In contrast, imaging for *astrocytoma* was more accurate, and the reviewer stated that, "[a]ccuracy was better for untreated AA [anaplastic astrocytoma] where 7 of 8 images were accurate and one was underestimated."

In comments on the Sponsor's data on glioblastoma, the FDA reviewer referred to the problem that, "FDA and its outside experts do not believe that tumor shrinkage or increase can be adequately assessed … because of their irregular configuration. Thus tumor response and tumor progression cannot be used as the principal basis for approval."

At this point, the take-home lesson is that, when conducting a clinical trial on a solid tumor that has an irregular shape, the Sponsor should consider using, as a primary endpoint, an endpoint that does not require measurements of tumor area or tumor volume.

e. FDA Approves Drug for Indication of Astrocytoma, but Refused to Approve Drug for Indication of Glioblastoma

The *Medical Review* stated that, "[t]he FDA reviewers did not believe that accurate tumor measurements could be obtained in … glioma [glioblastoma multiforme] patients thus confounding determination of progression free survival … [b]ased on these considerations the FDA review team believed that Temozolomide should not be approved for the treatment of … Glioblastoma Multiforme patients."

In contrast, the FDA granted approval for temozolomide for treating astrocytoma. To this point, the *Medical Review* stated, "[t]he applicant is requesting … approval based on objective tumor response rate in patients … FDA reviewers felt that these response rates and response durations … along with a satisfactory safety profile where sufficient to grant … approval."

f. Unreliability of Objective Response, Where Tumor Size Measurements Are Not Accurate

FDA officials have warned about the problem of basing a clinical trial on objective tumor response, in the situation where tumor size measurements are not accurate. McKee et al. (71) warn that, "[t]he uncertainty of radiographic tumor assessment may make radiographic-based endpoints, such as response rate … unreliable. Advanced mesotheliomas, gastric cancers, and locally advanced pancreatic cancers are examples of tumors for which radiographic assessments of the tumor are unreliable and an assessment of OS [overall survival] is necessary."

With regard to measuring the size of glioblastoma tumors, FDA officials acknowledged that, "GBMs are morphologically heterogeneous tumors with varying amounts of edema, necrosis … [b]ecause of the infiltrating nature of GBMs, the **accurate measurement of tumor diameters** on MRI poses problems, as was evident in the current trial, in which the **concordance of MRI readings by two neuroradiologists was only about 50%**" (72).

g. Accelerated Approval

Please note that the Sponsor's clinical trials for both types of glioma (glioblastoma, astrocytoma) were submitted by way of the FDA's accelerated approval pathway. Accelerated

[71]McKee AE, et al. The role of U.S. Food and Drug Administration review process: clinical trial endpoints in oncology. The Oncologist 2010;15(Suppl. 1):13–18.

[72]Cohen MH, et al. FDA drug approval summary: bevacizumab (Avastin®) as treatment of recurrent glioblastoma multiforme. The Oncologist 2009;14:1131–8.