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Cilengitide: Does It Really Represent a New Targeted Therapy for Recurrent Glioblastoma?

To the Editor: Reardon et al[1] are to be congratulated for their recently reported phase II trial of cilengitide for recurrent glioblastoma (GBM). I would like to make several comments regarding the report and the use of cilengitide to treat recurrent GBM.

It is curious that Reardon et al compared their study results to those of the prior temozolomide (TMZ) trial[2] for recurrent GBM, when it has become usual and customary in neuro-oncology trials involving the treatment of recurrent GBM to evaluate results on the basis of the aggregate phase II studies by Wong et al[3] (pre-TMZ era) and Lambert et al[4] (post-TMZ era). In both these studies, 15% progression-free survival at 6 months was demonstrated, providing a validated end point in trials of recurrent GBM, as opposed to response rates or overall survival. In addition, agents considered of interest for additional study in treating recurrent GBM require a 10% improvement in progression-free survival at 6 months (progression-free survival of at least 25%), a standard clearly not achieved in the cilengitide trial by Reardon et al. By this benchmark, the trial results are no more compelling than those of the recently reported trial of metronomic TMZ as treatment for recurrent GBM.[5] Viewed in this context, it is far from clear what advantage cilengitide offers over other agents previously studied for the treatment of recurrent GBM.

The remarkable response and survival benefit seen with the administration of bevacizumab, with or without a cytotoxic,[6,7] is a new complexity that has arisen in reporting results of phase II trials in recurrent GBM. Not reported in the cilengitide trial by Reardon et al was the number of patients treated with bevacizumab after treatment with cilengitide failed, a factor that likely affects overall survival by prolonging it.

Early reports on the use of cilengitide in the adjuvant treatment of GBM suggest stratification by tumor methylguanine methyltransferase (MGMT) expression best defines a patient subpopulation likely to benefit from adjuvant cilengitide treatment.[8] Patients with MGMT promoter methylation derive significant benefit from adjuvant cilengitide treatment. Reardon et al did not report response to salvage cilengitide as a function of MGMT expression, a probable biomarker predicting for response; this determination could permit selection of patients responsive to cilengitide.

Lastly, the use of an intravenous agent like cilengitide—administered twice per week without interruption except in the case of disease progression or treatment-related toxicity—likely negatively impacts quality-of-life and medical economic issues not addressed by Reardon et al. These comments are not meant to diminish the significant efforts of Reardon et al in exploring a novel targeted agent in the treatment of recurrent GBM. Rather, they are intended to ask how new agents like cilengitide should be integrated, if at all, into the care and management of patients with GBM.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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