Title

P09.59 Phase 2 trial of palbociclib in adult patients with recurrent Rb positive glioblastoma

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financed-health care system and favoring second-line treatment for recurrent glioblastomas was associated with significantly better overall survival.

P09.57 CLINICAL TRIALS OF VAL-083 IN PATIENTS WITH CHEMORESISTANT GLIOBLASTOMA

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Glioblastoma (GBM) is the most common CNS tumor. Patients with recurrent GBM have few treatment options and dismal prognosis. O^6-methylguanine-DNA-methyltransferase (MGMT) is correlated with resistance to standard of care treatment with temozolomide and poor patient outcomes. Dianhydrogalactitol (VAL-083) is a bi-functional alkylating agent with a distinct mechanism-of-action differentiating it from other alkylating agents used in the treatment of GBM and other CNS tumors. VAL-083 readily crosses the blood-brain barrier and accumulates in brain tumor tissue. VAL-083 has demonstrated MGMT-independent cytotoxicity in multiple GBM cell-lines and cancer stem cells and is able to overcome TMZ-resistance *in vitro* demonstrating a different mechanism of action. In multiple prior NCI-sponsored clinical trials VAL-083 showed promise against CNS tumors. We recently concluded a phase I/II clinical trial studying VAL-083 in recurrent GBM patients failing temozolomide and bevacizumab, and data suggests a potential for VAL-083 to offer clinically meaningful survival benefits in patients who have failed or are unlikely to respond to currently available chemotherapeutic regimens. In the phase I portion of the trial, VAL-083, 40 mg/m^2/day x 3 every 21 days was well-tolerated and this dose was selected for study in the phase II expansion phase. We are initiating multiple clinical trials targeting adult patients with chemoresistant GBM due to MGMT expression. Enrollment is anticipated to be initiated in early 2017. These trials include i) a pivotal, randomized Phase 3 study measuring survival outcome compared to "physician's choice" control, which, if successful, would serve as the basis for a New Drug Application (NDA) submission for VAL-083. The control arm will consist of a limited number of salvage chemotherapies currently utilized in bevacizumab-failed GBM. ii) A single-arm, biomarker-driven, Phase 2 study to determine if treatment of MGMT-unmethylated recurrent GBM with VAL-083 improves overall survival at 9 months, compared to historical control in bevacizumab-naïve patients (clinicaltrials.gov identifier: NCT02717962). iii) A single arm Phase 2 study to confirm the tolerability of DelMar's dosing regimen in combination with radiotherapy and to explore the activity of VAL-083 in newly diagnosed MGMT-unmethylated GBM patients whose tumors are known to express high MGMT levels. The results of these studies may support a new treatment paradigm in chemotherapeutic regimens for the treatment of GBM. Enrollment updates and study design details will be presented at the meeting.

P09.58 QUALITY OF RANDOMIZED CONTROLLED TRIALS REPORTING IN THE TREATMENT OF ADULT HIGH GRADE GLIOMAS

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INTRODUCTION: Randomized Controlled Trial (RCTs) is the gold standard to objectively assess the effect of a treatment. The RCTs methodology must be particularly rigorous to achieve strong evidence of efficiency. To help improve the quality of RCTs, a group of experts established a list of recommendations, adopted by most international journals, called the CONSORT (CONsolidated Standards of Reporting Trials) Statement. First published in 1996, it was actualised in 2001 and 2010. In this study, we assessed the implementation of the CONSORT Statement criteria in the field of adult high grade gliomas. We also aimed to identify criteria associated with higher quality of RCTs. METHODS: We searched PUBMED to retrieve all RCTs concerning high grade gliomas published between the 1st January 1990 and the 1st March 2016. The quality of these RCTs was assessed by completing a modified CONSORT Score containing 33 items. This work was done independently by two investigators and every discordance was resolved by consensus. We also extracted data that seemed relevant to assess the quality of RCTs. RESULTS: Eighty-four published RCTs were identified. The median CONSORT Score was 19 (range: 3-30). Items were not equally reported and items regarding the method of randomization, the blinding or the accessibility of the protocol were reported in less than 25% of RCTs which could raise important biases and led to inappropriate interpretation of the results. However, the CONSORT Score constantly improved over the years. Before the onset of the CONSORT Statement in 1996, the median CONSORT Score was 13 (range: 4-19) whereas it was equal to 18 (range: 3-26) for the period 1996-2004 and equal to 22 (range: 6-30) after 2005. A higher CONSORT Score was observed when RCTs were published in journal with impact factor above 10 (24 vs 17, p<0.001). RCTs that enrolled more than 200 patients had a significantly higher CONSORT Score (20.6 vs 16.4, p=0.004). CONCLUSION: This study demonstrated a continuous improvement over the years of the CONSORT Score of published RCTs in the field of high grade gliomas. We identified three factors associated with a better report of RCTs: the date of publication, the impact factor of the journal and the number of patients included in the study.

