

# It Is Time to Include Patients With Brain Tumors in Phase I Trials in Oncology

Patrick Y. Wen, *Center for Neuro-Oncology, Dana-Farber Cancer Institute; Brigham and Women's Hospital, Boston, MA*  
 David Schiff, *Neuro-Oncology Center, University of Virginia, Charlottesville, VA*  
 Timothy F. Cloughesy, *Neuro-Oncology Program, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA*  
 David A. Reardon, *Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC*  
 Tracy T. Batchelor, *Stephen E. and Catherine Pappas Center for Neuro-Oncology, Massachusetts General Hospital, Boston, MA*  
 Bruce A. Chabner and Keith Flaherty, *Massachusetts General Hospital Cancer Center, Boston, MA*  
 John F. de Groot and Mark R. Gilbert, *The University of Texas MD Anderson Cancer Center, Houston, TX*  
 Evanthia Galanis, *Mayo Clinic, Rochester, MN*  
 Susan M. Chang, *University of California, San Francisco, San Francisco, CA*  
 Gary K. Schwartz, *Memorial Sloan-Kettering Cancer Center, New York, NY*  
 David Peereboom, *Cleveland Clinic, Cleveland, OH*  
 Minesh P. Mehta, *Northwestern University, Chicago, IL*  
 W.K. Alfred Yung, *The University of Texas MD Anderson Cancer Center, Houston, TX*  
 Stuart A. Grossman, *Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*  
 Michael D. Prados, *University of California, San Francisco, San Francisco, CA*  
 Lisa M. DeAngelis, *Brain Tumor Center, Memorial Sloan-Kettering Cancer Center, New York, NY*

Traditionally, the majority of phase I studies of novel agents in oncology have excluded patients with primary brain tumors. Although phase I studies are designed to determine optimal dosing, efficacy data are increasingly used to look for a signal in particular tumors. Excluding patients with primary brain tumors from phase I studies results in a significant handicap in the identification of drugs that may be particularly active in these tumor types. In this era of targeted therapies, we suggest that the reasons for excluding these patients are largely obsolete. It is time to reconsider this practice and include patients with brain tumors in phase I trials in oncology.

Several reasons are given for the exclusion of patients with brain tumors from phase I trials. First, patients with brain tumors were historically treated with cytochrome P450 enzyme-inducing antiepileptic drugs (EIAEDs), such as phenytoin and carbamazepine, which potentially accelerated hepatic metabolism of the agent under study. As a result, a separate phase I study was often required for patients with brain tumors who were receiving EIAEDs, and the required dose to achieve the same exposure as that of patients not receiving an EIAED was often two- to three-fold higher.<sup>1-3</sup> Second, patients with brain tumors were perceived to be in poor condition with a short life expectancy and therefore likely to add to the potential adverse events associated with the study drug, and unlikely to remain stable for a sufficient length of time to allow toxicities to be evaluated during the required period. Third, patients with primary brain tumors were thought to be at increased risk for particular toxicities such as hemorrhage. Fourth, neurologic symptoms and signs from the tumor were believed to be difficult to separate from drug-related neurotoxicity. Fifth, the passage of many agents across the blood-brain barrier (BBB) was uncertain.

Another unspoken reason is that some medical oncologists are uncomfortable caring for patients with primary brain tumors, who are usually treated by neuro-oncologists.

However, most of the reasons for excluding patients with brain tumors from phase I trials are no longer valid. Few patients with brain tumors are now treated with traditional EIAEDs. Prophylactic antiepileptic drugs are not recommended, and the majority of patients who require antiepileptic drugs are treated with non-EIAEDs such as levetiracetam, pregabalin, lamotrigine, topiramate, and lacosamide. Currently, brain tumor trials routinely exclude patients who are receiving EIAEDs if the drug under investigation is metabolized by the cytochrome P450 system; this does not seem to affect accrual. There is no longer a need for separate phase I studies in patients with brain tumors; the maximum-tolerated dose determined in phase I trials for systemic cancers is also the maximum-tolerated dose for brain tumors. The frequent use of corticosteroids in patients with brain tumors is sometimes used as an argument against including these patients in phase I trials, but the effect of corticosteroids on drug exposure is minimal.

