Purpose:

In a *post hoc* analysis of the CATNON trial (NCT00626990), we explored whether adding temozolomide to radiotherapy improves outcome in patients with *IDH1/2* wildtype (wt) anaplastic astrocytomas with molecular features of glioblastoma [redesignated as glioblastoma, isocitrate dehydrogenase–wildtype (*IDH*-wt) in the 2021 World Health Organization (WHO) classification of central nervous system tumors].

Patients and Methods:

From the randomized phase III CATNON study examining the addition of adjuvant and concurrent temozolomide to radiotherapy in anaplastic astrocytomas, we selected a subgroup of *IDH1/2*wt and *H3F3A*wt tumors with presence of *TERT* promoter mutations and/or *EGFR* amplifications and/or combined gain of chromosome 7 and loss of chromosome 10. Molecular abnormalities including *MGMT* promoter methylation status were determined by next-generation sequencing, DNA methylation profiling, and SNaPshot analysis.

Results:

Of the 751 patients entered in the CATNON study, 670 had fully molecularly characterized tumors. A total of 159 of these tumors met the WHO 2021 molecular criteria for glioblastoma, *IDH*-wt. Of these patients, 47 received radiotherapy only and 112 received a combination of radiotherapy and temozolomide. There was no added effect of temozolomide on either overall survival [HR, 1.19; 95% confidence interval (CI), 0.82–1.71] or progression-free survival (HR, 0.87; 95% CI, 0.61–1.24). *MGMT* promoter methylation was prognostic for overall survival, but was not predictive for outcome to temozolomide treatment either with respect to overall survival or progression-free survival.

Conclusions:

In this cohort of patients with glioblastoma, *IDH*-wt temozolomide treatment did not add benefit beyond that observed from radiotherapy, regardless of *MGMT* promoter status. These findings require a new well-powered prospective clinical study to explore the efficacy of temozolomide treatment in this patient population.