Title

ACTR-10. A RANDOMIZED, PHASE I/II TRIAL OF IXAZOMIB IN COMBINATION WITH STANDARD THERAPY FOR UPFRONT TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED MGMT METHYLATED GLIOBLASTOMA (GBM) STUDY DESIGN

Journal

Neuro-Oncology, 20(suppl_6)

ISSN

1522-8517

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Publication Date

2018-11-05

DOI

10.1093/neuonc/noy148.045

Peer reviewed

3 dyspnea; grade 2 hemorrhage, non-neutropenic fever; and grade 1 hand-foot. CONCLUSIONS: Low-dose capecitabine is associated with a modest reduction in MDSCs and T-regs and a significant increase in CTLs. Toxicity has been manageable. Four of 7 evaluable patients have reached 6 months free of progression. Dose escalation continues.

ACTR-10. A RANDOMIZED, PHASE I/II TRIAL OF IXAZOMIB IN COMBINATION WITH STANDARD THERAPY FOR UPFRONT TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED MGMT METHYLATED GLIOBLASTOMA (GBM) STUDY DESIGN

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OBJECTIVE: To investigate the toxicity, tolerability and efficacy of the combination of ixazomib and standard chemoradiation therapy for newly diagnosed MGMT methylated GBM patients. BACKGROUND: GBM is the most aggressive primary malignant brain tumor. Standard therapy with temozolomide and radiotherapy after the surgery offers limited overall survival (OS). The median OS in patients with MGMT methylation is still less than 2 years. Our recent phase II clinical trial found that the addition of bortezomib, a proteasome inhibitor, to the standard therapy, offered mild survival benefit (19 months) for the entire group of GBM patients. However, significant improvement of OS and progression free survival (PFS) were found in the MGMT methylated patients when compared to MGMT unmethylated patients (OS: 49.4 vs 15.6 months, p=0.0002; PFS: 24.7 vs 5.1 months, p=0.00004) [Kong et al. Int J Radiation Oncology Biol Phys 2018]. Ixazomib is a newer generation of proteasome inhibitor and has demonstrated similar selectivity and potency to bortezomib in biochemical and cell-based assays. While bortezomib can be administered via injection, ixazomib is taken orally, which is more convenient. HYPOTHESIS: Adding ixazomib to standard therapy improve the survival of the patients with newly diagnosed MGMT-methylated GBM compared to standard therapy. STUDY DESIGN: This is a randomized, active controlled, open label phase I/II study of Ixazomib plus standard therapy versus standard therapy. Primary and secondary endpoints are PFS, 12, 24, 36 and 48 month survival rates and response duration. The study consists of two parts: In part I, the maximum tolerated dose (MTD) is decided by using 3 + 3 design with dose limiting toxicity (DLT) method. In part II, randomize the patients to the combination therapy or the standard therapy arm. Safety will be assessed by CTCAE V4.03. We will use Kaplan-Meier estimates for survival data and a stratified log-rank test for the randomization strata.

ACTR-12. PRELIMINARY SAFETY AND EFFICACY OF A PHASE II TRIAL OF 18F-DOPA PET-GUIDED, DOSE-ESCALATED RADIOTHERAPY IN THE TREATMENT OF GLIOBLASTOMA

