From the Editor

Central Nervous System Malignancies: What Next?

We know the future will outlast all of us, but I believe that all of us will live on in the future we make.

—Senator Ted Kennedy, December 1, 2008, 6 months after the diagnosis of a malignant brain tumor

One of the most devastating malignancies afflicting man is that of cancer in the central nervous system (CNS). Although that diagnosis in U.S. Senator Ted Kennedy raised its profile, the disease has largely hovered in the background—a predictable result of therapeutic disappointment. It is a disease whose outcome has not been substantially altered in 30 years, despite new molecular discoveries and numerous efforts to improve treatment. The experts brought together by Guest Editor Mark Gilbert in this CCR Focus highlight the new understanding of CNS malignancies and offer the prospect that we are at the threshold of a new era. Sequencing studies have identified mutations in many of the genes or upstream pathways that serve as coconspirators in other solid tumors, such as PTEN, p53, and Rb. Specific oncogenic drivers—a mutated and amplified EGF receptor, a mutated and amplified PDGF receptor, and mutated PI3K—have been found. Epigenetic aberrations have also been discovered—mutations in IDH1, IDH2, and the SWI/SNF chromatin regulator ATRX, occurring predominantly in lower-grade tumors; and mutations in the histone variant H3F3A in pediatric glioma. These are exciting discoveries that may offer new targets for clinical trials, but they as yet do not explain how distinctly poor the therapy for glioblastoma has been. One major effort has been the testing of antiangiogenic agents, in particular bevacizumab. Although its vascular or antipermeability properties may improve symptoms—not without value—an improvement in survival could not be demonstrated in randomized trials. As a result, some investigators are asking whether angiogenesis is a valid target while others are attempting to understand how glioblastoma circumvents this therapeutic approach. And, because in all oncologists "hope springs eternal," the progress and hope of immune therapies are now being brought to bear on CNS malignancies. Although immune-based therapies may evade resistance mechanisms that have thwarted small molecules, we must admit that we have ideas about drug resistance, but no actual data. Together, these CCR Focus articles point out the critical need for greater insights, robust data, novel drugs, and informative trials in CNS cancers. As with every CCR Focus, we hope to educate those interested but not expert in the field, and to inspire and encourage those working in the field.

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See all articles in this CCR Focus section, "Discoveries, Challenges, and Progress in Primary Brain Tumors."

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