Title

ACTR-23. MOLECULAR GENETIC, HOST-DERIVED AND CLINICAL DETERMINANTS OF LONG-TERM SURVIVAL IN GLIOBLASTOMA: FIRST RESULTS FROM THE BRAIN TUMOR FUNDERS' COLLABORATIVE CONSORTIUM

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OBJECTIVE: Tumor Treating Fields (TTFields) imply the administration of alternating electric fields to induce mitotic arrest in Glioblastoma (GBM) cells. Based on the specific mode of action, which requires continuous exposure of the malignant cell pool to TTFields, compliance to TTFields treatment is a crucial parameter for treatment success. Importantly, there is currently no data regarding predictive factors for individual compliance rate. We aim at using a standardized assessment battery to provide a specific psychological profile of GBM patients who choose or not choose to undergo TTFields treatment and distinguish between high and low compliance patients. **METHODS:** Forty adult patients treated for newly diagnosed GBM at the University Regensburg Medical Center will be recruited. The psychological assessment battery aims at assessing four categories relevant for treatment compliance: 1. Lack of communicative skills, 2. depressive and anxiety disorders, 3. interpersonal factors (e.g. social support), and 4. intrapersonal factors, (e.g. beliefs about benefit, self-efficacy). The study endpoints are: 1. willingness to undergo TTFields therapy and 2. compliance rate of the individual patient, provided by the technical support team. The first interview takes place after treatment consultation (T0), 2 weeks after diagnosis (T1), at the initiation of TTFields treatment (T2) and every 4 weeks during treatment either until second disease progression or after maximal 8 months' observation time per patient. Additionally, demographic (gender, age, marital status), clinical (KPI, extent of resection) and biological factors (MGMT promoter status, IDH1 mutation) will be assessed. **RESULTS:** The study has been approved by the local ethics committee and the first patients are about to be recruited. Updated results will be presented at the meeting.

ACTR-21. UPDATED RESULTS OF A PHASE I DOSE-ESCALATION, DOSE-EXPANSION STUDY OF DISULFIRAM AND ADJUVANT TEMOZOLOMIDE FOR NEWLY DIAGNOSED GLIOBLASTOMA

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BACKGROUND: Disulfiram has promising preclinical activity against glioblastoma (GBM) as well as synergy with temozolomide. In a phase I study for newly diagnosed GBM after chemoradiotherapy, we have previously shown the maximum tolerated dose (MTD) of disulfiram with adjuvant temozolomide is 500mg per day (QD). Here we report the updated results of the phase I study with a dose-expansion cohort with the addition of concurrent copper gluconate supplement. **METHODS:** The phase I study consisted of an initial dose-escalation phase of disulfiram 500-1000mg QD during adjuvant temozolomide, followed by a dose-expansion phase of disulfiram 500mg QD with concurrent copper 2mg three times daily (TID) during adjuvant temozolomide. Progression-free survival (PFS) and overall survival (OS) were determined from the start of adjuvant temozolomide/disulfiram. **RESULTS:** A total of 18 patients were enrolled: 7 patients received 500mg disulfiram, 5 patients received 1000mg disulfiram, and 6 patients received 500mg disulfiram with copper. At 1000mg disulfiram, 4 patients (80%) required dose discontinuation or reduction within the first month due to toxicity. At 500mg disulfiram, 1 patient (8%) required dose reduction during the first month, and 1 patients (8%) required dose discontinuation due to toxicity after 2.6 months. Addition of copper to disulfiram did not increase toxicity. Dose-limiting toxicities (DLTs) included delirium, motor neuropathy, ataxia, and nausea/diarrhea. After a median follow-up of 12.0 months, 16 patients have progressed, and 11 patients have died. Median PFS was 4.5 months (95% CI: 0.8–8.2), and 1-year PFS was 14% (95% CI: 0–30%). Median OS was 13.9 months (95% CI: 1.9–25.9), and 2-year OS was 28% (95% CI: 3–54%). **CONCLUSIONS:** The MTD of disulfiram at 500mg per day and copper 2mg TID can be safely combined with adjuvant temozolomide. A multi-institutional phase II study evaluating addition of disulfiram/copper to temozolomide for recurrent temozolomide-resistant GBM is ongoing (NCT03034135).