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BACKGROUND: 18F-DOPA-PET thresholds reliably delineate areas of high-grade astrocytoma not otherwise recognized with standard MRI and may more accurately identify regions of aggressive, high-density disease. Herein we report the preliminary safety and feasibility data from an ongoing phase II study (MC1374; R01CA178200) evaluating 18F-DOPA-PET guided-dose-escalated radiotherapy for glioblastoma. METHODS: Newly diagnosed glioblastoma patients without contra-indications to 18F-DOPA-PET are eligible for study enrollment. Target volumes include: CTV51Gy=T1-gadolinium contrast-enhancing (T1-CE) disease, T2 FLAIR signal abnormality, and low-grade 18F-DOPA-PET uptake, +1cm; CTV60Gy=T1-CE and high-grade 18F-DOPA-PET uptake, +1cm; and CTV76Gy=T1-CE and high-grade 18F-DOPA-PET disease without expansion all given in 30 fractions simultaneously. Patients are followed with 18F-DOPA-PET in addition to standard clinical follow-up. Safety stopping rule specifies that after 10 or more patients have been enrolled, if more than 10% experience any of the following adverse events considered to be at least possibly related to treatment, enrollment will be suspended: Grade 3 or 4 irreversible CNS toxicity, Grade 4 non-hematologic, non-CNS toxicity, any Grade 5 toxicity. Futility analysis (and primary study aim) is powered to consider a success to be an MGMT-unmethylated patient who is without progression within 6 months from the time of craniotomy. If 16 or more successes are observed in the first 25 evaluable patients study will continue. RESULTS: 77 patients have been accrued since December 2013 with 68 evaluable for toxicity. Grade 3 CNS necrosis was noted in 3 (4.4%) patients; 2 additional patients developed symptoms that resolved in the subsequent cycle so did not count towards stopping rule. Other grade 3+ toxicities include: 1 patient with pre-existing vision dysfunction had Grade 4 optic nerve dysfunction; 2 Grade 4 hematologic events and 1 Grade 5 event(sepsis) due to temozolamide-induced cytopenias. CONCLUSION: 18F-DOPA-PET -guided dose escalation appears reasonably safe and tolerable in patients with high-grade glioma.

ACTR-13. A BAYESIAN ADAPTIVE RANDOMIZED PHASE II TRIAL OF BEVACIZUMAB VERSUS BEVACIZUMAB PLUS VORINOSTAT IN ADULTS WITH RECURRENT GLIOBLASTOMA FINAL RESULTS

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BACKGROUND: Bevacizumab improves outcome and reduces symptoms in patients with recurrent glioblastoma (GBM). However, GBMs develop adaptive resistance to bevacizumab- mediated angiogenesis inhibition resulting in tumor recurrence. We hypothesized that vorinostat, a histone deacetylase (HDAC) inhibitor, with pleotropic antiangiogenic effects, would delay emergence of resistance to bevacizumab therapy and improve clinical outcome. METHODS: In this multicenter phase II trial utilizing a novel Bayesian design, patients with recurrent glioblastoma were adaptively randomized to bevacizumab alone or bevacizumab+vorinostat based on a primary endpoint of progression-free survival (PFS) such that patients had a higher likelihood of receiving the more efficacious treatment. Secondary end points were overall survival (OS) and quality of life assessment (MDASI-BT). Eligible patients were adults (≥ 18 yrs) with histologically confirmed GBMs recurrent after prior radiation and temozolomide therapy, adequate organ function, KPS≥ 60, and no prior bevacizumab/HDAC inhibitors. RESULTS: Ninety patients (bevacizumab+vorinostat:49, bevacizumab:41) were enrolled and 74 were evaluable for PFS (bevacizumab+vorinostat:44, bevacizumab:30). Grade 3 or greater toxicities in 85 evaluable patients included hypertension (n=37), neurological changes (n=2), anorexia (n=2), infections (n=9), wound dehiscence (n=2), DVT/PE (n=2), and colonic perforation (n=1). There was one treatment-related death due to pulmonary embolism. Upon multivariate analysis for bevacizumab+vorinostat vs bevacizumab, median PFS (3.7 vs. 3.9 months, p=0.94, HR 0.63 [95% CI 0.38, 1.06, p=0.08]) or median OS (7.8 vs. 9.3 months, p=0.64, HR 0.93 [95% CI 0.5, 1.6, p=0.79]) were not significantly different between the two arms. Ongoing analyses of patient reported outcomes (MDASI-BT) and plasma biomarkers will be reported. CONCLUSIONS: Combining bevacizumab with vorinostat did not result in improved PFS or OS compared with bevacizumab alone in patients with recurrent GBM. This trial is the first to test a Bayesian PFS-based adaptive randomized design in patients with primary brain tumors and demonstrates the feasibility of using adaptive randomization in a multicenter setting.

ACTR-14. PHASE I STUDY OF AZD1775 WITH RADIATION THERAPY (RT) AND TEMOZOLOMIDE (TMZ) IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA (GBM) AND EVALUATION OF INTRATUMORAL DRUG DISTRIBUTION (IDD) IN PATIENTS WITH RECURRENT GBM

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