NCT00931931: A Phase I Dose Escalation Study of Intratumoral Herpes Simplex Virus-1 Mutant HSV1716 In Patients with Refractory Non-Central Nervous System (Non-CNS) Solid Tumors/ Therapy for Relapse

	Status	Age Range (yrs.)	Sponsor	Protocol ID
Interventional	Currently Recruiting	13 to 30	CCHMC	NCT00931931

Outline

This is a single-site study.

Patients with relapsed solid tumors such as sarcomas and neuroblastoma have a poor survival, generally < 20%. There is an urgent need for new treatments that are safe and effective.

HSV1716 is a mutant herpes simplex virus (HSV) type I, deleted in the RL1 gene which encodes the protein ICP34.5, a specific determinant of virulence. Mutants lacking the RL1 gene are capable of replication in actively dividing cells but not in terminally differentiated cells - a phenotype exploited to selectively kill tumor cells. In previous clinical studies, HSV1716 has been shown to be safe when injected at doses up to 105 plaque forming units (pfu) directly into human high-grade glioma and into normal brain adjacent to tumour, following excision of high-grade glioma. In an extension study, HSV1716 has been shown to be safe when injected at a dose of up to 106 pfu directly into brain tumors. Replication of HSV1716 in human glioblastoma in situ has been demonstrated. Following a single administration of HSV1716 by direct injection into active recurrent tumor or brain adjacent to tumor, some patients have lived longer than might have been expected. This study seeks to evaluate the safety of a single injection of HSV1716 in the treatment of extracranial solid tumors in adolescents and young adults.

HSV1716 has also proved safe when given by direct intra-tumoural injection in patients with squamous carcinoma of the head and neck, and in patients with malignant melanoma.

Replication of HSV mutants in human sarcomas and neuroblastoma in cultured cells and human xenograft models has been demonstrated.

This study is designed in two parts. PART 1 of the study specifies a single virus injection. Participates who experience a partial response, or relapse following a complete response, may qualify for subsequent injections in PART 2, described in Section 16. PART 2 requires signing of a separate consent.

Objectives

Primary

To determine whether intratumoral injection of HSV1716, at dose levels shown to be safe for adult tumors, is safe in adolescents and young adults with non-CNS solid tumors.

Time Frame: Dose limiting toxicities will be assessed at 28 days after injection of HSV1716.

Designated as safety issue: Yes

Secondary

To measure antiviral immune response in patients with refractory cancer treated with HSV1716.

Time Frame: Antiviral immune response will be assessed 28 days after injection. Beginning at 1.5 years post injection, assessments will occur every 6 months. Beginning 5 years after the injection, assessments will occur annually until 15 years post injection.

Designated as safety issue: Yes

Projected Accrual

Twelve to eighteen people will take part in this study at Cincinnati Children's Hospital Medical Center.

In Part 1, there will be 3 subjects in the first dose level, and 3 for each site subset at the second dose level. With 3 site subsets, we anticipate 9 subjects at dose level 2, for a total of twelve subjects. More than twelve will be enrolled if any patient experiences a DLT. The maximum number of evaluable subjects is 18. Those who are eligible for additional injections may proceed to Part 2 of this study.

Entry Criteria

Inclusion Criteria

- Age: Subjects must be greater than or equal to 13 years and less than or equal to 30 years of age at the time of signing consent (study entry);
- Histologic Diagnosis: Subjects must have had histologic verification a non-CNS solid tumor at original diagnosis. The tumor must be amenable to HSV1716 administration without undue risk. Disease must be considered refractory to conventional therapy or for which no conventional therapy exists. There must be no available therapy with demonstrated clinical benefit for the subject as deemed by the subject's primary oncologist; Metastatic Disease: Subjects who have metastasis to the brain are eligible for this study; however, no metastatic sites within the brain will be considered for injection.
- Performance Level: Karnofsky greater than or equal to 50. Subjects who are unable to walk because of paralysis, but who are up in a wheelchair will be considered ambulatory for the purpose of assessing the performance score.
- Life Expectancy: Anticipated to be greater than or equal to 8 weeks from time of study entry;

