

Protocol Abstract and Schema

A Phase I Study of MK-0752 in Pediatric Patients with Recurrent or Refractory CNS Malignancies.

Description:

MK-0752 will be administered orally for 3 consecutive days of every 7 days for 28 days to children with recurrent or refractory central nervous system (CNS) malignancies. The starting dose is 200 mg/m²/day and inter-patient dose escalation or reduction will occur in set increments (to an estimated maximum of 400mg/m²/day). At the recommended MTD, we will treat a minimum of 6 evaluable patients who are < 12 years of age. Although the dose escalation will be based on toxicities observed during the first course, any grade 3/4 toxicities that occur after the first course will be documented and may warrant a review of the treatment regimen. Therapy may continue for 6 courses. If patients are deriving benefit from the therapy and have at least clinical and radiographic stable disease at the end of course 6, patients may continue therapy for an additional 13 courses (for a total of 19 courses) with the prior approval of the study Chair and representatives from Merck and Co.

Pharmacokinetics study is mandatory for study enrollment and protocol therapy.

Objectives:

Primary Objectives

1. To estimate the MTD and recommend a Phase II dose of MK-0752 administered for 3 consecutive days of every 7 days in 28 day cycles to children with recurrent or refractory CNS malignancies.

Secondary Objectives

2. To characterize the pharmacokinetics of MK-0752 administered on this schedule.
3. To document and describe toxicities associated with MK-0752 administered on this schedule
4. To preliminarily define the antitumor activity of MK-0752 within the confines of a Phase I setting.
5. To explore the incidence of NOTCH receptor and ligand expression and pathway activation in recurrent or refractory CNS tumor samples.
6. To estimate the fraction of cancer stem cells and their association with the tumor vasculature in recurrent or refractory CNS tumor samples.
7. To explore the pharmacogenetic polymorphisms in MK-0752 metabolizing enzymes and relate these polymorphisms to MK-0752 pharmacokinetics.
8. To explore the pharmacodynamic relationships between NOTCH-cleaved forms and NOTCH pathway target genes and MK-0752 pharmacokinetics.

Inclusion Criteria:

- Patient must be ≥ 3 years ≤ 21 years of age at registration.
- Patients with a histologically confirmed diagnosis of a primary CNS tumor (excluding histologically benign brain tumors (e.g. low-grade glioma)) that is recurrent, or refractory to standard therapy. All tumors must have histologic verification at either the time of diagnosis or recurrence **except** patients with intrinsic brain stem tumors. These patients must have radiographic evidence of progression.
- Patients with neurological deficits should have deficits that are stable for a minimum of 2 weeks prior to registration. A baseline detailed neurological exam should clearly document the neurological status of the patient at the time of registration on the study.
- Karnofsky Performance Scale (KPS for > 16 yrs of age) or Lansky Performance Score (LPS for ≤ 16 years of age) ≥ 60 assessed within two weeks prior to registration.
- Patients must have received standard therapy, refused standard therapy or have no other standard therapy options.
- **Baseline Adverse Events:** Patient must have recovered from the toxic effects of all prior therapy before entering this study. For those baseline adverse events attributable to prior therapy, recovery is defined as a toxicity grade ≤ 2 , using CTCAE v. 3.0, unless otherwise specified in the Inclusion and Exclusion Criteria.
- **Prior Therapy:** Patients must have:
 - o Received their last dose of known myelosuppressive anticancer chemotherapy at least three (3) weeks prior to study registration or at least six (6) weeks if nitrosourea.
 - o Received their last dose of other investigational or biologic agent ≥ 7 days prior to study registration.
 - In the event that a patient has received another investigational or biologic agent and has experienced \geq grade 2 myelosuppression, then at least three (3) weeks must have elapsed prior to registration.
 - If the investigational or biologic agent has a prolonged half-life then at least three (3) weeks must have elapsed prior to registration. Such patients should be discussed with the study chair prior to registration.
 - o Completed at least 3 half life periods from the last dose of monoclonal antibody prior to registration..
- **Radiation:** Patients must have received their last dose of radiation:
 - o ≥ 2 wks prior to study registration for local palliative XRT (small volume)
 - o ≥ 6 months prior to study registration for total body irradiation (TBI), or craniospinal XRT
 - o ≥ 6 wks prior to study registration for other substantial bone marrow irradiation

