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Phase II Study of Temozolomide for Relapsed Sensitive or Refractory Small Cell Lung Cancer

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Background: SCLC represents the most aggressive tumor of the neuroendocrine carcinomas. We designed this phase II study of temozolomide, a nonclassic oral alkylating agent, in patients with SCLC based on the following rationale: alkylating agents have established efficacy in SCLC; temozolomide penetrates into the CNS with the potential to treat brain metastases commonly seen in SCLC; SCLC has aberrantly methylated *MGMT*; anecdotal responses to temozolomide in patients with SCLC have been observed.

Methods: Temozolomide is administered to patients with relapsed sensitive (relapse after 60 days) or refractory (no response to initial therapy, or progression within 60 days) SCLC. Patients who have disease progression after 1 or 2 prior chemotherapy regimens are eligible. Additional eligibility criteria include Karnofsky performance status ≥ 60% and normal organ and marrow function. The primary endpoint is objective response rate. Temozolomide is administered daily for 21 consecutive days of a 28-day cycle. The starting dose for the first cycle is 75mg/m^2/day. For those patients without grade 3 or higher toxicities at that dose, in subsequent cycles a single dose escalation to 100mg/m^2/day is given. Treatment is to be continued until disease progression, unacceptable toxicity or withdrawal. The target accrual is 64 patients. *MGMT* promotor methylation status is assessed in available tissue and in peripheral blood.

Results: Twenty-five patients (12 men, 13 women) have been accrued to date, of which 16 patients have sensitive and 9 have refractory SCLC. Temozolomide was second- and third-line treatment for 13 and 12 patients, respectively. Thirteen patients have brain metastases. Of the 23 patients assessable for response, 3 patients have achieved a partial response and 6 patients have stable disease. All other patients have had progression of disease within one cycle of treatment. The overall response rate is 13%. Regressions have been observed in five patients with progressive brain metastases, including two patients with recurrent disease after prophylactic cranial irradiation and whole brain radiation therapy. Toxicities include: grade 3 lymphopenia (20%); grade 3 thrombocytopenia (4%); grade 1/2 fatigue (32%); grade 1/2 emesis (20%); and grade 3 rash/pruritus (8% each).

Conclusions: 1) In this ongoing trial, three partial responses have been seen in patients with sensitive SCLC. 2) Temozolomide causes regression in SCLC brain metastases. 3) Temozolomide is well tolerated when given on this dose and schedule. 4) At this time, seven samples analyzed for *MGMT* hypermethylation have not demonstrated methylation. *Supported by Schering-Plough.*