A Phase I dose escalation trial evaluating the impact of an in situ immunization strategy in Intra-Tumoral Injections of Pexa-Vec in combination with advanced solid tumors with injeacting lesions.

In situ immunization is a strategy where immunomodulatory products (such as PAMPS) are injected into one tumor site in order to use the tumor as its own vaccine and to trigger a systemic anti-tumor immune response.

We have recently shown that intratumoral (IT) PAMPS cure tumors via the activation of plasmacytoid dendritic cells, one of the most efficient subset of antigen presenting cells, and change their phenotype from tolerogenic to immunogenic. Of note, IT PAMPS synergize with anti-CTLA-4 to drive specific Tumor-Infiltrating T cells (TILs) to generate a systemic anti-tumor immune response able to eradicate distant, not injected, tumor sites, even in the central nervous system. Moreover, we formulate the hypothesis that IT treatment with an oncolytic virus (Pexa-Vec) could synergize with anti-CTLA4 therapy via oncolytic virus-induced tumor death & tumor-antigen release, GM-CSF-induced recruitment/maturation/activation of antigen presenting cells, and anti-CTLA-4 induced Tumor-Infiltrating T cells inhibition.

Pexa-Vec is a replication-competent, transgene-expressing therapeutic vaccinia oncolytic virus derived from the commonly used Western vaccine strain (Dryvax®, Wyeth laboratories). Pexa-Vec, manufactured by Transgene S.A. (Lillicourt-Graffenstaden, France) •. Three genetic modifications are included in Pexa-Vec: Thymidine kinase (TK) gene deactivation, GM-CSF gene insertion and LacZ gene insertion.

These genetic modifications allow a three-pronged mechanism of action with rapid onset including:

• Oncolytic: Pexa-Vec selectively replicates in and destroys cancer cells, while remaining inactive in normal cells.
• Stimulation of a systemic anti-tumor immune response through the expression of its transgene, GM-CSF, leading in the context of tumor lysis by DC expansion and increased tumor antigen presentation.
• Shutdown of blood flow into tumor tissue via infection of tumor-associated endothelial cells.

The dose escalation part follows a classical 3+3 design with 3 to 6 pts at each DLT depending of the number of DLT observed (maximum of 24 pts). In the extension part, according to the first stage of a Gehan design, 12 patients per cohort (I) will be enrolled (maximum of 36 pts).

Injections of Iplimunum and Pexa-Vec will be made into 1-5 tumors by the radiologist or other trained physician using imaging-guidance. Both IMPS should be prepared separately and injected in the same lesions with switch of syringes. Different tumors may be treated on each injection.

Pexa-Vec is a replication-competent vaccinia virus that is a modified form of the vaccinia virus that lacks the ability to replicate in normal cells but can replicate in cancer cells. It is used as a cancer vaccine to stimulate the immune system to attack and destroy cancer cells.

REFERENCES