P09.59 PHASE 2 TRIAL OF PALBOCICLIB IN ADULT PATIENTS WITH RECURRENT RB POSITIVE GLIOBLASTOMA

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Alterations in the CDK4/6 – RB signaling pathway are common causes of dysregulation of the cell cycle in many cancers, including glioblastoma. Palbociclib is an oral, highly selective, reversible inhibitor of CDK4/6, which leads to phosphorylation of RB and cell-cycle arrest. In a two-arm study, we evaluated the efficacy and safety of palbociclib in patients with recurrent glioblastoma. Notable eligibility criteria included confirmation of RB proficiency by IHC; ≤ 3 relapses; KPS ≥ 60; secondary glioblastomas were included; there were no limitation on prior treatments including bevacizumab. Patients were administered oral palbociclib 125 mg daily for 21 consecutive days followed by a 7 day break. Arm 1 planned for 15 patients to receive palbociclib for 7 days prior to indicated surgical resection for progression, followed by palbociclib. Arm 2 planned for 15 patients to receive palbociclib without additional resection. The primary objective was PFS-6, which was hypothesized to be 30% in this heavily pretreated population, and null hypothesis of 10%. Secondary objectives of toxicity, OS, and ORR. Exploratory results included biomarker assessment and pharmacodynamic effects for the surgical Arm 1 patients. A total of 22 patients were enrolled; 6 on Arm 1 and 16 on Arm 2. Median age for all arms was 47.5 years old (range 23 – 78 years old); 54% (12 patients) were male; and the median KPS was 90 (range 60 – 100). Palbociclib was started at first recurrence in 50% (11 patients – 3 in Arm 1 and 8 in Arm 2) of patients; at second recurrence in 36% (8 patients – 3 in Arm 1 and 5 in Arm 2); and at third recurrence in 14% (3 patients, all in Arm 2). Bevacizumab had previously been used in 77% (17 patients – 4 in Arm 1 and 13 in Arm 2) of cases. The trial was stopped early secondary to futility, with 95% (18 of 19) evaluable patients progressing within 6 months of intiating treatment. Four samples were available for immunohistochemistry for Rb and Ki67. There were no consistent changes in Rb expression or cell proliferation when compared to samples from diagnosis. Median progression free survival for all patients was 5.14 weeks (range 5 days – 142 weeks) and median overall survival was 15.4 weeks (range 2 – 274 weeks). Two patients (10%) had treatment related AEs that were grade ≥3. In this trial, palbociclib did not appear to have been an effective treatment for recurrent glioblastoma. However, this was a heavily pretreated patient population and targeting the CDK4/6 pathway may deserve further exploration.

P09.60 DETERMINATION OF DIFFERENT TUMORS REGIONS BY QUANTITATIVE MRI METHODS IN GLIOBLASTOMA

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BACKGROUND: Recently, many innovative MRI methods were generated to visualize different physiological and tumor biological aspects like the tumor microenvironment including the tumor oxygenation. In this study we want to generate diverse reference ranges of tumor regions in untreated glioblastoma patients. Standard values of quantitative MR imaging in these patients do not yet exist. METHODS: In this prospective study, we included 52 patients with a cerebral mass lesion who are radiologically suspicious for glioblastoma (GBM). Before patients underwent histological validation they received a conventional and a quantitative MRI (qMRI). The diagnosis was proven by stereotactic biopsy. Different areas of the presumably normal brain or the tumor were selected and the average value of the certain area was detected. RESULTS: Mean values of quantitative T1 und T2 maps in milliseconds (ms) were determined in 35 histopathologically proven GBM cases. Therefore, reference ranges for different areas (enhancing tumor, peritumoral edema, necrosis and contralateral, healthy control region) were recorded. We detected significantly prolonged qT1 and qT2 relaxation times in all tumor regions compare to the healthy control region. CONCLUSION: With our data different regions of the tumor are distinguishable by quantitative values. Correlations with histopathologic analysis are ongoing.