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Combination of Vorinostat with Whole-brain Radiotherapy in the Treatment of Brain Metastases

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Background

A third of patients with solid malignancies develop brain metastases. Expected overall survival is 4-7 months depending on age, performance status, and extracranial disease. Standard treatment is controversial; however, the majority of patients receive whole-brain radiation therapy at some point. Vorinostat (suberoylanilide hydroxamic acid, SAHA), an FDA-approved HDAC inhibitor, has been demonstrated to radiosensitize tumor cells in vitro, as assessed by both radiation-induced DNA damage and clonogenic cell survival (Munshi *et al. Molecular Cancer Therapeutics* 5, 1967-1974, 2006). We have shown that vorinostat downregulates key genes involved in double-strand DNA repair (Rad50, Rad51, XRCC2, XRCC3, XRCC6), as assessed by quantitative PCR. This suggests that the drug's mechanism of radiosensitization is epigenetic coordinated inhibition of the DNA repair process. We hypothesize that the combination of vorinostat with whole-brain radiation therapy will be both safe and efficacious.

Methods

This is a dose escalation phase I investigational trial, based on Fibonacci 3+3 design. Whole-brain radiation is delivered in daily fractions of 2.5 Gy over 3 weeks (total dose 37.5 Gy) delivered through parallel opposed fields. Vorinostat is delivered once daily on days of radiation therapy. Dose levels: increase from 200 mg PO qd to 400 mg PO qd in subsequent patient cohorts, with an option de-escalate if 200 mg is found overly toxic. Expected total accrual: 9-18 patients. Primary endpoint is tolerability; secondary endpoint is overall survival. Open to accrual at Thomas Jefferson University, Philadelphia PA; UT Southwestern Medical Center, Dallas, TX and Sheba Medical Center, Tel Aviv, Israel.

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