The role of chemotherapy for newly diagnosed anaplastic gliomas, particularly when combined with radiotherapy, has long been unresolved. Over the past few decades, despite no conclusive data, study findings have suggested that the addition of nitrosourea-based chemotherapy to radiotherapy could be beneficial. The NOA-04 trial revealed that initial treatment with chemotherapy (either temozolomide or procarbazine, lomustine, and vincristine [PCV]) or radiotherapy alone yielded similar results. Survival of patients with anaplastic glioma has been recognised as being strongly dependent on the presence or absence of the favourable 1p/19q co-deletion. This discovery resulted in secondary analyses of US and European trials, revealing improved survival in patients with co-deleted tumours who received combined radiation and PCV chemotherapy. Separately, clear benefits were found with adding temozolomide to radiotherapy to treat newly diagnosed glioblastoma, which led to investigations of whether radiation plus temozolomide would benefit patients with non-co-deleted anaplastic gliomas (ie, anaplastic astrocytomas).

In The Lancet, Martin van den Bent and colleagues report interim findings from the CATNON trial, an ambitious international collaboration launched in 2005 and the first glioma study to base eligibility on a molecular marker. The trial was designed to assess the effects of temozolomide concurrent with, and adjuvant to, radiotherapy in patients with 1p/19q non-co-deleted anaplastic gliomas. A 2×2 factorial design, creating four treatment groups (radiotherapy alone or with 12 cycles of adjuvant temozolomide or radiotherapy with concurrent temozolomide, with or without adjuvant temozolomide) was selected to answer two questions: whether use of concurrent temozolomide improves overall survival irrespective of treatment with adjuvant temozolomide, and whether administration of adjuvant temozolomide improves overall survival irrespective of concurrent treatment with temozolomide. The interim analysis presented addresses the second question in 745 patients. A significant overall survival benefit was seen with adjuvant temozolomide (5-year overall survival 55.9%, 95% CI 47.2–63.8 vs 44.1%, 36.3–51.6 without adjuvant temozolomide; hazard ratio for survival 0.65, 99.145% CI 0.45–0.93). Additionally, median progression-free survival increased from 19 to 43 months. The overall survival curves diverged throughout the reported follow-up and, therefore, the benefit might increase with additional follow-up. Although we will need to wait several years for the first question to be answered, these interim findings suggest a new standard of care for patients with non-co-deleted anaplastic gliomas that no longer involves receiving monotherapy with radiation or chemotherapy as initial treatment.

Like many positive studies, CATNON raises new questions, and the issues it set out to address have evolved substantially during patient accrual and data maturation. The discovery of IDH1 or IDH2 mutations in roughly 80% of grade II and III diffuse gliomas in 2009 substantiated their importance as pathogenic features. More than 90% of glioblastomas do not have these mutations, and lower-grade gliomas with wild-type IDH typically have a clinical course much closer to that of glioblastoma than grade-matched gliomas with mutant IDH. Revisions in 2016 to the WHO brain tumour classification created a category of anaplastic astrocytoma, IDH-mutated. This classification notes that anaplastic astrocytomas have the highest incidence of wild-type IDH among grade II and III diffuse gliomas,
and most of these share molecular features with wild-type IDH glioblastomas. Thus, some of the patients enrolled in CATNON had tumours that biologically were fundamentally different from what would now be viewed as appropriate for this study population (ie, IDH-mutated anaplastic gliomas). Consequently, van den Bent and colleagues are analysing the benefits of adjuvant temozolomide separately in participants with IDH-mutated and wild-type IDH tumours, although, unfortunately, no data are yet available. To this point, a post-hoc analysis of the RTOG 9402 study suggested a benefit in overall survival with radiotherapy and adjuvant PCV chemotherapy in patients who had non-co-deleted, IDH-mutated anaplastic gliomas.8

Important questions remain on the timing and duration of treatment with temozolomide. The CATNON data do not yet elucidate the role of concurrent temozolomide in anaplastic glioma, and clinicians will have to decide whether to give this drug during radiotherapy, as is done in the treatment of glioblastoma. CATNON chose to administer adjuvant temozolomide for 12 cycles partly because, unlike in glioblastoma, not all patients received the drug concurrently with radiotherapy. Two studies of glioblastoma, however, have suggested that there is no benefit beyond six cycles after radiotherapy.9,10

The suggestion by van den Bent and colleagues that the similarities between low-grade and anaplastic gliomas warrant consideration of adjuvant temozolomide in the former, based on the CATNON results, might be a stretch. IDH-mutated low-grade and anaplastic glioma tumours form a biological continuum,11 but the CATNON data stratified by IDH status have not yet been analysed. Moreover, in low-grade gliomas, data from a phase 3 study support use of PCV chemotherapy after radiotherapy, with particular benefit being seen in IDH-mutated tumours.12 The relative activity of temozolomide versus PCV in all low-grade gliomas remains unclear, although given the challenges of comparative trials, the favourable side-effect profile of temozolomide might make it more popular until more effective agents are developed.

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I declare no competing interests.