ACTR-22. RESULTS OF PHASE I OF THE PARADIGM TRIAL: A PHASE I DOSE ESCALATION STUDY OF OLAPARIB IN COMBINATION WITH SHORT COURSE RADIOTHERAPY IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA (GBM)

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BACKGROUND: Olaparib, a small molecule inhibitor of poly(ADP-ribose) polymerase (PARP), has radiosensitising properties in pre-clinical GBM models. Because radiopotentiation is observed only in proliferating cells, we hypothesised that olaparib would enhance tumour control without exacerbating normal brain toxicity in GBM patients receiving radiotherapy. Having shown that olaparib penetrates GBM at radiosensitising concentrations, we studied its safety and toxicity in combination with short-course radiotherapy in GBM patients ineligible for radical chemoradiation. **METHODS:** Patients aged ≥70 (WHO PS 0–1) or <70 (PS 2) with histologically confirmed GBM received oral olaparib commencing three days before and continuing throughout radiotherapy (40 Gray in 15 fractions) and for four weeks afterwards. Olaparib dose was escalated in a 3 + 3 cohort design. **RESULTS:** 16 patients (9 male, 7 female) were treated within four olaparib dose cohorts. Median age was 72 (range 44–78); four patients had WHO PS 0, eight PS 1 and four PS 2. Cohort 3 was expanded to six evaluable patients because one patient experienced the only dose-limiting toxicity observed in the study (agitation grade 3, CTCAE v.4). Serious adverse events were experienced by eight patients, of which only one (the DLT) was a serious adverse reaction. The recommended dose of olaparib for phase II testing in combination with short-course radiotherapy was determined to be 200 mg twice daily. **CONCLUSIONS:** As predicted by pre-clinical data, olaparib is extremely well tolerated in combination with short-course radiotherapy in elderly and poorer PS patients with newly diagnosed GBM. The recommended phase II dose of 200 mg twice daily is significantly higher than has been deliverable to date in extracranial tumour sites in which acutely responding, rapidly proliferating normal tissues were within the irradiated volume. A randomised double-blind phase II study of radiotherapy plus olaparib versus radiotherapy plus placebo is underway in patients aged ≥65 with MGMT unmethylated GBM.

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BACKGROUND: Survival in glioblastoma patients is usually in the range of 12–15 months, and less than 5% of patients survive 5 years from diagnosis. Little is known about factors influencing long-term survival. **METHODS:** A consortium generously funded by the Brain Tumor Funders'

Collaborative comprising more than 20 clinical sites in Europe, the US, and Australia registers patients with glioblastoma who survived for at least 5 years. The aim of the study is a better understanding of factors contributing to prolonged survival by assessment of (i) clinical features, (ii) molecular parameters, (iii) therapy and quality of life-related factors, and (iv) immunological parameters. The histopathological diagnosis of glioblastoma is centrally reviewed at study entry. Clinical characteristics including imaging data are collected at the European Organisation for Research and Treatment of Cancer (EORTC) in Brussels, Belgium. Comprehensive molecular analyses are performed at the German Cancer Research Center (DKFZ), Germany. Immunological parameters are analyzed in Zurich, Switzerland. Alive patients are followed by neurocognitive assessments additionally. **RESULTS:** At the cut-off of May 30, 2017, 182 patients have been registered by 17 sites; 107 patients are alive, more than half of which contribute to the neurocognitive assessments and patient-related outcome studies, as well as the immunological studies. First comprehensive results of disease characteristics with a cut-off of September 30, 2017, will be presented. **CONCLUSIONS:** The collaborative effort of this consortium by comprehensive characterization of molecular parameters, immunological aspects, and individual clinical and therapy-related determinants will contribute to a better understanding of factors that modulate the course of this disease.