- **Bone Marrow Transplant:** Patient must be:
 - o ≥ 6 months since allogeneic bone marrow transplant prior to registration
 - o ≥ 3 months since autologous bone marrow/stem cell prior to registration
 - o No evidence of active graft versus host disease.
- **Corticosteroids:** Patients who are receiving dexamethasone must be on a stable or decreasing dose for at least 2 weeks prior to registration.
- **Growth factors:** At least 7 days since the completion of therapy with a hematopoietic growth agent (filgrastim, sargramostim, and erythropoietin) and 14 days for long-acting formulations.
- **Anticonvulsants:** If taking anticonvulsants, patients must be on anticonvulsants which are not considered enzyme inducing anticonvulsants.
- **Organ Function:** Documented within 14 days of registration and within 7 days of the start of treatment.

Bone Marrow:

- o Absolute neutrophil count $\geq 1000/\mu\text{l}$
- o Platelets $\geq 100,000/\mu\text{l}$ (unsupported)
- o Hemoglobin ≥ 8 g/dL (may receive RBC transfusions)

Renal:

- o Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73m²
- or
- o A serum creatinine based on age as follows:

Age (years)	Maximum Serum Creatinine (mg/dL)
≤ 5	0.8
>5 to ≤ 10	1
>10 to ≤ 15	1.2
>15	1.5

Hepatic:

- o Bilirubin ≤ 1.5 times upper limit of normal for age
- o SGPT (ALT) ≤ 2.5 times institutional upper limit of normal for age

Nutrition: Albumin ≥ 2.5 g/dL.

Other: Normal Sodium, Potassium, Magnesium & Calcium values. If serum Calcium is below the institutional lower limits of normal, then ionized serum Calcium needs to be above the institutional lower limits of normal.

- Female patients of childbearing potential must not be pregnant or breast-feeding. Female patients of childbearing potential must have a negative serum or urine pregnancy test.
- Patients of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study.

- Signed informed consent according to institutional guidelines must be obtained. For patients treated in the expanded MTD cohort, informed consent must also include consenting to the PK studies.

Exclusion Criteria

- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that would compromise the patient's ability to tolerate protocol therapy or would likely interfere with the study procedures or results.
- Patients receiving any other concurrent anticancer or investigational drug therapy.
- Patients is taking enzyme inducing anticonvulsant drugs.
- Patients with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.
- Prior therapy with MK-0752

Rationale:

The NOTCH pathway plays a central role in normal neural stem cell regulation and maintenance. Recent data indicate that most brain tumors including gliomas, medulloblastomas and ependymomas (28; 29) are maintained by rare fractions of stem cell-like cancer cells. In addition NOTCH signaling has been reported to be important in medulloblastoma pathogenesis, its amplification has been identified in a subgroup of posterior fossa ependymomas and high-levels of NOTCH ligands (Delta 1, Jagged 1 and 2) expression have been identified in high-grade gliomas.

MK-0752 is an orally active inhibitor of gamma secretase. This drug significantly inhibits the cleavage of known substrates of gamma secretase such as amyloid precursor protein (APP) and NOTCH. MK-0752 reduces formation of the A β 40 peptide in a dose dependent manner *in vitro* with IC₅₀ values in low nanomolar range. Although, MK-0752 was initially developed as a treatment for Alzheimer Disease, there is increasing interest in the applicability of this drug to the treatment of cancer. Indeed, MK-0752 has been shown to inhibit gamma secretase-mediated cleavage of NOTCH with an IC₅₀ of 55 nM.

Schema:

