

04-C-0001: Phase II Study of Sequential Gemcitabine Followed by Docetaxel for Recurrent Ewing's Sarcoma, Osteosarcoma, or Unresectable or Locally Recurrent Chondrosarcoma

Gemcitabine and docetaxel are active antineoplastic agents with a broad spectrum of clinical activity. The primary objective of this study is to determine the objective response rate of sequential gemcitabine-docetaxel in patients with recurrent Ewing's sarcoma, recurrent osteosarcoma, and unresectable or locally recurrent chondrosarcomas. Additionally, the pharmacokinetics of gemcitabine and docetaxel will be studied in this patient population and when available, tumor samples for cDNA microarray analysis of gene expression and development of cell lines and xenotransplantation models will be obtained. The study will be conducted with the Sarcoma Alliance for Research through Collaboration (SARC).

ELIGIBILITY CRITERIA:

- **Age:** ≥ 4 years
- **Histologic diagnosis:**
 - recurrent high grade osteosarcoma, Ewing's sarcoma, unresectable or locally recurrent unresectable chondrosarcoma.
 - Histological diagnosis from initial diagnosis is acceptable for local recurrences, however, biopsy confirmation is strongly recommended.
 - For isolated pulmonary recurrences, biopsy is required.
- **Measurable Disease**-defined as lesions that can be measured in at least one dimension by medical imaging techniques. Ascites, pleural effusions, and bone marrow disease will not be considered measurable disease.
- **Performance Status:** ECOG performance status of ≤ 2
- **Osteosarcoma and Ewing's sarcoma:** Must have progressed after standard therapy, and may have received no more than 2 additional salvage regimens.
- **Chondrosarcoma:** must be unresectable or locally recurrent and unable to be completely resected.
- **Prior therapy:**
 - Patients must have recovered (defined as toxicity $<$ grade 2) from toxic effects of all prior therapy before entering onto study.
 - A treatment free interval of at least 2 weeks since the last dose of myelosuppressive therapy is required.
 - At least 6 month interval since last dose of myeloablative therapy or total body irradiation is required.
 - A minimum of 6 weeks since local radiation and 4 months from extensive radiation (greater than 50% of pelvis or crainial spinal radiation) is required.
 - Patients who received filgrastim on a previous cycle of chemotherapy must be off filgrastim for at least 72 hours prior to entry onto study.
- **Hematologic function:** Adequate bone marrow function with an ANC $\geq 1500/\text{mm}^3$, platelet count $\geq 100,000 \text{ mm}^3$ (transfusion independent) and hemoglobin $> 8.0 \text{ g/dl}$ (transfusions permitted).
- **Renal function:** serum normal age adjusted serum creatinine (see table below) or creatinine clearance or radioisotope GFR $> 70 \text{ ml/min/1.73 m}^2$. For patients over 18 years of age, creatinine must be \leq upper limit of normal range.

Age (Years)	Maximum Serum Creatinine (mg/dl)
< 5	0.8
5 ≤ age ≤ 10	1.0
10 < age ≤ 15	1.2
15 < age ≤ 18	1.5

- **Hepatic function:** Must have adequate liver function, defined as bilirubin within normal limits, SGPT (ALT) ≤ 2.5 x the upper limit of normal. For patients with documented Gilbert syndrome, total bilirubin >ULN may be acceptable if the Principal Investigator in consultation with Medical Affairs approves a special exemption for treatment on this protocol.
- **Neuropathy:** Sensory or Motor neuropathy due to prior chemotherapy, if present, must be ≤ grade 1. Neuropathy (Sensory or Motor) due to prior surgery or tumor involvement must be ≤ grade 2 and stable or improving.
- **Childbearing or child-fathering potential:** must be willing to use a medically acceptable form of birth control, which may include abstinence, while being treated on this study and for 3 months afterwards.
- **Informed consent:** All patients or their legal guardians (if the patient is less than 18 years of age) must sign a document of informed consent indicating their awareness of the investigational nature and the risks of the study. When appropriate the patient will be included in all discussions in order to obtain assent.

EXCLUSION CRITERIA:

- Pregnant or breast feeding females
- Prior treatment with gemcitabine or taxanes
- Active or uncontrolled infection
- History of known hypersensitivity reaction to docetaxel or other agents formulated in polysorbate 80.
- Recipient of prior allogeneic transplants.

PRETREATMENT EVALUATION:

- History and Physical: documentation of neurological exam, performance status, height, weight, and BSA
- Labs: CBC/diff, platelets, Na, K, Cl, CO₂, BUN, serum glucose, serum creatinine, serum bilirubin, alkaline phosphatase, SGPT, SGOT, LDH, Mg, Ca, phosphorus, uric acid, beta HCG for females of child-bearing age.
- Imaging Studies: CT scan and/or MRI of index lesion(s), chest CT and bone scan

GENERAL TREATMENT PLAN:

- Chemotherapy will include: On day 1 of each cycle, gemcitabine will be administered. On day 8, gemcitabine will be administered followed by docetaxel.
- Filgrastim (5 μg/kg) will be administered subcutaneously daily beginning 24 hours after administration of docetaxel and will continue until post nadir ANC ≥ 1200/μL or pegfilgrastim (Neulasta™) can be administered subcutaneously as a single dose (6mg) per cycle to patients weighing ≥ 45 kg (99 lbs).

- Cycles will be repeated every 21 days unless the patient experiences unacceptable toxicity or progressive disease. A maximum of 14 cycles of therapy can be administered.

PHARMACOKINETICS:

- Pharmacokinetic evaluation of gemcitabine and docetaxel will be performed during cycle 1 ONLY. Blood samples for the determination of gemcitabine (and its metabolite dFdU) will be obtained prior to infusion, at 75 and 85, 95, 105 and 120 minutes, after the start of the 90 minute infusion on day 1 and day 8 of cycle 1. Additionally, on day 8, docetaxel pharmacokinetics will be performed. Blood samples for determination of docetaxel concentrations will be collected prior to infusion, 55 minutes (5 minutes prior to the end of infusion), 30 minutes post infusion, 4 hr and 24hr post infusion.

CORRELATIVE STUDIES:

- Tumor Biology: tumor tissue will be processed for development of cell lines and murine xenotransplant models.

ACCRUAL:

- The trial is approved but not yet open for patient accrual. Please call (Donna Bernstein 301-435-7804, or Elizabeth Fox 301-402-6641) to determine if enroll has begun. Patients meeting eligibility criteria can be referred to the Pediatric Oncology Branch NCI or any SARC participants.