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### *Cancer Therapy: Clinical*

# Phase I Trial of Single-Dose Temozolomide and Continuous Administration of $O^6$ -Benzylguanine in Children with Brain Tumors: a Pediatric Brain Tumor Consortium Report

Alberto Broniscer<sup>1</sup>, Sridharan Gururangan<sup>6</sup>, Tobey J. MacDonald<sup>7</sup>, Stewart Goldman<sup>8</sup>, Roger J. Packer<sup>7</sup>, Clinton F. Stewart<sup>2</sup>, Dana Wallace<sup>3</sup>, Mary K. Danks<sup>4</sup>, Henry S. Friedman<sup>6</sup>, Tina Y. Poussaint<sup>9</sup>, Larry E. Kun<sup>5</sup>, James M. Boyett<sup>3</sup>, Amar Gajjar<sup>1</sup> for the Pediatric Brain Tumor Consortium

**Authors' Affiliations:** Departments of <sup>1</sup> Oncology, <sup>2</sup> Pharmaceutical Sciences, <sup>3</sup> Biostatistics, <sup>4</sup> Molecular Pharmacology, and <sup>5</sup> Radiological Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee; <sup>6</sup> Department of Pediatrics, The Preston Robert Tisch Brain Tumor Center at Duke, Duke University Medical Center, Durham, North Carolina; <sup>7</sup> Department of Neurology, Children's National Medical Center, Washington, District of Columbia; <sup>8</sup> Children's Memorial Hospital, Chicago, Illinois; and <sup>9</sup> Department of Radiology, Children's Hospital of Boston, Boston, Massachusetts

**Requests for reprints:** Alberto Broniscer, Department of Oncology, St. Jude Children's Research Hospital, 332 North Lauderdale, Mail Stop 260, Memphis, TN 38105. Phone: 901-495-4925; Fax: 901-521-9005; E-mail: alberto.broniscer@stjude.org.

**Purpose:** To estimate the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of escalating doses of temozolomide combined with  $O^6$ -benzylguanine in patients  $\geq 21$  years with recurrent brain tumors.

**Experimental Design:** Treatment strata consisted of patients who had previously received no or local radiotherapy (Str1) and patients who had undergone craniospinal radiotherapy or myeloablative chemotherapy (Str2). One-hour i.v. administration of  $O^6$ -benzylguanine at 120 mg/m<sup>2</sup> was followed by 48-h continuous infusion at 30 mg/m<sup>2</sup>/day. Single-dose temozolomide at five dosage levels (267, 355, 472, 628, and 835 mg/m<sup>2</sup>) was given at least 6 h after completion of  $O^6$ -benzylguanine bolus. Treatment was repeated after recovery from toxicities at least 4 weeks apart for a maximum of 12 courses. Dose escalation followed the modified continual reassessment method. Pharmacokinetic analyses of temozolomide and 5-triazeno imidazole carboxamide (MTIC) were done in 28 patients.

**Results:** A total of 44 and 26 eligible patients were enrolled on Str1 and Str2, respectively. Median age at study entry in each stratum was 8.6 and 11.3 years, respectively. Predominant diagnoses were high-grade/brainstem glioma in Str1 and medulloblastoma in Str2. Whereas the estimated MTDs of temozolomide for Str1 and Str2 were 562 and 407 mg/m<sup>2</sup>, respectively, the doses recommended for phase II investigations are 472 and 355 mg/m<sup>2</sup>, respectively. DLTs were predominantly neutropenia and thrombocytopenia. Three patients with gliomas experienced centrally confirmed partial responses to therapy. Four patients completed all planned therapy. Temozolomide and MTIC exposures were statistically associated with temozolomide dosage.

<http://clincancerres.aacrjournals.org/cgi/content/abstract/13/22/6712>

<http://www.brainlife.org/>

**Conclusions:** The current schedule of temozolomide and  $O^6$ -benzylguanine is safe and showed modest activity against recurrent brain tumors in children.