**Pediatric Preclinical Testing Program (PPTP) Evaluation of the DNA Methylation Agent Temozolomide**

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**ABSTRACT**

**Background.** Temozolomide is a DNA methylating agent that has been approved in the United States for treatment of astrocytoma. This drug in many ways resembles more established compounds, such as dacarbazine and procarbazone, in that it gives rise to a methylating diuretic (MT) inhibition of DNA methyltransferase. Temozolomide, however, differs from these other compounds in that it possesses a drug residue that can be metabolized to a more active methylating drug (MTM) by the action of the enzyme dihydrofolate reductase (DHFR).

**Objectives.** To evaluate the in vitro and in vivo activity of Temozolomide in pediatric preclinical testing panel xenograft models, and to determine the clinical settings where this drug would be most useful.

**Methods.** The PPTP (Protein-Protein Interactions and DNA Methylation) evaluation of the DNA methylation agent Temozolomide was conducted with the NCI Drug Repository. Two hundred and fifty-two compounds were tested in vitro, and 204 xenografts were tested in vivo.

**Results.** Temozolomide resulted in significant activity in 19/252 tested compounds. Three hundred and fifty xenograft models were tested in vivo, and 204 models with measurable xenografts were tested in vivo.

**Conclusions.** Temozolomide demonstrated significant activity in 7/10 solid tumor xenograft models. The results suggest that temozolomide may have potential for clinical use in the treatment of pediatric cancer.

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**PPTP IN VITRO & IN VIVO TESTING MODELS**

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<th>Compound</th>
<th>IC50 (µM)</th>
<th>EFS T/C</th>
<th>Heat map</th>
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<td>Temozolomide</td>
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**TEMOZOLOMIDE IN VIVO ACTIVITY**

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**IN VIVO RESULTS AND CONCLUSIONS**

- Temozolomide (100 µg/kg daily x 5) caused regressions in 19/20 solid tumors and 5/8 evaluable ALL models, but with excessive toxicity.
- Retesting at 66 µg/kg (daily x 5) resulted in exclusion of 2/9 models due to toxicity. Only 2/7 evaluable models responded.
- Dosing temozolomide at 66 µg/kg may more closely approximate temozolomide plasma exposure in patients.
- Of 17/30 responding tumor models 7 are MGMT-negative, 3 MLH1-negative, and 11 have wild type p53.
- All 7/7 MGMT-negative tumor models responded irrespective of p53 genotype.
- At higher temozolomide concentrations that exceed those tolerated in humans, the relationship between temozolomide activity and MGMT expression is lost in both the in vitro and the in vivo settings.