infection. Interestingly, plaque formation and syncytial fusion, which are characteristic for melanoma VZV replication, rarely occurred within glioma cell lines. Cell cultures harvested from normal brain specimens also exhibited ORF63/ORF68 expression but showed delayed single cell death (16±4 days after VZV infection). Interestingly, besides established VZV infected melanoma cells, permissive VZV replicating hMSCs have also been highly suitable for cellular vehicles in glioma cell infection.

Conclusion: Wild-type VZV efficiently replicates within glioma cell cultures causing broad oncolytic cell death in vitro. The underlying mechanisms causing infections devoid of characteristic plaque formation are still unknown. Since hMSCs are known to have an intrinsic tumor cell tropism, autologous VZV-replicating hMSCs could be applicable as cellular vehicles for local oncolytic glioma cell infection. Further investigations have to address sufficient glioma cell selectivity in VZV replication with respect to the normal brain parenchyma.

O19. A MULTICENTER STRATIFIED PHASE II STUDY OF CETUXIMAB FOR THE TREATMENT OF PATIENTS WITH RECURRENT HIGH-GRADE GLIOMA

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Background: An increased copy number and mutation of the epidermal growth factor receptor (EGFR) gene are frequently found in high-grade gliomas (HGG). We investigated the activity of the EGFR-blocking monoclonal antibody cetuximab (Erbitux) for the treatment of patients (pts) with recurrent HGG following surgery, RT, and chemotherapy.

Methods: Eligible adult pts were treated with cetuximab (400 mg/m^2 2 h i.v. on d1 and weekly 250 mg/m^2 1 h i.v. thereafter). Pts were stratified in 2 treatment arms according to the amplification status of the EGFR gene of their high-grade glioma (determined by fluorescence in situ hybridization on archival tumor material).

Results: Between May 2005 and December 2007 a total of 55 pts with performance status 0–2 initiated treatment with cetuximab (28 pts with and 27 pts without an increased EGFR copy number, 17F/38M, median age 53 years [range 32–73]). Cetuximab was generally well tolerated. During a total of 765 treatment weeks the most frequent treatment-related adverse events were: skin toxicity (grade 2, n=12; grade 3, n=5), thrombocytopenia (grade 2, n=1; grade 3, n=2), confusion/diminished consciousness (grade 3, n=4 pt), lymphopenia (grade 4, n=1), infusion related allergic reaction (grade 2, n=1), intratumoral hemorrhage (grade 2, n=1), diarrhea (grade 2, n=1), and fatigue (grade 2; n=3). A dose reduction of cetuximab (to 200 mg/m² weekly) was necessary in 3 pts. After a median follow-up of 17 months, 8 pts are alive (4 are still receiving cetuximab) and 47 pts have died. The disease control rate (DCR) was 36% (3 pts [5.5%] had a PR and 16 pts [29.1%] had SD); 36 pts (65.4%) had PD. The median PFS was 1.9 months (95% CI 1.6–2.2); median OS was 5.0 months (95% CI 4.4–5.7). The 6-month PFS and OS rates were 8.7 % and 35%, respectively. No significant correlation was found between EGFR amplification and DCR or survival. Whereas PFS was <5 months in 49/54 of pts (91%) with a follow-up of >5 months, a subgroup of 5 pts (9%) have a PFS of >9 months (range 9.5 to >18.5). This subgroup consisted of 4 pts with de novo glioblastoma (3 without and 1 with EGFR amplification) and 1 pt with an anaplastic astrocytoma with EGFR amplification.

Conclusions: Cetuximab as a single agent was safe and well tolerated in this population of pretreated patients with recurrent HGG. Durable disease control was observed in a small subgroup of patients but was not predicted by EGFR amplification at initial diagnosis.