ACTR-24. THE ESTIMATED LONG-TERM SURVIVAL BENEFIT OF ADDING TTFIELDS TO THE STANDARD OF CARE FOR GLIOBLASTOMA PATIENTS

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BACKGROUND: Glioblastoma (GBM) is the most aggressive form of primary brain cancer. The EF-14 trial for GBM patients reported a 5-year survival rate of 12.8%, the first report from a large randomized controlled trial of 5-year survival greater than 10%. The increased survival compared to previous studies was achieved by adding tumor treating fields (TTFields) to the existing standard of care of radiochemotherapy. An understanding of the predicted long-term prognosis for GBM patients is important to facilitate good clinical, personal and policy decision-making, as survival at 5 years continues to improve. **OBJECTIVE:** To estimate the mean lifetime survival benefit for GBM patients of adding TTFields to the existing standard of care. **METHODS:** Standard regression-based parametric extrapolations of overall survival were constructed and were fit to the EF-14 trial data. These models underestimated the reported long-term GBM survival rates. Parametric models assume a constant hazard function, which was not observed in the EF-14 trial or epidemiological data, resulting in the underestimation. Survival was instead modelled using a previously described method that synthesized EF-14 trial data with GBM epidemiological data and general population survival rates. **RESULTS:** The estimated mean lifetime survival from initiation of adjuvant treatment was 4.2 years with TTFields and 2.4 years without it, an increase of 1.8 years. The estimated incremental life years gained (LYG) was 1.3 years when a 3% discount rate was applied to future survival benefits. TTFields-treated survivors who survived to 2 years were estimated to have a 20.7% chance of surviving to 10 years. **CONCLUSIONS:** The analysis indicated that treating GBM patients with TTFields substantially increased mean lifetime survival, consistent with the clinical findings of the EF-14 trial. Current GBM treatment strategies offer improved prognoses compared to past therapies, and should be considered by physicians, patients and payers in GBM treatment decisions.

ACTR-25. PHASE I/II STUDY OF TEMOZOLOMIDE PLUS NIMUSTINE CHEMOTHERAPY FOR RECURRENT MALIGNANT GLIOMAS: KYOTO NEURO-ONCOLOGY GROUP

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The objective of this phase I/II study was to examine the efficacy and toxicity profile of temozolomide (TMZ) plus nimustine (ACNU). Patients who had received a standard radiotherapy with one or two previous chemoregimens were enrolled. In phase I, the maximum-tolerated dose (MTD) by TMZ (150 mg/m2/day) (Day 1–5) plus various doses of ACNU (30, 35, 40, 45 mg/m2/day) (Day 15) per 4 weeks was defined on a standard 3 + 3 design. In phase II, these therapeutic activity and safety of this regimen were evaluated. Forty-nine eligible patients were enrolled. The median age was 50 years-old. Eighty percent had a KPS of 70–100. Histologies were glioblastoma (73%), anaplastic astrocytoma (22%), anaplastic oligodendroglioma (4%). In phase I, 15 patients were treated at four cohorts by TMZ plus ACNU. MTD was TMZ (150 mg/m2) plus ACNU (40 mg/m2). In phase II, 40 patients were treated at the dose of cohort 3 (MTD). Thirty-five percent of patients experienced grade 3 or 4 toxicities, mainly hematologic. The overall response rate was 11% (4/37). Sixty-eight percent (25/37) had stable disease. Twenty-two percent (8/37) showed progression. Progression-free survival (PFS) rates at 6 and 12 months were 24% (95% CI, 12–35%) and 8% (95% CI, 4–15%). Median PFS was 13 months (95% CI, 9.2–17.2 months). Overall survival (OS) at 6 and 12 were 78% (95% CI, 67–89%) and 49% (95% CI, 33–57%). Median OS was 11.8 months (95% CI, 8.2–14.5 months). This phase I/II study showed a moderate toxicity in hematology and may has a promising efficacy in OS, without inferiority in PFS

