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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.
This trial is sponsored by F. Hoffman-La Roche Ltd.

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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

3 treatment groups. 134 patients received study medication (96 GBM, 38 AA). Trabedersen was administered intratumorally for up to 11 treatment cycles (7d on, 7d off).
Results: In both trabedersen groups, trabedersen treatment led to long-lasting remissions in AA and GBM patients with tumor remissions exceeding by far the treatment period.
In AA patients, 10 μM trabedersen was superior to standard chemotherapy for progression rate (PR, $p = 0.0032$) and overall response rate (CR+PR, $p = 0.034$) at 14 months. About twice as many AA patients from the 10 μM trabedersen group survived 2 years compared to standard chemotherapy (83.3% vs. 41.7%, $p = 0.09$). A median overall survival benefit of 17.4 months was found for 10 μM trabedersen-treated AA patients compared to standard chemotherapy.
In GBM patients, trabedersen was as efficacious as standard chemotherapy and patients showed a long-term reduction in the risk to die. In a subgroup of GBM patients with favorable prognostic factors (age $\leqslant$ 55yr, KPS>80%) the 24-month survival rate was favorable for the 10 μM trabedersen compared to the standard chemotherapy group (44.4% vs. 13.3%).
Conclusions: The Phase IIb study showed that trabedersen as monotherapy had a higher efficacy than standard chemotherapy in AA patients and was as efficacious or even better as standard chemotherapy in GBM patients. Based on these results, the Phase III study G005 SAPPHIRE was designed as a confirmatory, randomized, multinational, active-controlled study in patients with recurrent/refractory AA. Main objective is to evaluate progression and survival rates of 10 μM trabedersen compared to standard chemotherapy (TMZ or BCNU). The study has started and patient enrollment is ongoing. A Phase III study in GBM patients is in preparation.

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Cisplatin and Temozolomide in heavily pretreated and poor performance status (PS) patients with temozolomide refractory glioblastoma

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Background: There is pre-clinical evidence of synergism between cisplatin and temozolomide due to higher inhibition of O^6-alkyl-guanine-alkyltransferase (*AGAT*), an enzyme involved in the mismatch repair system. In earlier clinical studies this combination, used as first-line treatment, appeared active against glioblastomas and so it is now regarded as second-line treatment. Considering heavily pretreated and poor status population, the primary end point of the present phase II study was response rate and toxicity evaluation while secondary end points included progression-free survival at 6 months (PFS-6).
Patients and Methods: we enrolled 19 heavily pretreated patients (PTS) with temozolomide refractory glioblastoma (most patients already treated with second surgery, Carmustine Wafer, first and second-line chemotherapy). Median age was 62 (range 18−79); male/female = 11/8; Median PS was 2 (PS = 1 in 2 PTS, PS = 2 in 13 PTS and PS = 3 in 4 PTS). Each patient received cisplatin at the dose of 75 mg/m^2 on day 1 and temozolomide at the dose of 150 mg/m^2 on days 1 to 5 every 21 days until progression or major toxicity.
Results: a total of 79 cycles were delivered (median for each patient = 4). Toxicity was manageable and mostly of grade 1−2: haematological, gastroenterological (nausea and vomiting) and fatigue. We obtained an overall response rate of 29.4% with no complete response. The disease control rate (responses plus stabilizations) was of 64.7%. The median time to progression was of 3.8+ (range 0.7−19+) months and the PFS-6 was of 32%, encouraging considering our heavily pretreated and poor PS population.
Conclusion: the combination of temozolomide and cisplatin is safe and effective in the treatment of refractory temozolomide glioblastomas even in heavily pretreated patients with poor PS.

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The prognostic significance of volumetry in patients with glioblastoma multiforme (GBM)

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Background: The importance of tumor volume as a prognostic factor in GBM is highly controversial. In this study a computer-based application was used in order to assess several tumor-related volumes from hard copies and a survival analysis was conducted in order to evaluate the prognostic significance of pre- and postoperative volumetric data in patients with GBM.
Materials and Methods: We prospectively analyzed 65 patients suffering from GBM who underwent radiotherapy with concomitant and adjuvant temozolomide. For the purpose of volumetry T1 and T2-weighted MR sequences were used, acquired both pre- and post surgically. Since the MR scans were not available in electronic format, but only in hard copies, they were digitized, by means of a commercial high resolution scanner. Before determining tumor volume with our specialized software, images were converted to the widely used DICOM format with a different computer application. The volumes measured on preoperative MRIs were necrosis, enhancing tumor and edema (including the tumor) and on postoperative ones, net enhancing tumor and net edema. Age, performance status (PS) and type of operation were also included in the multivariate analysis. Overall survival (OS) and progression free survival (PFS) were measured from the time of operation.
Results: In the univariate Cox analysis, volume of postoperative enhancing tumor was significant for OS ($p = 0.001$) and volume of preoperative necrosis was significant for PFS ($p = 0.023$). In the multivariate analysis preoperative T2 abnormality was found significant for OS ($p = 0.023$), preoperative necrosis for PFS ($p = 0.020$) and postoperative enhancing tumor for both OS and PFS ($p < 0.001$ and $p = 0.042$, respectively). Furthermore, the multivariate analysis confirmed the importance of age and PS in PFS and OS of patients.
Conclusions: Our findings implicate that both pre- and postoperative volumetric data play a significant role in the prognosis of patients with GBM. Further studies are definitely required in order to clarify the importance of these factors.

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Short course of hypofractionated radiotherapy and concomitant temozolomide in patients affected with glioblastoma with V-VI prognostic classes – a pilot study

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Purpose: To evaluate outcome and toxicity profile of glioblastoma (GB) patients treated with hypofractionated radiotherapy (HPF) (Roa 2004) and concomitant Temozolomide (TMZ) (Stupp 2005) in unfavorable V and VI prognostic classes (Mirimanoff 2006).
Materials and Methods: We are monitoring clinical outcome, survival, and acute and long term toxicities of patients treated with HPF scheme (40 Gy in 15 fractions, 2.66 Gy/fraction) concomitantly with TMZ (75 mg/m^2 for 2 patients and 85 mg/m^2 for 8 patients) for 21 days, followed by adjuvant TMZ (150−200 mg/m^2). Median progression free survival time (MPFST) and median survival time (MST) are calculated from surgical procedure.
Results: Eleven patients have been recruited till 4/2009, 10 of them are able to be validated (6 men and 4 women; median age of 69 years). Classification according to the RTOG/EORTC recursive partitioning analysis was as follows: class V for 4 patients and class VI for 6 patients. Surgery consisted of partial resection (n = 3) or only biopsy (n = 7). Gene promoter MGMT methylation was observed in 7 cases.
Median survival time was 19.8 weeks (r 4.8−69.3). MPFST was 12.9 weeks (r 4.8 to 45.14 w). Acute toxicity was mild. Only 4 patients had alopecia grade 2, and one case had pneumonitis grade 3. Three patients died during treatment because of progression disease. No long term neurological complications have been found. Steroid dependence was observed in 7 patients. After progression, 3 patients were entered in schedule of CPT-11 and bevacizumab, with MRI and SPECT monitoring.
Conclusions: Hypofractionated RT concomitantly with temozolomide can be used for selected poor prognostic GB patients to reduce the overall treatment time, without apparent increased toxicity. Improvement of overall survival in comparison with other series seems not be reached. This study reflects the bias of other trials which do not show the real daily clinical practice. Methylation of MGMT gene promoter is not related with PFS and OS, and poor medical conditions are more important than other factors.