Jennerex(JX-594): Safety Study of Recombinant Vaccinia Virus to Treat Refractory Solid Tumors in Pediatric Patients

Type	Study Design	Model	Masking	Age Range	Primary Purpose
Interventional	Non-Randomized	Single Group Assignment	Open Label	2 to 21 years	Treatment

Purpose

This is a Phase I, open-label, dose-escalation trial in pediatric patients with advanced/metastatic, unresectable solid tumors refractory to standard therapy and/or the patient does not tolerate standard therapies. Tumors are likely to include neuroblastoma, lymphoma, Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma, non-rhabdomyosarcoma soft tissue sarcomas, and malignant peripheral nerve sheath tumors. Benign tumors are excluded. These tumor types were selected because evidence of biological activity was observed in cancer cells lines and ex vivo infected primary human tissue samples, specifically pediatric cancer types such as sarcomas and neuroblastomas.

Outcome Measures

Primary Outcome Measures

- Determine the maximally-tolerated dose (MTD) and/or maximum-feasible dose (MFD) of JX-594
- Determine the maximally-tolerated dose (MTD) and/or maximum-feasible dose (MFD) of JX-594 administered by intratumoral (IT) injection in pediatric patients with advanced/metastatic, unresectable refractory solid tumors
- Determine the safety/toxicity of JX-594 administered by IT injection in this patient population

Secondary Outcome Measures

- Determine the JX-594 pharmacokinetics and pharmacodynamics over time following IT injection in this patient population
- Determine the immune response to JX-594 following IT injection in this patient population

Intervention Details:

- Drug: Recombinant Vaccinia GM-CSF; RAC VAC GM-CSF (JX-594) Intratumoral Injection Dosage from 1x106 pfu/kg to 3x107 pfu/kg is administered once to 1-3 injectable tumors in pediatric patients.

Eligibility

- Ages eligible for study: 2 Years to 21 Years
- Genders eligible for study: male and female
- Accept healthy volunteers: no

Criteria

Inclusion Criteria

- Age between 2 and 21 years
- Histologically-confirmed, advanced/metastatic non-CNS solid tumor that is relapsed and/or refractory to standard therapy (progressive disease despite therapy) and/or the patient does not tolerate standard therapy. Non-CNS solid tumors are eligible and are likely to include such histologies as neuroblastoma, Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma, non-rhabdomyosarcoma soft tissue sarcomas, and malignant peripheral nerve sheath tumors.
- Cancer is not surgically resectable for cure
- At least one measurable tumor mass by CT/MRI (i.e. lesion that can accurately be measured in at least one dimension with longest diameter ≥ 1 cm) and that can be injected by direct visualization/palpitation or by imaging-guidance (CT or ultrasound)
- Expected survival for approximately 12 weeks or longer
- Lansky Score ≥ 50
- Total bilirubin ≤ 2.5 × ULN
- AST, ALT ≤ 2.5 × ULN
- Serum creatinine ≤ 1.8 x ULN
- INR ≤ 1.5 x ULN
- Hematologic parameters: Patients can be transfused to meet these entry criteria.
  - Hemoglobin ≥ 9 g/dL
  - For bone marrow negative patients: ANC ≥ 750 cells/ mm3 and platelet count ≥ 75,000 plts/mm3
  - For bone marrow positive patients: ANC ≥ 750 cells/ mm3. Platelet count recovery is not a requirement, but platelets should be transfused to ≥ 75,000 plts/ mm3 prior to treatment.
- CD4 count ≥ 200/mm3. Patients who demonstrate intact delayed-type hypersensitivity (DTH) via skin immune response to common antigens (e.g. candida, mumps) are also eligible.
- For patients who are sexually active, able and willing to abstain from sexual activity for 3 weeks following treatment with JX-594. Thereafter, able and willing to use accepted birth control methods through 3 months after last treatment with JX-594. [Acceptable birth control methods include contraceptive pills, condom, IUD, diaphragm or sponge + spermicide, or other methods with >97% effectiveness]
- Able and willing to sign an Institutional Review Board (IRB)/Research Ethics Board (REB)-approved written consent form (patient and/ or parents/guardians).
- Able and willing to comply with study procedures and follow-up examinations, including compliance with the "Infection Control Guidelines for Patients" contained within the written consent form (patient and/ or parents/guardians).

Exclusion Criteria

- Pregnant or nursing infant
- Injected tumor(s) in location that would potentially result in significant clinical adverse effects if post-treatment tumor swelling were to occur or if deemed unsafe by investigator (e.g. tumors impinging on the upper airway or affecting biliary tract drainage, adherent to and/or invading a major vascular structure, CNS, etc.)
- Brain metastases, unless surgically resected and/or irradiated. (Brain metastases cannot be considered as a site for injection).
- Patients with lymphomas

- Use of high dose systemic corticosteroids or other immune suppressive medication within 3 weeks of first treatment (e.g. cortisone, dexamethasone, hydrocortisone, prednisone, prednisolone, interferon, cisplatin, doxorubicin, fluorouracil, etc.). * Note: patients taking low-dose corticosteroids for the treatment of nausea and/or taking maintenance corticosteroids for adrenal insufficiency are permitted to enroll.
- Known infection with HIV or known underlying genetic immunodeficiency disease
- Treatment of the injected tumor(s) with radiotherapy, chemotherapy, surgery, or an investigational drug within 3 weeks prior to first treatment
- Clinically significant active infection or uncontrolled medical condition considered high risk for investigational new drug treatment (e.g. pulmonary, neurological, cardiovascular, gastrointestinal, genitourinary)
- History of exfoliative skin condition (e.g. severe eczema, ectopic dermatitis, or similar skin disorder) requiring systemic therapy
- Clinically significant and/or rapidly accumulating ascites, peri-cardial and/or pleural effusions (e.g. requiring drainage for symptom control)
- Severe or unstable cardiac disease which may include, but is not limited to, any of the following within 6 months prior to screening: myocardial infarct, unstable angina, congestive heart failure, myocarditis, arrhythmias diagnosed and requiring medication, or any clinically-significant change in cardiac status
- Current, active, progressing CNS malignancy, including carcinomatosis meningitis (definitively surgically resected or irradiated metastases allowed)
- Pulse oximetry O2 saturation <90% at rest
- Use of anti-viral, anti-platelet or anti-coagulation medication (for example, heparin, warfarin, aspirin, ticlopidine, clopidogrel, dipyridamole) [Patients who discontinue such medications within 7 days prior to first treatment may be eligible for this study. Any required, chronic medications indicated for other medical issues should not be discontinued in order to meet eligibility criteria for this trial without consultation with both the patient and the treating physician.] Note: Low Dose Heparin to maintain patency of venous catheters is permitted.
- Patients with benign tumors
- Inability or unwillingness to give informed consent (patient or parent/guardian) or comply with the procedures required in this protocol
- Vaccination with a live virus (i.e. measles, mumps, rubella, etc) < 30 days prior to first treatment
- Patients with household contacts who meet any of these criteria will be excluded unless alternate living arrangements can be made during the patient's active dosing period and for three weeks following the last dose of study medication:
  - Women who are pregnant or nursing an infant
  - Children < 1 years old
  - People with skin disease (eczema, atopic dermatitis and related diseases)
  - Immunocompromised hosts (severe deficiencies in cell-mediated immunity, including AIDS, organ transplant recipients, hematologic malignancies)

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