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**Congress Report: ASCO 2011 - The Neurooncology Perspective**

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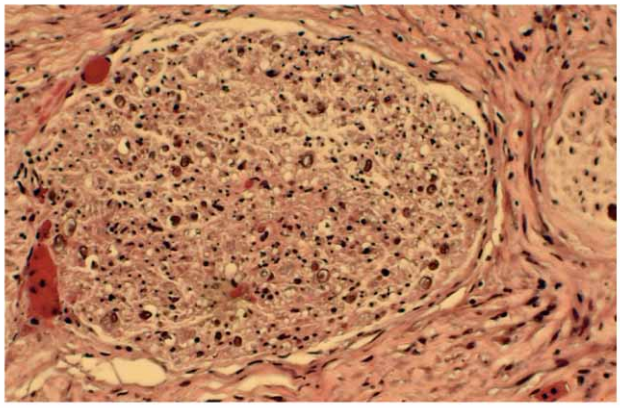

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# Congress Report: ASCO 2011 – The Neurooncology Perspective

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## RTOG-0S25: The Standard Remains!

We expected another brain tumour focus for the ASCO 2011 meeting, following the remarkable success of the EORTC 26981/22981/NCIC CE.3 trial in 2004. RTOG-0525/EORTC 26052 (http://clinicaltrials.gov, NCT00304031), the largest brain tumour trial ever performed (abstract 2006) aimed at demonstrating that the intensification of temozolomide maintenance treatment of glioblastoma is superior to the standard of care. The data were presented by the principal investigator, **Mark Gilbert, MD**, from the MD Anderson Cancer Center in Houston on behalf of the RTOG, the leading cooperative group, in the oral abstract session on June 5, 2011.

The rationale of this trial was based on several studies that had shown a prolonged exposure to temozolomide to deplete O6-methyl-guanyl-methyl-transferase (MGMT) activity in blood cells. It was believed that this process could potentially increase the antitumour activity of the drug in patients with putatively MGMT-active (unmethylated) tumours. Additionally, patients with formal sensitivity to the drug (methylated promoter) should benefit from the about 2.1-fold exposure of temozolomide. In brief, both ideas were proven to be wrong. Overall survival for arm 1 (standard temozolomide) was 16.6 months and 14.9 months for the dose-dense temozolomide arm. Those patients with a methylated MGMT promoter (30 %) had a significantly better progression-free (PFS) and overall survival (OS). In fact, the known depletion of MGMT activity in blood cells may just have led to the increased toxicity of the dose-dense therapy arm.

## MGMT and Beyond: Steps Towards Personalised Medicine

Although this trial clearly failed the primary endpoint, it is important and will guide future research and trial development. First, the neurooncology community has proven to manage the successful conduct of a large trial with prospective tissue collection and central molecular testing of MGMT. Second, there is a clear answer to a relevant clinical hypothesis. Third, due to the large amount of fresh-frozen tissue in addition to the paraffin-embedded samples, **Ken Aldape, MD,** could present first data on a new molecular risk classification with 4 groups spanning a median survival from 12–26 months. The biomarkers evaluated were isocitrate dehydrogenase 1 mutations, the glioma-CpG island methylator phenotype, a microarray-based mRNA panel with 17 candidates, and a novel MGMT promoter methylation assay (abstract LBA 2000).

Two other interesting abstracts on the topic of MGMT were presented by the German Glioma Network and the group in Los Angeles. **Michael Weller, MD,** presented a high frequency of > 50 % MGMT-methylated tumours in a cohort of patients > 70 years of age. This high frequency contrasts with the poor prognosis in this age group. Interestingly, the study indicated a predictive role of the MGMT methylation status for the PFS to chemo- and/or radiotherapy (abstract 2001). Lai et al used a combined immunohistochemical (IHC) and promoter methylation assessment approach and found the best prognostic values for the combination of IHC (with a cut-off at 30 % staining) and methylation assessment, which preferentially should be done with bisulfite sequencing, as compared to either marker alone (abstract 2003).

## Glioblastoma: No Promising New Agent Ahead

The Eli Lilly trial S039 in patients with newly diagnosed glioblastoma without methylation of the MGMT promoter presented by the Heidelberg group (abstract 2007) looked at the radiosensitizing properties of the protein kinase C beta inhibitor, enzastaurin. Despite some encouraging results in the PFS rate at 6 months (PFS-6) the trial did not reach its primary endpoint of a PFS-6 of 55 % with the observed rate of 51.8 % (confidence interval: 38.1–63.9). Here, the question emerges how much mono-compound activity is necessary to dare performing a trial even if the main rationale is to demonstrate a radiosensitizing effect. **Dr Eisenstat** presented trial data of yet another approach to target EGFR in recurrent malignant glioma (abstract 2010). Afatinib (BIBW 2992), an irreversible erbB family blocker, was studied alone or in combination with a dose-dense temozolomide regimen for 21/28 days. The control was 21/28 days temozolomide only. Interestingly, the dose-dense temozolomide regimen was quite active with a progression-free survival rate at 6 months (PFS-6) of 22 % in the mono-compound arm and 17 % in the combination with afatinib. Afatinib alone with 3 % did not produce a meaningful PFS-6. Hence, the major outcome of this trial and other activities in recurrent glioma may be that dose-dense temozolomide does not have a role in the first-line but potentially second-line treatment.

## Debate over PCNSL

The Berlin group aimed at presenting prognostic factors for the PCNSL-SG1 trial (abstracts 2004 and 2005). Although of interest, their approach to leave out the impact of therapy as potential prognosticator raised considerable concern and led

to helpful suggestions by **Lisa de Angelis** on how to improve the analysis.

## Conclusions

In summary, the talks but also other presentations at this year's ASCO demonstrated considerable activity in the field. Compared to earlier years, the slots for neurooncology-related topics and presentations are getting wider. The relevance of biomarker assessment and new drug development specifically for brain tumours and conducted by brain tumour specialists is largely recognized. Despite some negative trials and specifically the disappointment with the RTOG0525 trial the community is optimistic that we will have another "Brain Tumour ASCO" in the near future.

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