Aim: Despite standard therapy for GBM, median survival is 1-2 years. Abnormal epidermal growth factor receptor (EGFR) expression and signaling are common in GBM. ABT-414 is a unique antibody-drug conjugate, with a toxic payload (monomethylauristatin F) targeted to active EGFR or mutant EGFRvIII, that has demonstrated high antitumor activity in preclinical GBM tumor models.

Methods: Objectives were to evaluate the safety, pharmacokinetics (PK), and the maximum tolerated dose (MTD) of ABT-414 when administered every 14 days with concurrent RT and TMZ in newly diagnosed GBM. Adverse events, PK parameters, objective response (RANO), and tumor tissue EGFR biomarkers were assessed. Dose escalation was determined by the exposure-adjusted continual reassessment method (EACRM).

Results: As of April 9, 2014, 22 pts were treated (13/9 Male/Female, median age 58 years, range 34-79). Common treatment-emergent adverse events (TEAEs, ≥ 5 pts) included fatigue (n= 11); blurred vision (n = 10); thrombocytopenia (n = 8); AST increase (n = 9); ALT increase (n = 8); nausea (n = 7); eye pain (n = 6); lacrimation increase (n = 6); dry eye, headache, and constipation (n = 5 each). Grade 3/4 TEAEs (≥ 2 pts) included lymphopenia (n = 3); eye toxicity (n = 3); brain edema, ALT, AST (n = 2 each). Grade 3/4 TEAEs (≥ 2 pts) included lymphopenia (n = 3); eye toxicity (n = 3); brain edema, ALT, AST (n = 2 each). Doses from 0.5 - 3.2 mg/kg have been explored. Dose limiting toxicities primarily affecting the eye (keratitis) and liver occurred at the 2, 2.6, 3.0, and 3.2 mg/kg doses. The EACRM has predicted 2.4 mg/kg as the MTD. Confirmatory safety data are being collected. PK data from 9 subjects in the dose range of 0.5 - 3 mg/kg indicate that exposure (Cmax and AUC) of ABT-414 appeared to be dose proportional with a half-life of approximately 11 days. Efficacy endpoints are not yet mature. Patient samples are being evaluated for EGFR expression, amplification and EGFRvIII status to determine which marker best associates with clinical benefit.

Conclusions: PK and safety data support a dose of 2.4 mg/kg as the predicted MTD. Preliminary safety data demonstrate increased liver and eye toxicities in addition to common RT + TMZ toxicities. Further follow-up may demonstrate whether ABT-414 improves outcome.

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