- Subjects must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study;
- Myelosuppressive chemotherapy: Must not have received within 28 days of entry onto this study (42 days if prior nitrosourea) accompanied by hematopoietic recovery, or 14 days of stopping non-myelosuppressive therapy as long as hematopoietic requirements are met;
- Biologic (anti-neoplastic agent): Must not have received within 28 days of entry onto this study;
- No Radiation Therapy greater than or equal to 14 days for local palliative XRT (small port): greater than or equal to 6 months must have elapsed if prior craniospinal XRT or if greater than or equal to 50% radiation of pelvis; greater than or equal to 42 days must have elapsed if other substantial bone marrow radiation;
- Immunoablative or myeloablative Stem Cell Transplant (SCT): greater than or equal to 6 months must have elapsed from prior autologous transplant. Subjects must not have graft versus host disease post autologous transplant;
- Investigational agent: > 28 days must have elapsed from treatment with a different investigational agent;
- Subjects with seizure disorder may be enrolled if on anticonvulsants and well controlled.
- At the time of enrollment, specified CNS conditions must be < Grade II toxicity per CTCAE 3.0 criteria;
- All subjects must have adequate blood counts defined as: peripheral absolute neutrophil count (ANC) greater than or equal to 750/uL, Platelet count greater than or equal to 100,000/uL (may be a post transfusion value), Hemoglobin greater than or equal to 9.0 gm/dL (may be a post transfusion value)
- Adequate renal function defined as:Serum creatinine less than or equal to 1.5 x upper limit of normal (ULN) for age or creatinine clearance or radioisotope GFR greater than or equal to 70 ml/min/1.73 m2;
- Adequate liver function defined as: Total bilirubin less than or equal to 2.0 x ULN for age, and SGPT (ALT) less than or equal to 2.5 x ULN for age and albumin greater than or equal to 2g/dL, GGT < 2.5 x ULN
- Adequate cardiac function as defined by: Shortening fraction >25% by echocardiogram or ejection fraction above the institutional lower limit of normal by MUGA, No focal wall motion abnormalities as determined by either of the above studies, EKG without evidence of ischemia or significant arrythmia
- Adequate coagulation as defined by:PT/INR and PTT <1.5 x ULN for age;
- Infectious Disease: Documented evidence of negative tests for the presence of Hepatitis B surface antigen, Hepatitis C antibody, HIV1 and HIV2 antibodies within the three months preceding study entry. Subjects who do not have such evidence must undergo appropriate testing prior to virus administration;
- Lesion Size: The targeted lesion must be at least 18 mm in each of 3 dimensions as determined by CT or MRI scans. Lesions not meeting this requirement may be used if volumetric measurements show it to be greater than or equal to 3mL.

Exclusion Criteria

- Stem cell transplant: No subjects who have received an allogeneic hematopoietic stem cell transplant are eligible;
- Pregnancy or Breast-Feeding: There is no available information regarding human fetal or teratogenic toxicities. Pregnant women are excluded and pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method from the time of study entry to a period of no less than four months post the final HSV1716 injection. For the same period of time, women who participate in this study must agree not to breast feed;
- Consent: Unable or unwilling to give voluntary informed consent / assent;
- Leukemia: Subjects with leukemia are not eligible for study participation;
- Infection or any other severe systemic disease or medical or surgical condition deemed significant by the principal investigator;
- Administration of any unlicensed or investigational product within 4 weeks of entry to the study;

- Growth factor(s): No PEG-GCSF within 14 days of virus injection;
- Anti_HSV antivirals: Subjects whose physicians determine that anti-HSV antiviral therapy (such as acyclovir, ganciclovir, foscarnet, etc.) cannot be safely discontinued from 2 days prior to the injection to 28 days following the injeciton should not be in the study.
- Subjects who have other conditions which in the opinion of the investigator contra-indicate the receipt of HSV1716 or indicate subject's inability to follow protocol requirements.

Patient Characteristics

- **Age**: Subjects must be ≥13 years and ≤30 years of age at the time of signing consent (study entry).
- **Histologic Diagnosis**: Subjects must have had histologic verification of a Non-CNS solid tumor at original diagnosis. The tumor must be amenable to HSV1716 administration without undue risk. Disease must be considered refractory to conventional therapy or for which no conventional therapy exists. There must be no available therapy with demonstrated clinical benefit for the subject as deemed by the subject's primary oncologist.
- **Metastatic Disease**: Subjects who have metastasis to the brain are eligible for this study; however, no metastatic sites within the brain will be considered for injection.
- **Performance Level**: Karnofsky ≥ 50. Subjects who are unable to walk because of paralysis, but whoare up in a wheelchair will be considered ambulatory for the purpose of assessing the performance score.
- **Life Expectancy**: Anticipated to be ≥ 8 weeks from time of study entry.

Prior Concurrent Therapy

- Subjects must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.
- Myelosuppressive chemotherapy: Must not have received within 28 days of entry onto this study (42 days if prior nitrosourea drug) accompanied by hematopoietic recovery or 14 days of stopping non-myelosuppressive therapy as long as hematopoietic requirements are met;
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