SILLAJEN

A Novel Oncolytic Immunotherapy in Hepatocellular Carcinoma

Please consider this research study for your patients with advanced HCC who are eligible to receive sorafenib therapy and are systemic therapy naive. It offers a combination of the latest science, a promising oncolytic immunotherapy, in addition to sorafenib (Nexavar), the standard of care for HCC.

Discover Pexa-Vec for Your Patients with Advanced HCC

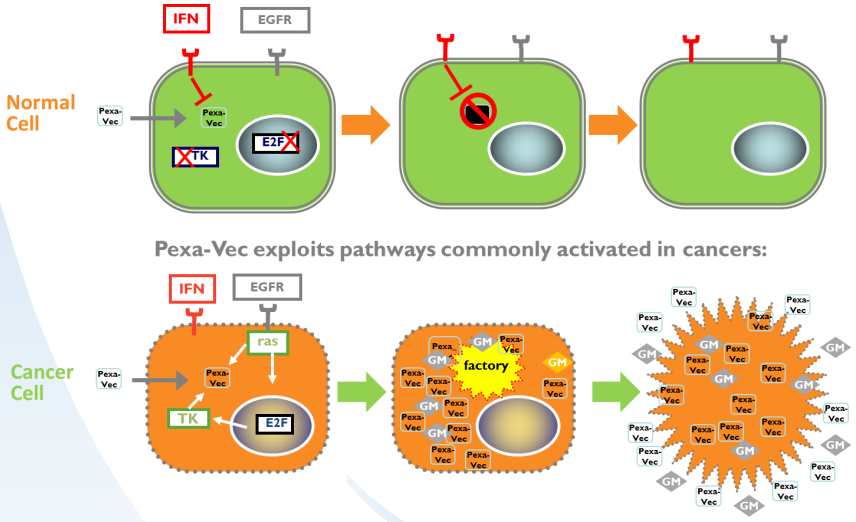
Designed to Selectively Target and Destroy Cancer Cells

The investigational therapy, Pexa-Vec, is an attenuated vaccinia virus engineered to stimulate anti-tumor immunity and directly lyse tumor cells. Pexa-Vec has enhanced cancer selectivity through the deactivation of its thymidine kinase (TK) gene, and it has been engineered to express the granulocyte-macrophage colony stimulating factor (GM-CSF) gene to stimulate a systemic anti-tumor immune response. Researchers believe that Pexa-Vec may be a systemic treatment of HCC by inducing tumor necrosis and shrinkage of both injected and non-injected tumors after direct intratumoral delivery.

The PHOCUS Study is a global, phase 3 research study for patients with advanced, unresectable HCC who are eligible to receive sorafenib (Nexavar®).

Final data from a randomized dose-ranging phase 2 study of Pexa-Vec in mainly sorafenib naïve patients with advanced HCC demonstrated that the risk of death for patients who received Pexa-Vec at the high dose was markedly reduced (by nearly 60 percent; hazard ratio = 0.41) when compared to patients randomized to a low dose control (one-tenth of the high dose). The median overall survival for high and low dose groups was 14.1 months versus 6.7 months, respectively (p = 0.020 for superiority of the high dose). Pexa-Vec was well-tolerated with patients experiencing transient flu-like symptoms that generally resolved within 24 hours.

Complementary Mechanisms of Action: Oncolysis, Vascular Ablation, and Active Immunotherapy



Pexa-Vec is engineered to have multiple mechanisms of action. These include 1) the direct lysis of cancer cells through cancer-selective viral replication; 2) the reduction of the tumor's blood supply via infection of tumor associated vasculature; and 3) the activation of systemic anti-cancer immunity. It is hypothesized that this multi-faceted mechanism of action could help Pexa-Vec overcome the development of resistance seen with standard anti-neoplastic agents.

