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# Evolving Role of Vorinostat Combined with Radiation Therapy in the Treatment of Brain Tumors, from the Lab to the Clinic

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## Purpose/Objective(s)

Radiation therapy (RT) is a critical element in the treatment of both brain metastases and glioblastoma (GBM). Temozolomide (TMZ) has an established role in the upfront treatment of GBM. Down-regulated mismatch repair (MMR) is a known mechanism of resistance to TMZ. Vorinostat (SAHA), an HDAC inhibitor, has successfully been combined with a number of cytotoxic agents, including ionizing radiation (IR). We performed a series of preclinical and clinical studies to examine the role of SAHA in the treatment of brain tumors.

## Material/Methods, Preclinical

Experiments were performed with 2 GBM cell lines. DNA double strand breaks were quantified by both neutral-comet assay and gamma-H2AX immunohistochemistry. For the neutral comet assay the 'olive moment' represents DNA damage. For gamma-H2AX assay, the percentage of cells with more than 3 foci was scored.

## Methods, Clinical

A multicenter dose-escalation phase I trial, based on Fibonacci 3+3 design is being conducted. Whole-brain radiation is delivered in daily fractions of 2.5 Gy over 3 weeks (total dose 37.5 Gy). 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 cohorts. Expected total accrual: 9-18 patients. Primary endpoint: tolerability.

## Results, Preclinical

In the absence of drug, radiation-induced DNA-double strand breaks were almost completely repaired within 24-hours. Both TMZ + IR, and SAHA + IR increased the olive moment compared to IR alone (24 hour post IR time-point). Surprisingly, when TMZ and SAHA were combined together with IR, the olive moment decreased to 6.5 as compared to TMZ + IR alone 8.7 ( $p < 0.05$ ). Similarly, in the absence of IR, SAHA was found to decrease TMZ-induced DNA damage. Comparable results were obtained with gamma-H2AX assay and with the 2nd cell line. On qPCR, SAHA decreased expression of key genes involved in

MMR. Despite this, clonogenic radiation survival assays demonstrated TMZ + SAHA to be more effective than TMZ alone in potentiating the cytotoxic effect of IR.

## Results, Clinical

Initial results indicate that low dose Vorinostat combined with RT is well tolerated, dose escalation is continuing.

## Conclusion

SAHA shows promise as a radiosensitizer for brain tumors. The discrepancy between DNA-damage and clonogenic-cell-survival assays suggests that SAHA's mechanism of radiosensitization may involve more than potentiation of DNA-damage. The efficacy of Vorinostat combined with temozolomide requires further investigation. Future clinical trials will investigate short-course dose-escalated drug schedules.