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CTNI-21: PHASE I STUDY OF BTK INHIBITOR IBRUTINIB WITH TEMOZOLOMIDE AND RADIATION IN NEWLY-DIAGNOSED GliOBLASTOMA (EQUILIBRIUM): FINAL TRIAL REPORT
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BACKGROUND: Glioblastoma carries dismal prognosis for which novel therapeutics are urgently needed. Ibrutinib, an oral small molecule inhibitor of BTK, has been shown in preclinical models to inhibit cancer stem cells in glioblastoma. We sought to investigate safety and tolerability of ibrutinib for newly-diagnosed glioblastoma (nGBM). METHODS: EQUILIBRIUM was a prospective, phase I trial conducted in nGBM patients with KPS ≥ 70% and normal organ function. Patients received standard of care chemoradiation plus ibrutinib in a 3 + 3 dose-escalation design (level 1: 420 mg daily, level 2: 560 mg daily, level -1: 280 mg daily). Primary study objective was to determine maximum tolerated dose (MTD) of ibrutinib in combination with radiotherapy (RT) of 60 Gy over 6 weeks with/without 75 mg/m² of temozolomide (TMZ) in MGMT methylated and unmethylated cohorts respectively. Secondary objective was to determine safety, overall survival (OS), and progression-free survival. RESULTS: 26 patients were enrolled, with 12 (46%) females. Median age was 61.5 years (range 76-22). 15 (58%) patients were MGMT methylated and 11 (42%) were unmethylated. Dose-limiting toxicities (DLTs) were observed at all dose levels of ibrutinib+RT arm. MTD of ibrutinib was noted to be 420 mg daily with RT+TMZ in methylated arm. In Ibrutinib+RT+TMZ arm, median cycles of TMZ were 4 (range 0-6) and of ibrutinib were 3 (range 0-26). Median OS for MGMT methylated arm was 26.0 (22.0-NA) months and for MGMT unmethylated cohort was 14.0 (8.54-NA) months. Median OS for EGFR-amplified was 29.5 (21.9-NA) months and for EGFR-non-amplified was 21.8 (16.6-NA) months. 2-year OS for MGMT methylated arm was 56% (34-95%) and for MGMT unmethylated arm was 2% (6-70%). CONCLUSIONS: 420 mg of Ibrutinib daily is safe and feasible with TMZ and RT for nGBM. Ibrutinib appears promising compared to historical outcomes in MGMT methylated patients. EGFR-amplified patients potentially derive significant benefit. Trial information: NCT03535330.