

## PROTOCOL ABSTRACT AND SCHEMA

### **PBTC-019: A Phase I Pharmacokinetic Optimal Dosing Study of Intrathecal Topotecan for Children with Neoplastic Meningitis**

#### ***Description:***

This is a multi-center, non-randomized pharmacokinetically-guided optimal dosing study of intraventricular topotecan in children with neoplastic meningitis. Topotecan will be administered daily for five consecutive days utilizing the schema shown in the Schema below. Concomitant chemotherapy to control systemic disease or bulk CNS disease is allowable provided that the systemic chemotherapy is not an investigational agent or one of the following: high-dose methotrexate ( $> 1\text{g/m}^2$ ), high-dose cytarabine ( $> 1\text{g/m}^2$ ), 5-fluorouracil, capecitabine, thiotepa, a nitrosourea, or topotecan. The starting dose for this trial was derived from pharmacokinetic simulations that utilized data from a prior phase I study of intrathecal topotecan. The simulations were performed to estimate the length of time that ventricular CSF concentrations of topotecan lactone would remain above an optimal “target level” of 1 ng/mL. One of the primary objectives of this study is to estimate the dose of intrathecal topotecan that will result in CSF lactone concentrations exceeding 1 ng/mL for at least eight hours after an intrathecal injection. Dose escalations for patient cohorts will be conducted following the traditional phase 1 design in order to determine the maximum tolerated dose (MTD). The MTD will be called pharmacokinetically optimal if that dose achieves the targeted PK parameter in at least 23 of 25 patients treated at that dose level.

#### ***Primary Objectives:***

1. To estimate the MTD of intrathecal topotecan administered daily for 5 consecutive days.
2. To describe the toxicities and define the dose-limiting toxicity of intrathecally administered topotecan following intraventricular administration daily for 5 consecutive days.
3. To determine if the MTD of intrathecal topotecan is also a pharmacokinetic optimal dose as defined by topotecan lactone concentrations in the cerebral CSF.

#### ***Secondary Objectives:***

1. To provide preliminary descriptions of the anti-tumor activity of intraventricular topotecan observed in the heterogeneous diseases that will be treated in this trial.
2. To investigate MMP, VEGF, and other potential biological markers in the CSF of patients with neoplastic meningitis prior to and throughout treatment with intrathecal topotecan.
3. To further describe the CSF pharmacokinetics of topotecan following intrathecal administration.
4. To investigate the feasibility of central review imaging following treatment and to correlate observed effects with response to intrathecal therapy.

#### ***Eligibility Criteria – Inclusion***

1. Age: Patients must be  $\geq 3$  years and  $\leq 21$  of age at study registration.

2. Diagnosis: Patients must have neoplastic meningitis secondary to an underlying leukemia/lymphoma or a solid tumor (including primary CNS tumors or carcinomas of unknown primary site) for which there is no conventional therapy. Patients with CNS leukemia/lymphoma must be refractory to conventional therapy, including XRT (i.e., 2<sup>nd</sup> or greater relapse). Neoplastic meningitis is defined as follows:
  - 2.1. Leukemia/Lymphoma: CSF cell count > 5/ $\mu$ L AND evidence of blast cells on cytopspin preparation or by cytology.
  - 2.2. Solid tumor: Presence of tumor cells on cytopspin preparation or cytology OR the unequivocal presence of meningeal disease on MRI scans.
3. Patients who have leukemia/lymphoma: Patients with CNS leukemia or lymphoma must have a negative bone marrow aspirate assessed within two weeks prior to registration.
4. Performance Status: Karnofsky Performance Scale (KPS for > 16 yrs of age) or Lansky Performance Score (LPS for  $\leq$  16 years of age)  $\geq$  60 assessed within two weeks prior to registration. Patients who are unable to walk because of paralysis, but who are in a wheelchair, will be considered ambulatory for the purposes of the performance score.
5. Recovery from Prior Therapy: Patients must have recovered from the acute neurotoxic effects of all prior chemotherapy, biological therapy, immunotherapy, or radiotherapy prior to entering this study and must be without uncontrolled significant systemic illness (e.g. infection).
  - 5.1. Chemo: Patients must have received their last dose of systemically administered therapy specifically for the treatment of their leptomeningeal disease (must be discussed with study chair) at least three (3) weeks prior to study registration. Patients must have received their last dose of intrathecal therapy at least one (1) week (2 weeks if intrathecal DepoCyt) prior to study registration.
  - 5.2. XRT: Patients must have had their last fraction of craniospinal irradiation  $\geq$  8 weeks prior to study registration.
6. The following laboratory values must be assessed within two (2) weeks prior to registration. Laboratory tests should be repeated within 48 hours of beginning therapy, if there has been a significant clinical change.

