

## ADVL0918: A Phase 1 Study of Temeirolimus in Combination With Irinotecan and Temozolomide in Children, Adolescents, and Young Adults With Relapsed or Refractory Solid Tumors

Type	Status	Age Range (yrs.)	Sponsor
Treatment	Active	1 - 21	CCHMC

### Outline

This is a multicenter study, dose-escalation study of temsirolimus.

Patients receive temsirolimus IV over 30 minutes on days 1 and 8 and irinotecan hydrochloride and oral temozolomide on days 1-5. Courses repeat every 21 days for up to 12 months in the absence of disease progression or unacceptable toxicity.

Some patients undergo bone marrow collection at baseline and during study for temsirolimus-induced changes in mTOR pathway proteins by flow cytometric analysis and immunoblotting.

After completion of study therapy, patients are followed up for 30 days.

### Purpose

This phase I trial is studying the side effects and the best dose of temsirolimus when given together with irinotecan hydrochloride and temozolomide in treating young patients with recurrent or refractory solid tumors.

### Rationale

Temsirolimus may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Drugs used in chemotherapy, such as irinotecan hydrochloride and temozolomide, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Giving temsirolimus together with combination chemotherapy may kill more tumor cells.

### Objectives

#### Primary

- To estimate the maximum-tolerated dose or recommended phase II dose of temsirolimus administered in combination with irinotecan hydrochloride and temozolomide in children, adolescents, and young adults with recurrent or refractory solid tumors.
- To define and describe the toxicities of this regimen in these patients.

#### Secondary

- To preliminarily define the antitumor activity of this regimen in these patients.
- To collect preliminary data regarding the biologic effects of temsirolimus on proteins involved in signaling pathways of interest in these patients. (Exploratory)

## Eligibility

Ages available for study: 1 to 21 years

## Disease Characteristics

- Histologically confirmed solid tumor at original diagnosis or relapse except for the following, which do not require biopsies:
  - Intrinsic brain stem tumors
  - Optic pathway gliomas
  - Pineal tumors with elevations of serum, CSF alpha-fetoprotein, or beta-HCG
- Recurrent or refractory disease
- Measurable or evaluable disease
- Disease for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life
- Patients with CNS tumors must have been relatively stable for  $\geq 1$  week

## Patient Characteristics

- Karnofsky performance status (PS) 50-100% (patients  $> 16$  years of age) OR Lansky PS 50-100% (patients  $\leq 16$  years of age)
- ANC  $\geq 1,000/\text{mm}^3$
- Platelet count  $\geq 100,000/\text{mm}^3$  (transfusion independent)
- Creatinine clearance or radioisotope GFR  $\geq 70 \text{ mL/min/1.73m}^2$  OR a serum creatinine based on age and/or gender as follows:
  - $\leq 0.6 \text{ mg/dL}$  (1 to  $< 2$  years of age)
  - $\leq 0.8 \text{ mg/dL}$  (2 to  $< 6$  years of age)
  - $\leq 1.0 \text{ mg/dL}$  (6 to  $< 10$  years of age)
  - $\leq 1.2 \text{ mg/dL}$  (10 to  $< 13$  years of age)
  - $\leq 1.5 \text{ mg/dL}$  (male) or  $1.4 \text{ mg/dL}$  (female) (13 to  $< 16$  years of age)
  - $\leq 1.7 \text{ mg/dL}$  (male) or  $1.4 \text{ mg/dL}$  (female) ( $\geq 16$  years of age)
- Bilirubin  $\leq 1.5$  times upper limit of normal (ULN)
- ALT  $\leq 110 \text{ U/L}$
- Serum albumin  $> 2 \text{ g/dL}$
- PT  $< 1.2$  times ULN
- Serum triglycerides  $\leq 300 \text{ mg/dL}$
- Serum cholesterol  $\leq 300 \text{ mg/dL}$
- Random or fasting blood glucose normal
- Normal pulmonary function tests, including DLCO, if clinically indicated (e.g., dyspnea at rest, known requirement for supplemental oxygen)
- Patients with seizure disorder allowed provided it is well controlled with non-enzyme-inducing anticonvulsants

- Nervous system disorders resulting from prior therapy  $\leq$  grade 2
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception
- No uncontrolled infection
- No patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study
- No history of allergic reactions attributed to compounds of similar composition to irinotecan hydrochloride, temozolomide, or temsirolimus
- No evidence of graft-vs-host disease

### Prior Concurrent Therapy

- Fully recovered from all prior anticancer therapy
- More than 3 weeks since prior myelosuppressive therapy (6 weeks for nitrosourea)
- At least 14 days since prior long-acting growth factor (e.g., Neulasta) OR 7 days for short-acting growth factor
- At least 7 days since prior biologic agent that is not a monoclonal antibody (e.g., platelet infusions)
- At least 6 weeks since prior immunotherapies (e.g., tumor vaccines)
- At least 3 half-lives since prior monoclonal antibody therapy
- At least 2 weeks since prior local palliative radiotherapy (small port)
  - At least 24 weeks since prior total-body irradiation, craniospinal radiotherapy (RT), or RT to  $\geq$  50% to the pelvis
  - At least 6 weeks since prior substantial bone marrow RT
- At least 12 weeks since prior stem cell transplantation or stem cell infusion without RT
- Prior irinotecan hydrochloride, temozolomide, and temsirolimus as single agents or a combination of 2 of the 3 drugs, including irinotecan hydrochloride and temozolomide, allowed
  - No prior combination of the 3 agents
- Concurrent corticosteroids allowed provided dose has been stable or decreasing for 7 days
  - Intermittent use of corticosteroids to manage infusional reactions is allowed
- More than 6 weeks since prior major surgery
  - Recent minor surgical procedures (e.g., vascular catheter placement, bone marrow evaluation, or laparoscopic surgery) allowed
- No other concurrent investigational drugs
- No other concurrent anticancer agents, including chemotherapy, RT, immunotherapy, or biologic therapy
- No concurrent enzyme-inducing anticonvulsants
- No concurrent CYP3A4 inducers or inhibitors including any of the following:
  - Erythromycin
  - Clarithromycin
  - Ketoconazole
  - Azithromycin
  - Itraconazole
  - Grapefruit juice
  - St. John wort
- No concurrent therapeutic anticoagulants, including aspirin or low molecular weight heparin
- No concurrent angiotensin-converting enzyme (ACE) inhibitors

- No concurrent cyclosporine, tacrolimus, or other agents to prevent either graft-versus-host disease post-bone marrow transplant or organ rejection post-transplant

**For More Information Contact:**

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