ACTR-26. TOXICITY AND EFFICACY OF LOMUSTINE PLUS BEVACIZUMAB IN RECURRENT GLIOBLASTOMA PATIENTS

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BACKGROUND: Bevacizumab combined with chemotherapy has shown high response rates in recurrent glioblastoma patients and responding patients have improved survival and quality of life. The Danish treatment recommendations for recurrent glioblastoma patients were recently changed by replacing irinotecan with lomustine in the bevacizumab combination regimen. **AIM:** To evaluate the toxicity and efficacy of lomustine plus bevacizumab in recurrent glioblastoma patients by comparing the treatment with irinotecan plus bevacizumab. **PATIENTS:** The study included recurrent glioblastoma patients treated according to two different treatment protocols at Rigshospitalet. Cohort 1: Seventy consecutive, non-selected patients treated with lomustine 60 mg/m2 every 6 weeks and bevacizumab 10 mg/kg every 2 weeks (Lom-Bev). Cohort 2: A total of 219 patients treated with irinotecan 125 mg/m2 (if EIAED 340 mg/m2) and bevacizumab 10 mg/kg every 2 weeks (Iri-Bev). **METHODS:** Comparison analyses of toxicity and efficacy between the two treatment regimens were performed by the Fisher's Exact test and Kaplan-Meier method. To compare survival outcome between responding patients of the two treatment regimens a landmark analysis was performed. Clinical and molecular factors were screened for association with response, progression-free survival (PFS) and overall survival (OS) using logistic and Cox regression analyses. **RESULTS:** Lom-Bev patients had a significantly higher frequency of hematological toxicity and less gastrointestinal toxicity compared to Iri-Bev. The response rate was 37% for Lom-Bev and 30% for Iri-Bev. Median PFS was 23 weeks for Lom-Bev and 21 weeks for Iri-Bev (P=0.86). Median OS was 37 weeks for Lom-Bev and 32 weeks for Iri-Bev (P=0.47). **CONCLUSION:** In recurrent glioblastoma patients treated outside clinical trials lomustine plus bevacizumab is safe. However, hematological toxicity is a dose limiting factor. No significant difference between Lom-Bev and Iri-Bev were observed with regard to progression-free survival or overall survival when considering the whole group of recurrent glioblastoma patients. Updated results will be presented.

ACTR-27. COMPLIANCE AND TREATMENT DURATION PREDICT SURVIVAL IN A PHASE 3 EF-14 TRIAL OF TUMOR TREATING FIELDS WITH TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

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Tumor treating fields (TTFields) are a physical anti-mitotic treatment modality characterized by their immediate mode of action and lack of a half-life. It has been shown previously that average monthly compliance with TTFields is correlated with overall survival in recurrent glioblastoma. A ≥75% compliance, i.e. an average daily use of at least 18h/d, has been suggested as a target for patients with recurrent glioblastoma when receiving TTFields as monotherapy. In the EF-14 phase 3 trial in newly diagnosed glioblastoma, TTFields were applied together with temozolomide (TTFields/TMZ) and led to superior progression free (PFS) and overall survival (OS) compared to TMZ alone. Patients in the TTFields/TMZ arm received TTFields for a median of 8.2 months (95%CI 7.9–9.3), with 13%, 3%, 1% and <1% of patients on therapy at 2, 3, 4 and 5 years, respectively. We looked at different TTFields compliance bins and correlated them with PFS and OS compared to TMZ alone. The results show a threshold value of 50% average monthly compliance with TTFields is needed in order to obtain extension of both PFS (HR 0.70 95%CI 0.47–1.05) and OS (HR 0.67 95%CI 0.45–0.99) versus TMZ alone. A trend in favor of longer PFS