O20. PHASE II STUDY OF ANTINEOPLASTONS A10 AND AS2-1 INFUSIONS (ANP) IN PATIENTS WITH RECURRENT ANAPLASTIC ASTROCYTOMA

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Anaplastic astrocytomas (AA) (WHO grade III) constitute less than 10% of all gliomas. The prognosis for patients with these tumors is poor; even with the most aggressive therapies, including surgery and adjuvant radiation therapy and chemotherapy, the 5-year survival for newly diagnosed patients is currently less than 30%. For recurrent AA the overall survival is less than 2 years. The purpose of this study is to evaluate the outcome of adults with recurrent AA treated with ANP in an FDA-monitored phase II clinical trial. ANP affects multiple targets, and its components have different mechanisms of action. A10 interferes with signaling in the AKT2 and MYCC pathways, blocks expression of TGFB1, activates the PTEN and MAD tumor suppressor genes, and normalizes nuclear transport by decreasing the expression of RANBP1, which may restore the activity of the mutated INI protein. AS2-1 interferes with signal transmission in the RAS and BCL2 pathways and activates expression of the tumor suppressors TP53 and p21. Twenty assessable adults, all diagnosed with AA, whose ages ranged from 20 to 51 years (median age 41 years), were involved in this study. The tumor recurred in all patients after radiation therapy, and 55% of patients received additional chemotherapy before the recurrence. ANP was administered intravenously daily through a subclavian venous catheter via a double-channel infusion pump. The median duration of treatment was 6.5 months and the median of average dosages of A10 was 5.8 g/kg/day and of AS2-1 was 0.24 g/kg/day. The treatment was well tolerated with only one case of a serious toxicity of hypernatremia. Complete response (CR) was achieved in 15%, partial response (PR) in 10%, stable disease (SD) in 45%, and progressive disease in 30% of patients. Overall survival (OS) at 2 years was 35%. The median of progression-free survival based on K-M was 10.3 months. These results compare favorably with the outcome of standard treatment. In conclusion, ANP is well tolerated and provides encouraging results in the treatment of recurrent AA and merits further investigation in a randomized phase III trial in comparison to standard treatment.

O21. A RANDOMIZED TRIAL OF PROCARBAZINE, CCNU AND VINCRISTINE (PCV) VS. TEMOZOLOMIDE (5-DAY OR 21-DAY SCHEDULE) FOR RECURRENT HIGH-GRADE GLIOMA (MEDICAL RESEARCH COUNCIL TRIAL BR12, ISRCTN83176944)

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Background: Nitrosourea-based chemotherapy (NBC) is a widely used treatment for patients (pts) with recurrent high-grade glioma (HGG) who have not received prior chemotherapy. Although temozolomide (TMZ) is increasingly used, it has never been directly compared with NBC. We report results of a Cancer Research UK–funded randomized trial of PCV vs. TMZ and comparison of two dosing schedules of TMZ at first recurrence of HGG.

Methods: Chemo-naïve pts with radiologically confirmed, recurrent HGG, considered fit for chemotherapy were randomized through the MRC Clinical Trials Unit in the ratio 2:1:1 to PCV, TMZ-5, and TMZ-21. The TMZ schedules were 200mg/m^2 for 5 days (TMZ-5) or 100 mg/m^2 for 21 days (TMZ-21), both schedules repeated every 28 days for up to 9 cycles or until progression. PCV comprised procarbazine 100 mg/m^2 p.o. days 1–10, CCNU 100 mg/m^2 p.o. day 1, and vincristine 1.5 mg/m^2 (max 2 mg) i.v. day 1; cycles repeated every 6 weeks for up to 6 cycles or until progression. The primary (1^o) comparison is PCV vs. TMZ (either schedule); the 1^o outcome is survival, and the trial is powered to detect a 2–3 month increase in median survival with TMZ corresponding to hazard ratios (HR) of 0.75 and 0.67, respectively. We require 380 deaths to detect HRs of 0.67 with 95% power and 0.75 with 80% power, α=0.05 (2-sided). To observe 380 deaths, a maximum of 500 pts randomized over 4 years was anticipated, with a planned subgroup analysis in 300 glioblastoma multiforme (GBM) pts. Progression-free survival (PFS) at 3 months is the 1^o outcome for the comparison of the two TMZ schedules. 220–250 pts randomized with respect to dose would provide 80% power to detect absolute differences of 15%–20% in PFS rates at 12 weeks.

Results: Accrual began in July 2003 and closed on January 31, 2008. 447 pts were randomized. Approximately 75% of pts have GBM tumors. We anticipate 380 deaths by July 2008, when the majority of patients will have completed treatment, and we will conduct the primary analysis at this time. The data to be presented will therefore include treatment compliance and toxicity data, the intent-to-treat logrank analysis of survival for the TMZ and PCV arms in the whole trial population and the GBM subgroup and the PFS logrank analysis for the PCV vs. TMZ comparison, and for the two TMZ schedules individually.

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