

01-C-0091: A Phase I Trial and Pharmacokinetic Study of Tariquidar (XR9576), a P-Glycoprotein Inhibitor, in Combination with Doxorubicin, Vinorelbine or Docetaxel in Pediatric Patients with Refractory Solid Tumors Including Brain Tumors

Pgp is a 170 kDa plasma membrane glycoprotein that functions as a non-specific energy-dependent drug efflux pump. Pgp is expressed in a variety of normal human tissues. Pgp over-expression in tumor cells results in a multidrug resistance phenotype by preventing the intracellular accumulation of a variety of chemotherapeutic agents. XR9576 is a specific Pgp inhibitor that blocks Pgp function for up to 24 hours after a single dose without significant toxicity in animals and humans. In adults XR9576 in combination with doxorubicin, paclitaxel, or vinorelbine is well tolerated, and only minor alterations in the clearance and drug exposure (area under the concentration time curve, AUC) of the anticancer drugs have been observed. A phase I trial and pharmacokinetic study of intravenous XR9576 in children with refractory solid tumors including brain tumors will be conducted. XR9576 will be administered in combination with doxorubicin, vinorelbine, or docetaxel.

ELIGIBILITY CRITERIA:

Age: Patients must be ≥ 2 years and ≤ 18 years of age.

Diagnosis: Histologically confirmed solid tumors which may include but are not limited to rhabdomyosarcoma and other soft tissue sarcomas, Ewing's sarcoma family of tumors, osteosarcoma, neuroblastoma, Wilms' tumor, hepatic tumors, germ cell tumors, and primary brain tumors. In patients with brain stem or optic gliomas the requirement for histological confirmation may be waived.

Measurable/Evaluable disease: Patients must have measurable or evaluable tumors.

Prior Therapy:

- The patient's cancer must have relapsed after or failed to respond to frontline curative therapy and there must not be other potentially curative treatment options available. Curative therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities.
- Patients must have had their last dose of radiation therapy at least four weeks prior to study entry, their last dose of chemotherapy at least 21 days prior to study entry (28 days for nitrosoureas), and their last dose of any investigational cancer therapy at least 30 days prior to study entry.
- Patients must have recovered from the toxic effects of all prior therapy before entry onto this trial.
- Patients with brain tumors must be on a stable or tapering dose of corticosteroids for 7 days prior to the baseline scan performed for the purpose of assessing response to therapy on this study.
- Patients should be off colony stimulating factors such as G-CSF, GM-CSF, erythropoietin, and IL-11 for at least 72 hours prior to study entry.
- Lifetime cumulative dose of anthracycline:
- Restrictions on the prior cumulative dose of anthracyclines only apply to patients who will receive doxorubicin in combination with tariquidar.
- The lifetime cumulative dose of anthracycline must be ≤ 300 mg/m² in patients who will receive doxorubicin in combination with tariquidar, if the anthracycline was administered as a bolus injection without a cardioprotectant (e.g., dexrazoxane) OR if the patient had mediastinal radiation.
- The lifetime cumulative dose of anthracycline must be ≤ 400 mg/m², if the anthracycline was administered by continuous infusion or with a cardioprotectant and the patient has not had mediastinal radiation.

Performance status: Patients should have an ECOG performance status of 0, 1, or 2 (See Table below). Patients who are unable to walk because of paralysis or weakness, but who are up in a wheelchair will be considered ambulatory for the purpose of calculating the performance score.

Score	Clinical Status
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden
4	Bedridden

Hematological Function: Patients must have adequate bone marrow function, defined as a peripheral absolute granulocyte count of $\geq 1,500/\mu\text{L}$, hemoglobin ≥ 8 gm/dl, and a platelet count $\geq 100,000/\mu\text{L}$.

Hepatic Function: Patients must have adequate liver function, defined as bilirubin within normal limits, SGPT (ALT) $< 2 \times$ the upper limit of normal.

Renal Function: Patients must have an age-adjusted normal serum creatinine (see Table below) OR a creatinine clearance ≥ 60 mL/min/1.73 m².

Age (Years)	Maximum Serum Creatinine (mg/dl)
≤ 5	0.8
$5 < \text{age} \leq 10$	1.0
$10 < \text{age} \leq 15$	1.2
> 15	1.5

Cardiac function: Patients who will receive doxorubicin must have normal cardiac ejection fraction on Echocardiogram. An Echocardiogram need not be performed in patients who will receive docetaxel or vinorelbine.

Informed consent: All patients or their legal guardians (if the patients is <18 years old) must sign a document of informed consent indicating their understanding of the investigational nature and the risks of this study before any protocol related studies are performed (This does not include routine laboratory tests or imaging studies required to establish eligibility). When appropriate, pediatric patients will be included in all discussions in order to obtain verbal assent.

Durable Power of Attorney (DPA): Patients who have brain tumors and who are ≥ 18 years of age will be offered the opportunity to assign a DPA so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired.

EXCLUSION CRITERIA:

- Clinically significant unrelated systemic illness, such as serious infections, hepatic, renal or other organ dysfunction, which in the judgment of the Principal or Associate Investigator would compromise the patient's ability to tolerate and of the agents in this trial or are likely to interfere with the study procedures or results.
- Patients with a history of bone marrow transplantation within the previous 4 months or extensive radiotherapy (craniospinal radiation, total body radiation, or radiation to more than half of the pelvis).

- Pregnant or breast feeding females are excluded because tariquidar in combination with a cytotoxic drug may be harmful to the developing fetus or nursing child.
- Patients currently receiving other investigational agents.

PRETREATMENT EVALUATION:

- History and physical (including neuro exam), documentation of signs and symptoms and measurable disease, height, weight, BSA
- Laboratory work to assess blood counts, organ function, and metabolic status
- Radiologic evaluation within the 2 weeks prior to start of therapy
- Echocardiogram must be performed within 2 weeks only for patients who will receive doxorubicin in combination with tariquidar (XR9576). A twelve-lead ECG in patients who will receive docetaxel or vinorelbine

GENERAL TREATMENT PLAN:

- This is a dose escalation trial of tariquidar (XR9576) in separate patient cohorts with fixed doses of the anticancer drugs. The anticancer agent will be individualized based on the patient's diagnosis and prior therapy. For cycle 1, tariquidar (XR9576) will be administered alone iv over 30 minutes to study its acute toxicity, pharmacokinetics and pharmacodynamics. Tariquidar will then be given again approximately 48 hrs later prior to the chosen anticancer agent. To assess Pgp function ^{99m}Tc Sestamibi Scintigraphy will be performed before and after the first dose of tariquidar (XR9576) during cycle one only. Pgp function is also assessed in CD56 positive PBMC before and after XR9576.

PHARMACOKINETICS AND PHARMACODYNAMICS:

- Pharmacokinetics will be obtained after administration of tariquidar (XR9576) when given alone and again when given in combination with the chosen anticancer agent during cycle only.
- To assess Pgp function ^{99m}Tc Sestamibi Scintigraphy will be performed before and after the first dose of tariquidar (XR9576) during cycle one only. Pgp function is also assessed in CD56 positive PBMC before and after XR9576.

ACCRUAL:

- Open to accrual. Patients meeting eligibility criteria can be referred to the Pediatric Oncology Branch, NCI, for evaluation and treatment. Patients should bring to NIH a summary of previous treatment, most recent laboratory work, copies of most recent radiologic studies including 2 scans that document disease progression from last treatment, and original pathology slides and report. When available, frozen tissue (previously obtained) will be requested for PGP staining at the NIH.