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Nimotuzumab and radiotherapy in children and adolescents with brain stem glioma: preliminary results from a Phase II study

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Background: Several EGFR-targeting products have been approved worldwide for the treatment of different tumor localizations. Nimotuzumab is a humanized, anti-EGFR monoclonal antibody registered in several countries for the treatment of advanced head and neck cancer and recurrent glioma. A Phase II, open label clinical trial was designed to evaluate the progression-free survival rate at 6 months, as well as the overall survival, of children and adolescents newly diagnosed with brain stem gliomas treated with nimotuzumab in combination with external beam radiotherapy
Material and Methods: Newly diagnosed patients with clinical and radiological evidence of brain stem tumor, aged between 3−18 years, Karnofsky >40, adequate renal, liver and hematological functions, were eligible. Nimotuzumab was administered at a dose of 150 mg/m^2 weekly for 12 weeks concomitantly with external beam radiotherapy (induction therapy). Treatment consolidation consisted of similar doses of nimotuzumab at a 2-week interval except in cases of significant deterioration of the performance status. Tumor evaluation was performed using MRI every 12 weeks.
Results: Ten patients have been enrolled in this study to date. After completing induction therapy, 8 patients were evaluable for response, 7 patients achieved stable disease (SD), while 1 patient progressed. After 24 weeks, 6 patients were evaluable and all of them showed at least disease stabilization. At the 48 week evaluation there were 3 evaluable patients and 2 of them had partial responses. The most frequent adverse event was grade 1−2 mucositis. None of the patients developed skin rash. The study is ongoing and updated results will be presented.
Conclusions: Nimotuzumab is safe. Preliminary results suggest efficacy of the humanized anti-EGFR MAb in combination with radiotherapy in children and adolescents newly diagnosed with brain stem glioma. Trial continuation is warranted.

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Combined treatment with antiangiogenic and anti-EGFR agents in glioblastoma

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Background: Malignant gliomas are the most common and aggressive primary brain tumors. Sunitinib is an oral, small-molecule, receptor tyrosine kinase inhibitor (TKI), simultaneously targeting platelet-derived growth factor receptors (PDGFR) and vascular endothelial growth factor receptors (VEGFR). Lapatinib is an ATP-competitive dual TKI for epidermal growth factor receptor (EGFR) and HER2/neu (ErbB-2). Our aim was to assess *in vitro* the effect of sunitinib and lapatinib applied either alone or in combination on proliferation, apoptosis, invasion and release of MMP-2 into the culture medium of U87 and M059K human glioblastoma cell lines. The effect of lapatinib in the formation of EGFR-integrin b1 complex was also assessed.
Material and Methods: U87 and M059K cells were cultured as recommended by ATCC. Cells were treated with Sunitinib and Lapatinib at various concentrations. The proliferation of cells was determined by 3-[4,5-dimethylthiazol-2-yl]-2,5-dimethyltetrazolium bromide (MTT) assay. Apoptosis/necrosis was evaluated with Annexin V/iodised propidium binding assay. Migration assays were performed in 24-well microchemotaxis chambers, using uncoated polycarbonate membranes with 8 μm pores. The release of MMP-2 into the culture medium of cells was measured by zymography, whereas immunoprecipitation and western analysis were conducted so as to detect the formation of EGFR-integrin complex.
Results: The application of both agents, either alone or in combination, was associated with a statistically significant reduction in proliferation and chemotactism in both cell lines. An induction of apoptosis in both cell lines after the application of the agents tested, either alone or in combination was also observed. MMPs levels were down-regulated in M059K cells, especially when the combination of both agents was added. There was no change of MMPs levels in U87 cells. Finally, lapatinib intercepted the formation of EGFR-integrin b1 complex in U87 cells.
Conclusions: Our results bolster the argument that lapatinib and sunitinib may exert a strong inhibitory effect on both cell lines. Combinational dosing of these agents has a better and stronger effect in the above mentioned parameters than each one of them alone.

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Addition of bevacizumab to the multi-modality standard of care in patients with newly diagnosed glioblastoma: a phase III trial

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Background: Glioblastoma multiforme (GBM) is a highly vascularised tumour that over expresses vascular endothelial growth factor (VEGF), a key mitogen for astrocytes and a mediator of tumour angiogenesis. Preclinical data in glioma models suggest benefits of targeting VEGF or its receptors on tumor control, with supra-additive effect when combined with radiation (RT). Although a significant survival benefit has been shown with the current frontline standard of care (SoC) consisting of surgery then concurrent RT and temozolomide (TMZ) followed by maintenance TMZ, further improvements still need to be made as GBM remains a disease with a high unmet medical need. Bevacizumab (BV; Avastin®), a humanised monoclonal antibody that inhibits VEGF, has shown clinical benefit in relapsed GBM when used alone or in combination with irinotecan: overall survival (OS), progression-free survival (PFS) and objective response rates compare favourably with historical controls. Steroid use was decreased and toxicity was manageable. The activity of BV in relapsed GBM and preliminary data in the first-line setting provides a strong rationale for evaluating its activity in patients with newly diagnosed GBM (nd-GBM) when added to the current SoC in a prospective, randomised trial.
Methods: Study BO21990 (AVAGLIO) is an ongoing randomised, double-blind, placebo (PBO)-controlled, phase III study that aims to recruit 920 patients. Patients are eligible if aged ⩾18 year with histologically confirmed nd-GBM and a WHO performance status of ⩽2. Study treatment comprises concurrent RT (60 Gy, 2 Gy fractions 5 days/wk) and oral TMZ (75 mg/m^2/day for a maximum of 49 days) plus either IV BV (10 mg/kg q2w) or PBO for the first 6 wks of treatment. After a 28 day treatment break, patients continue on maintenance TMZ (150–200 mg/m^2/day for the first 5 days of a 28 day cycle) and either BV (10 mg/kg q2w) or PBO for 6 cycles. Patients then continue on BV (15 mg/kg q3w) or PBO until disease progression or unacceptable toxicity. Co-primary endpoints are OS and PFS. Secondary endpoints are survival at 1 and 2 years, QoL and tolerability.
Results: An overview of the preclinical and preliminary clinical data that supports the evaluation of BV in patients with nd-GBM and study design details for BO21990 will be presented.
Conclusions: This phase III study will investigate the efficacy and safety of BV when added to the current SoC in nd-GBM.
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Trabedersen (AP 12009) in recurrent or refractory high-grade glioma patients: results of a phase IIb study and outlook

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Background: TGF-β2 plays a significant role in proliferation, migration, and immunosuppression. Trabedersen is a TGF-β2-specific inhibitor. Aim of the Phase IIb study was to evaluate efficacy and safety of trabedersen compared to standard chemotherapy in recurrent/refractory high-grade glioma (HGG) patients.
Methods: Phase IIb study G004 (NCT00431561; sponsor: Antisense Pharma, GER) was a multinational, open-label, randomized and active-controlled dose-finding study. Two doses of trabedersen (10 μM/80 μM) were compared to standard chemotherapy (TMZ or PCV) with regard to response rate, survival, and safety. Patients with recurrent/refractory HGG (AA, WHO grade III and GBM, WHO grade IV) were randomized into the