*Electrolytes:*

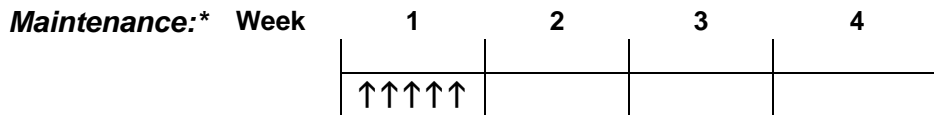
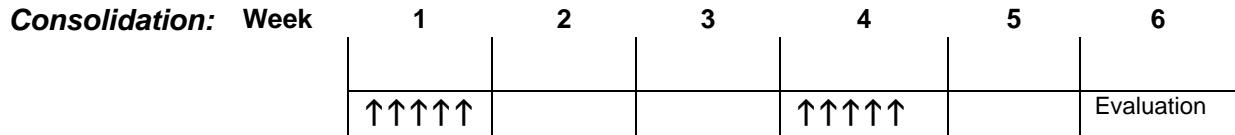
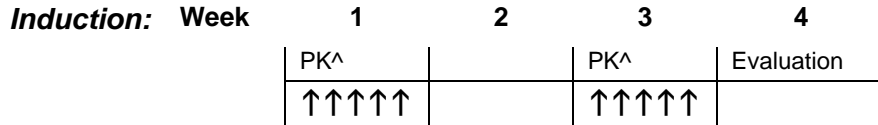
  - Sodium:  $\geq$  125 and  $\leq$  150 mEq
  - Calcium:  $\geq$  7 mg/dL
  - Magnesium:  $\geq$  0.7 mg/dL
7. Intraventricular access device: Patients must have or be willing to have an intraventricular access device such as an Ommaya reservoir.
8. Female patients of childbearing potential must have a negative serum or urine pregnancy test prior to registration. Patient must not be breast-feeding.
9. 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.

10. Signed informed consent according to institutional guidelines must be obtained.

***Eligibility Criteria - Exclusion:***

1. CSF Flow: Patients with clinical evidence of obstructive hydrocephalus are not eligible for this protocol. Patients with compartmentalization of CSF flow, as documented by radioisotope Indium<sup>111</sup> or Technetium<sup>99</sup>-DTPA flow study are not eligible for this protocol. Requirement for CSF flow studies are:
  - 1.1. Solid or CNS tumor patients: Nuclear medicine CSF flow studies are required within 7 days prior to registration in all patients with underlying solid or CNS tumors. Informed consent must be obtained prior to the CSF flow study.
  - 1.2. Leukemia or lymphoma patients: Nuclear medicine CSF flow studies are only required if CSF analysis or an MRI suggests that there may be a blockage to CSF flow. The study must be obtained within 7 days prior to registration. Informed consent must be obtained prior to the CSF flow study.
2. Underlying illness: Patients with any significant medical illnesses that, in the investigator's opinion, cannot be adequately controlled with appropriate therapy or would compromise a patient's ability to tolerate this therapy.
3. Concomitant Therapy: Patients receiving other therapy (either intrathecal or systemic) designed to treat their leptomeningeal disease are not eligible for this study. **Note:** Patients receiving concomitant chemotherapy to control systemic disease or bulk CNS disease will be eligible, provided that the systemic chemotherapy is not an investigational agent or one of the following: high-dose methotrexate (> 1g/m<sup>2</sup>), high-dose cytarabine (> 1g/m<sup>2</sup>), 5-fluorouracil, capecitabine, thiotepa, a nitrosourea, or topotecan. Please discuss plans for systemic therapy with the Study Chair prior to study entry.
4. Patients with a ventriculoperitoneal (VP) or ventriculoatrial (VA) shunt are not eligible unless they are completely shunt-independent, e.g., shunts that have an on/off valve that is always in the "off" position.
5. Patients must be free of uncontrolled infection, except HIV patients with AIDS-related lymphomatous meningitis.
6. Patients currently receiving or who have received an investigational agent within the 14 days prior to study registration. The 14 day period should be extended if the investigational agent is known to have delayed toxicity.
7. Patients with impending spinal cord compression or other CNS involvement requiring emergent local XRT (e.g., acute visual loss secondary to optic nerve involvement).
8. Patients receiving concomitant radiation therapy to the CNS. **Note:** Patients may receive radiation therapy to extra-CNS sites, e.g. painful bone metastases not in the craniospinal axis.

## SCHEMA



\* Repeat x 11 courses of maintenance.

Disease evaluations should be performed every 3 courses during maintenance and as clinically indicated.

<sup>^</sup> PK = pharmacokinetics.

All patients will have serial CSF sampling following the first dose of intraventricular drug (Day 1, week 1).

Consenting patients will have serial CSF sampling after an intralumbar topotecan dose (Day 1, week 3).

↑↑↑↑↑ = 5 consecutive days of intrathecal topotecan.  
 All doses are intraventricular except for Day 1, week 3 as noted above.