The condition of patients with brain tumors is usually no worse than that of patients with systemic cancer. Patients with brain tumors are often relatively young (median age of patients in glioblastoma trials is about 55 years) and have few systemic comorbidities. They tend to have had relatively few prior treatments with systemic agents and there are no systemic metastases, so organ function is generally good and often better than that of patients with systemic cancer who enter phase I trials. Patients with glioblastoma who have recurrent disease and reasonable performance status usually have a life expectancy of 4 to 7 months,<sup>4,5</sup> which is

comparable to or better than the expected survival of patients with other solid tumors who have exhausted standard treatment options, and the vast majority of patients with glioblastoma are able to remain on study long enough for drug toxicity to be evaluated adequately.

Multiple phase I trials conducted exclusively in patients with brain tumors failed to demonstrate an increased risk of CNS hemorrhage, including those that evaluated bevacizumab and other antiangiogenic agents; in these studies, the risk of hemorrhage proved to be modest.<sup>6-8</sup> Differentiating drug-related neurotoxicity from the effects of the tumor is similar to separating drug toxicity effects on other organs from the effects of systemic metastases. In reality, differentiating tumor-related neurologic symptoms from potential drug toxicity is straightforward and rarely causes confusion.

The drug's ability to pass through the BBB is an area of valid concern. Although the center of most high-grade primary brain tumors often has a disrupted BBB, the ability of a drug to reach peripheral areas of the tumor where the BBB is relatively intact is also important for it to achieve a therapeutic benefit. Drug structure, molecular weight, lipophilicity, potential impact of drug efflux pumps, and preclinical biodistribution studies should provide some guidance as to whether a drug can cross the BBB. If there is evidence that the drug can pass through the BBB, there is no reason to exclude patients with primary brain tumors from the phase I study. Conversely, if preclinical studies suggest that drug penetration may be limited, it may be reasonable to consider excluding patients with brain tumors from the phase I study. However, even this situation is complex. Agents that target the tumor stroma or vasculature may not need to pass through the BBB to be effective. In addition, there are examples of large antibodies, such as rituximab in primary CNS lymphoma<sup>9</sup> and bevacizumab in glioblastoma,<sup>6,7</sup> with which therapeutic effects were seen despite concerns about the ability of these agents to pass through the BBB.

In this era of targeted therapy, we hope to include all tumors in phase I studies on the basis of the presence of the correct molecular target, rather than having protocols routinely exclude patients with primary brain tumors. For instance, because the phosphatidylinositol 3'-kinase (PI3 kinase) pathway is activated in the majority of patients with glioblastoma (15% have *PIK3CA* or *PIK3R1* mutations and 40% to 50% have loss or mutation of phosphatase and tensin homolog deleted on chromosome 10),<sup>10</sup> it would be advantageous to include glioblastomas in trials of PI3 kinase inhibitors if those inhibitors have reasonable access across the BBB. Excluding patients with brain tumors will slow our ability to find better treatments for these patients for whom so few effective therapies exist, and potentially means a lost opportunity to identify a responsive tumor type. Temozolomide is one of the few drugs that is approved for high-grade gliomas, and inclusion of patients with brain tumors into the phase I trial determined the fate of this important agent.<sup>11</sup> Activity was seen in patients with high-grade gliomas, and eventually the drug received approval from the US Food and Drug Administration for both recurrent anaplastic gliomas and newly diagnosed glioblastoma. If this drug had been evaluated only in systemic cancers, it is unlikely that its activity against primary brain tumors would have been identified, and as a result, one of the few outcome-changing drugs in glioma treatment would not have become an option for our patients.

The inclusion of patients with primary brain tumors in phase I studies may increase the complexity of those studies, given that the response criteria for systemic tumors<sup>12</sup> and primary brain tumors<sup>13</sup> are different. However, the added complexity is relatively modest. Recently, medical oncologists conducting phase I studies and neuro-oncologists at a limited number of centers have been working together to include patients with brain tumors in protocols when a strong scientific rationale exists. Unfortunately, at most centers, this does not occur. It would be of benefit to both patients and pharmaceutical companies to include patients with primary brain tumors in the majority of phase I trials in oncology.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