A Potential Option for Your Patients with Advanced HCC

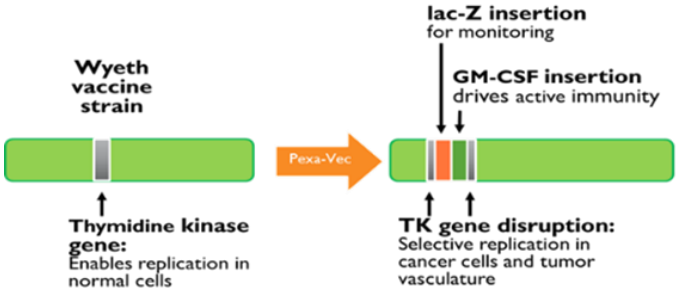
The **PHOCUS** Study is a phase 3 randomized, open-label, trial of Pexa-Vec plus sorafenib versus sorafenib in patients with advanced HCC who are systemic therapy naive. The study is being conducted to determine and compare overall survival for patients in the two treatment arms. The **PHOCUS** Study may provide another potential treatment option to patients. Please consider discussing this study opportunity with your patients.

Rationale for Potential Anti-Tumor Activity of Pexa-Vec

Pexa-Vec is a replication-competent, transgene-expressing therapeutic vaccinia virus. It has been genetically modified by the deactivation of its TK gene and insertion of the genes encoding human GM-CSF and *Escherichia coli* beta-galactosidase (lac-Z). Pexa-Vec has been designed to selectively replicate in and destroy cancer cells, while at the same time stimulating a systemic anti-tumoral immune response.

The three genetic modifications to Pexa-Vec:

1) TK gene deactivation
2) GM-CSF gene insertion under control of the synthetic early-late promoter
3) Lac-Z gene insertion under control of the p7.5 promoter



The TK gene was deactivated to decrease virulence by restricting viral replication to proliferating cells. The cDNA for the human GM-CSF gene was inserted into the TK gene to help elicit an immune response to tumor cells both at the site of viral replication and in distance metastases. The lac-Z gene was also inserted into the TK gene to facilitate selection of recombinant plaques and to allow monitoring of viral replication in tumor

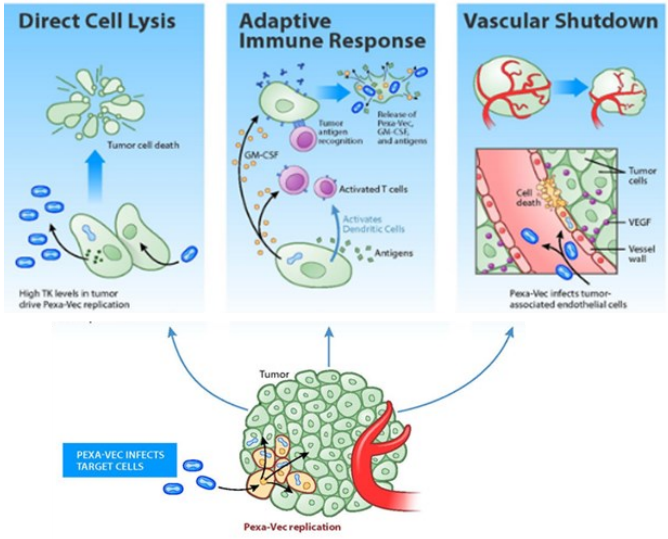
Pexa-Vec in Action

The investigational therapy Pexa-Vec is designed to target advanced HCC the following three ways:

REPLICATION: Direct cancer cell lysis secondary to cancer -selective viral replication

REDUCTION: Interruption of the tumor's blood supply via infection of tumor associated vasculature

RESPONSE: Activation of systemic anti-cancer immunity



Study Design

Participants will be randomly assigned to one of two treatment arms, having an equal chance of receiving Pexa-Vec followed by sorafenib or sorafenib alone.

Arm A: Pexa-Vec followed by Sorafenib

- Participants will visit the study center approximately 14 times over 18 weeks.
- All Pexa-Vec treatments (3) will be given by intratumoral injections into liver tumors.
- Following Pexa-Vec injection series completion, patients will receive sorafenib starting at week 6 of the study

Arm B: Sorafenib

- Participants will visit the study center approximately 12 times over 18 weeks and receive sorafenib as per standard of care.

In both groups, sorafenib is allowed to continue as long as the patient is clinically benefitting from the treatment and at least until progression or unacceptable toxicity occurs.

Every Referral Matters

Before referring a patient, please take a moment to see if they meet, or are expected to meet, the following key eligibility criteria:

⇒ Have not received sorafenib or any other systemic therapy for HCC

⇒ Have not had locoregional therapy within 28 days prior to randomization

⇒ Have a life expectancy of at least 3 months

If you have patients who may be eligible to receive sorafenib but have not yet started treatment, now is the time to introduce clinical trials as a consideration.