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Phase I study of adavosertib with radiation therapy and temozolomide in newly diagnosed glioblastoma and intratumoral drug levels in recurrent glioblastoma

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Abstract

Purpose: Adavosertib is an oral small molecular inhibitor of Wee1. The Adult Brain Tumor Consortium performed a phase I study of adavosertib, radiation (RT) and temozolomide (TMZ) in newly diagnosed glioblastoma (GBM) as well as a surgical window of opportunity study in recurrent GBM.

Patients and methods: The maximum tolerated dose (MTD) of adavosertib was determined in adult patients with newly diagnosed GBM using a standard 3+3 design in 2 separate cohorts: with concurrent RT/TMZ or with adjuvant TMZ. A combination cohort with both concurrent and adjuvant adavosertib at MTD followed. We also performed intratumoral drug distribution studies in recurrent GBM patients undergoing surgery.

Results: As separate cohorts, MTD for concurrent adavosertib with RT/TMZ was 200 mg daily M-F x 6 weeks during RT and for adjuvant adavosertib with TMZ was 425 mg daily for 5 days of each 28-day cycle. However, 6/12 patients experienced DLTs in the combination cohort. The mean ratio of the intratumoral-to-plasma concentration of adavosertib was 4.18 ± 3.36 for contrast-enhancing tissue and 0.74 ± 0.63 in non-enhancing tissue.

Conclusions: Adavosertib 200 mg daily M-F x 6 weeks with RT/TMZ and 425 mg daily on a 5d/28d cycle with TMZ had an unacceptable DLT rate. Additional dose levels in combination cohorts resulted in DLTs and we deemed concurrent adavosertib too toxic for further examination. Adavosertib 425 mg daily on a 5d/28d cycle with adjuvant TMZ is the recommended phase II dose. Tissue PK in tissue homogenates and by microdialysis provided complementary information about drug penetration.