Phase 0 Trial of AZD1775 in First-Recurrence Glioblastoma Patients.


1 Ivy Brain Tumor Center, Barrow Neurological Institute, Phoenix, Arizona. nader.sanai@bnaneuro.net.
2 Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut.

Purpose: AZD1775 is a first-in-class Wee1 inhibitor with dual function as a DNA damage sensitizer and cytotoxic agent. A phase I study of AZD1775 for solid tumors suggested activity against brain tumors, but a preclinical study indicated minimal blood-brain barrier penetration in mice. To resolve this controversy, we examined the pharmacokinetics and pharmacodynamics of AZD1775 in patients with first-recurrence, glioblastoma. Experimental Design: Twenty adult patients received a single dose of AZD1775 prior to tumor resection and enrolled in either a dose-escalation arm or a time-escalation arm. Sparse pharmacokinetic blood samples were collected, and contrast-enhancing tumor samples were collected intraoperatively. AZD1775 total and unbound concentrations were determined by a validated LC/MS-MS method. Population pharmacokinetic analysis was performed to characterize AZD1775 plasma pharmacokinetic profiles. Pharmacodynamic endpoints were compared to matched archival tissue. Results: The AZD1775 plasma concentration-time profile following a single oral dose in patients with glioblastoma was well-described by a one-compartment model. Glomerular filtration rate was identified as a significant covariate on AZD1775 apparent clearance. AZD1775 showed good brain tumor penetration, with a median unbound tumor-to-plasma concentration ratio of 3.2, and achieved potential pharmacologically active tumor concentrations. Wee1 pathway suppression was inferred by abrogation of G2 arrest, intensified double-strand DNA breakage, and programmed cell death. No drug-related adverse events were associated with this study. Conclusion: In contrast to recent preclinical data, our phase 0 study of AZD 1775 in recurrent glioblastoma indicates good human brain tumor penetration, provides the first evidence of clinical biological activity in human glioblastoma, and confirms the utility of phase 0 trials as part of an accelerated paradigm for drug development in patients with glioma. Clin Cancer Res; 1-9. ©2018 AACR.

PMID: 29798906 DOI: 10.1158/1078-0432.CCR-17-3348