Phase I trial of TRC102 (methoxyaminyl HCl) with temozolomide (TMZ) in patients with solid tumors and lymphomas


1National Cancer Institute, Division of Cancer Treatment and Diagnosis, Bethesda, MD 2Dept. of Medicine–Oncology, Stanford, Palo Alto, CA 3Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc., Frederick, MD

Background

Among the various mechanisms by which resistance to chemotherapy can develop, the base excision repair (BER) pathway is thought to play a major role in promoting resistance to both alkylating and antimetabolite chemotherapy. TRC102 acts through a novel mechanism to inhibit BER and has shown chemosensitization in in vitro models of human cancer, suggesting that TRC102 may enhance the activity of alkylating and antimetabolite chemotherapy in patients [1]. Published studies indicate that TRC102 has the ability to interrupt the process of BER by binding to apurinic/pyrimidinic (AP) sites produced during the initial step of BER [2]. TRC102-bound AP sites are not substrates for apurinic endonuclease (APE), which performs an essential step in BER; they are, however, substrates for topoisomerase II (topo II), and in vitro studies of cancer cells that contain high levels of topo II indicate that TRC102 effectively potentiates the activity of chemotherapy [3].

The ability of TRC102 to potentiate chemotherapeutic activity was initially demonstrated in the using the alkylating agent temozolomide (TMZ) [3, 4]. Collectively, the available data indicate that treatment of cancer cells with temozolomide produces N7-methylguanine and N3-alkylguanine DNA adducts that activate BER to generate AP sites within double-stranded DNA. In vitro studies of cancer cells that contain high levels of topo II indicate that TRC102 effectively potentiates the activity of chemotherapy [3].

Study Schema & Trial Design

Main eligibility criteria:

• solid tumor patients whose disease has progressed on standard therapy
• ECOG ≤ 2
• normal organ function

Main exclusion criteria:

• symptomatic CNS metastases or carcinomatous meningitis
• pregnant or nursing women
• unstable medical illnesses
• HIV+ on protease inhibitors

Primary Objectives

• Explore the progression-free survival rate of this combination in patients with CRC, NSCLC, and GCOV.

Secondary Objectives

• Determine and characterize the effects of study treatment on erythrocytes and characterize the clinical presentation of hemolysis observed in earlier study subjects.
• Explore the progression-free survival rate of this combination in patients with CRC, NSCLC, and GCOV.

Radiological and Correlative Outcomes

TRC102 inhibits BER and prevents DNA repair that occurs in response to TMZ therapy.

Summary + Future Directions

TRC102 inhibits BER and prevents DNA repair that occurs in response to TMZ therapy.

The side effect profile of this combination is manageable, with anemia as the dose-limiting toxicity.

The combination is active, with 4 PRs and 1 SD noted during the escalation and expansion cohorts.

The推荐 phase 2 dose is 125 mg TRC102 and 150 mg/m² TMZ, days 1-28 q 28 days.

The combination is active, with 4 PRs and 13 SDs noted during the escalation and expansion cohorts.
