mg orally twice a day or placebo, plus temozolomide at 200 mg/m<sup>2</sup> orally once a day on days 1 to 5 every 28 days. This trial showed that prinomas-

tat added to temozolomide compared with temozolomide alone did not improve 1-year survival rate (44% vs 58%) or PFS (4.5 vs 6 months). The main side effects related to prinomastat were myalgias and arthralgias with swelling in 55% of patients compared with 20% of patients receiving placebo.<sup>150</sup>

## Proteasome Inhibitors

### PS-341

**Drug Overview**<sup>151-156</sup>: The ubiquitin/proteasome system is the main posttranscriptional degradation mechanism of proteins involved in cell cycle, DNA transcription and repair, apoptosis, angiogenesis, and cell growth. Target molecules of this system include p53, mdm2, p21, p27, Rb, cyclins A, B, and E, IκB, NF-κB, Bcl-2, Bax, and caspase-3. The development of drugs that work on the ubiquitin/proteasome system is a potential anticancer strategy. The prototype drug of this class is PS-341 (Velcade), active as a single agent on murine and human xenograft models by enhancing apoptosis, specifically against transformed cells.<sup>153</sup> PS-341 arrests cells in G<sub>2</sub>-M phase, inducing apoptosis of these cells with simultaneous phosphorylation of Bcl-2.<sup>156</sup>

**Clinical Trials**: As with COL-3, a phase I trial (NABTT-9910) is in progress testing PS-341 in patients with recurrent or progressive gliomas. The drug is given intravenously twice a week for 4 weeks, with 2 weeks of rest before a new course starts. This trial is currently active for patients not taking EIAEDs.<sup>157</sup>

## Cyclooxygenase-2 Inhibitors

The cyclooxygenase and lipoxygenase pathways are present and active in normal and tumoral astrocytes.<sup>158</sup> Although the role of arachidonic acid metabolism is still unclear, there is evidence that eicosanoids have a wide range of functions in cerebral physiology. In disease, eicosanoids promote tumor growth, neovascularization, and migration.<sup>159,160</sup> Treatment with cyclooxygenase inhibitors suppresses growth and induces apoptosis. In the early 1990s, Blomgren et al<sup>159</sup> and Gáti et al<sup>161,162</sup> showed that the growth of human glioma cells was inhibited in vitro by compounds interfering with arachidonic acid metabolism, suggesting that lipoxygenase inhibitors could be potential candidates for the treatment of malignant gliomas.

### Celecoxib

**Drug Overview**<sup>163,164</sup>: Celecoxib (Celebrex) is a nonsteroidal anti-inflammatory drug that inhibits

prostaglandin synthesis by specifically inhibiting the cyclooxygenase-2 (COX-2) enzyme. This enzyme is overexpressed in gastric,<sup>165</sup> esophageal, and colorectal carcinomas,<sup>166</sup> and its expression may be important in carcinogenesis. COX-2 enzyme is also upregulated in high-grade human gliomas and is inversely related to patient survival by a mechanism that appears to be independent of p53 immunostaining, bcl-2 expression, loss of p16 or retinoblastoma protein expression, or high MIB-1 expression.<sup>167</sup> The inhibition of COX-2 enzyme activity reduced the proliferation and migration of human glioblastoma cell lines.<sup>168</sup>

**Clinical Trials**: Experimental work with retinoids in head and neck squamous cell cancer has shown a suppression of EGF-induced COX-2 expression, suggesting that this may be one mechanism for the anticancer properties of retinoids. Therefore, combining a COX-2 inhibitor with a retinoid may enhance suppression of COX-2 expression in human gliomas. Because of potential interactions and unique independent modes of action, the combination of isotretinoin with celecoxib may represent a rational therapy for high-grade gliomas. A phase II trial (ID02-306) to treat recurrent or progressive malignant gliomas is open at the M. D. Anderson Cancer Center, using a specific COX-2 inhibitor, celecoxib, plus isotretinoin (c-RA).<sup>169</sup> Isotretinoin is given orally for 21 days at 100 mg/m<sup>2</sup> per day in two divided doses, and celecoxib 400 mg is given orally twice a day for 21 days concurrently with isotretinoin. The objective of the trial is to assess efficacy as measured by PFS and toxicity.

## Conclusions

The elucidation of the signaling pathways responsible for the malignant phenotype is now being translated into cancer treatment strategies. Initial efforts have focused on the use of single agents, directed at specific molecular targets. Although precedence exists in cancer for this single-agent approach, such as the use of STI571 for chronic myelogenous leukemia, most other efforts have been disappointing. It is clear that the complexity and cross-talk between signal transduction pathways limits the potential efficacy of targeting a single receptor or molecule. Therefore, future treatment paradigms will likely need to consider a combination of treatment approaches with multiple inhibitors or a combination of these pathway-specific treatments with traditional cytotoxic drugs. Furthermore, new strategies are needed to determine the optimal dosing and effectiveness of these agents by evaluating the molecular effects as the endpoint rather than the traditional maximally tolerated dose and/or overall tumor response. This will require protocol designs

with tissue sampling and the development of surrogate markers of molecular changes.<sup>170</sup>

The number of new agents under development poses a challenge for evaluation. In vitro and animal models will help to screen the activity and benefits of combinations, but a larger number of potential treatment regimens will need to be tested. Novel trial designs, including the use of factorial paradigms, are needed to optimize the evaluation of these new treatments.

The future of treatments for malignant brain tumors will likely include agents that specifically target molecular pathways. We have the challenging task of determining the best treatments by integrating protocol design with the rapid advances in molecular profiling of tumors and imaging technology. The great potential benefit of these new treatments offers hope for significant improvement in the prognosis for patients with primary brain tumors.

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