**Employment or Leadership Position:** Minesh P. Mehta, Pharmacyclics (C) **Consultant or Advisory Role:** Timothy F. Cloughesy, Roche (C); Tracy T. Batchelor, Roche (C), Amgen (C), Merck (C); Bruce A. Chabner, sanofi-aventis (C), Allergan (C), Epizyme (C), PharmaMar (C), GlaxoSmithKline (C), Peregrine Pharmaceuticals (C), Onyx Pharmaceuticals (C); John F. de Groot, Genentech (C); Minesh P. Mehta, Merck (C), TomoTherapy (C); W.K. Alfred Yung, Merck (C), Novartis (C), Edens (C); Stuart A. Grossman, Merck (C), Roche (C), Diffusion Pharmaceuticals (C), Tau Pharmaceuticals (C), Medimmune (C) **Stock Ownership:** Bruce A. Chabner, PharmaMar, Gilead, Epizyme, Human Genome Sciences, Onyx Pharmaceuticals, Exelixis, Merck, Rigil Pharmaceuticals, Seattle Genetics; Minesh P. Mehta, Pharmacyclics, TomoTherapy **Honoraria:** Timothy F. Cloughesy, Genentech, Roche, AstraZeneca, Agios, Eli Lilly; Bruce A. Chabner, Eli Lilly; Minesh P. Mehta, Merck; W.K. Alfred Yung, Merck, Novartis, Edens **Research Funding:** Tracy T. Batchelor, Pfizer, AstraZeneca, Millennium; John F. de Groot, AstraZeneca, Adnexus; Susan M. Chang, Novartis, Schering-Plough; W.K. Alfred Yung, Novartis, Daiichi **Expert Testimony:** None **Other Remuneration:** None

#### AUTHOR CONTRIBUTIONS

**Administrative support:** Patrick Y. Wen

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

#### REFERENCES

1. 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* 12:4899-4907, 2006
2. Raizer JJ, Abrey LE, Lassman AB, et al: A phase I trial of erlotinib in patients with nonprogressive glioblastoma multiforme postirradiation therapy, and recurrent malignant gliomas and meningiomas. *Neuro Oncol* 12:87-94, 2010
3. Fetell MR, Grossman SA, Fisher JD, et al: Preirradiation paclitaxel in glioblastoma multiforme: Efficacy, pharmacology, and drug interactions—New Approaches to Brain Tumor Therapy Central Nervous System Consortium. *J Clin Oncol* 15:3121-3128, 1997
4. Lamborn KR, Yung WK, Chang SM, et al: Progression-free survival: An important end point in evaluating therapy for recurrent high-grade gliomas. *Neuro Oncol* 10:162-170, 2010
5. Wick W, Puduvalli VK, Chamberlain MC, et al: Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol* 28:1168-1174, 2010
6. Friedman HS, Prados MD, Wen PY, et al: Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* 27:4733-4740, 2009

7. 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* 27:740-745, 2009

8. Batchelor TT, Duda DG, di Tomaso E, et al: Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. *J Clin Oncol* 28:2817-2823, 2010

9. Batchelor TT, Grossman SA, Mikkelsen T, et al: Rituximab monotherapy for patients with recurrent primary CNS lymphoma. *Neurology* 76:929-930, 2011

10. Cancer Genome Atlas Research Network: Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* 455:1061-1068, 2008

11. Newlands ES, Blackledge GR, Slack JA, et al: Phase I trial of temozolomide (CCRG 81045; M&B 39831; NSC 362856). *Br J Cancer* 65:287-291, 1992

12. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45:228-247, 2009

13. Wen PY, Macdonald DR, Reardon DA, et al: Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. *J Clin Oncol* 28:1963-1972, 2010

DOI: 10.1200/JCO.2011.36.6328; published online ahead of print at [www.jco.org](http://www.jco.org) on July 18, 2011



### Be the First to Hear When New Clinical Cancer Research is Published Online

By signing up for *JCO's* Early Release Notification, you will be alerted and have access to new articles posted online every Monday, weeks before they appear in print. All Early Release articles are searchable and citable, and are posted on [JCO.org](http://JCO.org) in advance of print publication. Simply go to [jco.org/earlyrelease](http://jco.org/earlyrelease), sign in, select "Early Release Notification," and click the SUBMIT button. Stay informed—sign up today!



American Society of Clinical Oncology