Progress has been slow in improving survival in patients with glioblastoma, the most fatal and frequent malignant brain tumour. However, since a phase 3 clinical trial reported that use of temozolomide with and after radiotherapy was superior to radiotherapy alone, hopes have been raised for continued improvement, and as such, substantial steps were taken in 2010.

Standard care for patients with glioblastoma is temozolomide-based radiochemotherapy; however, median overall survival is still about 15 months. Many new agents have been tested alone or as add-ons to the temozolomide regimen for improving outcome. One striking example is cilengitide, a novel integrin inhibitor, for which phase 1 and 2 studies of its use as a single agent in recurrent glioblastoma had shown good safety profiles and promising antitumour activity.

Consequently, cilengitide was added to temozolomide with radiotherapy in a phase 1 and 2a study that showed that the combination was well tolerated, with median progression-free survival (PFS) and overall survival of 8 months and 16·1 months, respectively. These survival benefits were increased in patients who had tumours in which the O6-methylguanine-DNA methyltransferase (MGMT) promoter was methylated. Cilengitide is now being studied in a randomised phase 3 trial (the CENTRIC study) as first-line chemoradiotherapy for patients with methylated MGMT promoters. Examples of the use of targeted therapies are the randomised phase 3 trials testing bevacizumab, a humanised monoclonal antibody against vascular endothelial growth factor (VEGF), in patients with newly-diagnosed glioblastoma, undertaken by the Radiation Therapy...
Oncology Group (RTOG 0825 [NCT00884741]) and Roche (AVAglio [NCT00943826]), both of which are currently recruiting participants. These trials are based on the excellent overall response rate and PFS at 6 months (PFS-6) reported in the BRAIN study of bevacizumab for the treatment of patients with recurrent glioblastoma (long-term survival data were updated in 2010).3

Although the temozolomide regimen has antitumour activity, high-grade gliomas recur within a year, and treatment options are then limited. Temozolomide is a DNA alkylating agent that induces cytotoxic O6-methylguanine lesions in the DNA of tumour cells, which are effectively repaired by MGMT; in this way, the tumour cells eventually remove this cytotoxic DNA damage, leading to resistance to temozolomide. When repairing O6-methylguanine lesions, MGMT covalently accepts the methyl adduct to its active cysteine residue in a stoichiometric manner, thereby losing its enzymatic activity (that is the reason why MGMT is called a suicide enzyme); this process leads to a stage in which an increased dose of temozolomide might deplete MGMT activity and overcome temozolomide resistance. A phase 2 trial (the RESCUE study)4 of continuous dose-dense temozolomide in patients with recurrent glioblastoma previously treated with a standard temozolomide regimen showed that continuous dose-dense temozolomide was well tolerated and resulted in a PFS-6 of 23.9%. Patients who had early recurrent glioblastoma during temozolomide cycles, and those who relapsed after completing adjuvant temozolomide, had higher PFS-6s of 27.3% and 35.7%, respectively, than did those who recurred on temozolomide for more than six adjuvant cycles, who had a PFS-6 of only 7.4%. These findings suggest that previous heavy exposure to temozolomide might hamper the efficacy of this strategy. Interestingly, PFS-6s were similar regardless of the methylation status of the MGMT promoter in these patients, perhaps suggesting that this regimen depletes MGMT. Whether continuous temozolomide is better than other dose-dense temozolomide regimens, such as the 7 days on and 7 days off (7/7) or the 21 of 28 days (21/28) regimen in patients who were treated with concurrent temozolomide and radiotherapy, are ongoing and will be reported soon.

Accurate determination of the efficacy of new therapies needs well designed, widely accepted criteria for assessing tumour response and progression. The Macdonald criteria, using two-dimensional tumour measurements of the contrast-enhancing component of tumours, have been the gold standard.1 However, there is increasing evidence that these criteria might be insufficient for assessing outcomes after radiochemotherapy (because of "pseudoprogression"), or after antiangiogenic therapy (because of "pseudoresponse"), and in patients with tumours that do not have a contrast-enhancing component. Therefore, the international Response Assessment in Neuro-Oncology (RANO) working group has been developing updated criteria to be used in clinical trials.6 These criteria include definitions and guidance for the treatment of patients with measurable and non-measurable disease and those with multiple lesions, and strict rules for determining first progression and eligibility for enrolment in clinical trials; they also provide a more precise definition of treatment response, which incorporates MRI, non-enhancing disease, and clinical factors. The criteria will evolve to include diagnostic and neurocognitive measurements.

The Cancer Genome Atlas (TCGA) Research Network is generating a comprehensive catalogue of genomic abnormalities in glioblastoma.7 In 2010, gene-expression profiling of 200 glioblastoma samples and two healthy brain samples identified four molecular subtypes: classic, proneural, neural, and mesenchymal, with differing genetic lesions and clinical behaviour.8 Epigenetic analysis of methylation alterations in 272 glioblastomas identified a distinct molecular subgroup with hypermethylation at a large subset of genetic loci, thus named glioma-CpG island methylator phenotype (G-CIMP).9 This feature, perhaps combined with other molecular characteristics, might prove to have diagnostic and prognostic value in future studies.

Patients with primary CNS lymphoma (PCNSL), a rare malignant brain tumour affecting elderly people, have poor survival, even after high-dose methotrexate (HD-MTX) followed by whole-brain radiotherapy (WBRT). Although this regimen may extend survival from 12–18 months to 30–60 months, it is associated with intolerable long-term neurotoxic effects. A
randomised phase 3 clinical trial in 551 patients with PCNSL investigated the omission of WBRT from the first-line HD-MTX-based chemotherapy. Although PFS was longer in patients treated with WBRT (but not statistically significant), median overall survival was similar in both treatment groups, with a lower incidence of treatment-related neurotoxic effects in complete responders when WBRT was omitted or delayed. These findings suggest that the gain of PFS by radiotherapy needs to be balanced against potential delayed cognitive dysfunction.

Neuro-oncology has become a prime example of a multidisciplinary field, which includes novel techniques in surgery, radiotherapy, targeted chemotherapies, drug delivery, and molecular genetics for a concerted onslaught on these devastating diseases. Achievements in bringing these new approaches into clinical trials over the past few years, especially in 2010, have shown acceleration towards truly personalised medicine that would previously not have been possible. Many of these trials are accruing patients now and will soon report their findings. We can look forward to these findings with great anticipation and the widely held conviction that these diseases can be beaten.

Motoo Nagane
Department of Neurosurgery, Kyorin University Faculty of Medicine, Mitaka, Tokyo 181-8611, Japan
nagane-nsu@umin.ac.jp
I declare that I have no conflicts of interest. I thank Prof Webster K Cavenee (Ludwig Institute for Cancer Research, San Diego, CA, USA) for critical reading of the commentary.