MULTICENTER PHASE-2 GENE THERAPY TRIAL FOR ADVANCED PANCREATIC CANCER: RATIONALE AND DESIGN

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Rationale: Incidence and mortality of pancreatic cancer (PDAC) are increasing in France. There is an urgent need in novel treatment. Gene therapy is one of these innovative approaches that we have developed in collaboration with InvivoGen Company. The proof of concept was conducted with the CYL-02 compound GMP grade produced by invivoGen, a plasmid encoding for SST2 and DCK::UMK genes complexed to a synthetic vector PolyEthyleneImine. SST2 gene encodes for somatostatin receptor subtype 2 and DCK::UMK is a fusion between two cDNAs each coding for an enzyme critical for Gemcitabine intracellular metabolism. We demonstrated that CYL-02 induced a significant “regression” of experimental primary pancreatic tumors when injected intratumorally (1, 2).

Phase 1 trial: the first in man trial was conducted in Toulouse. THERGAP-1 protocol was based on two Endoscopic Ultrasound-guided direct intratumoral injections (at one month interval) of increasing doses of CYL-02 (125 to 1000 µg) followed by Gemcitabine infusions within 2 months. After inclusion of 22 unresectable PDAC patients we demonstrated the excellent feasibility and safety. Primary tumor was reduced in size at one month and remained stable at 2 months with no metastatic progression. In locally advanced PDAC and naïve of treatment, the median progression-free survival and overall survival were respectively of 5.75 and 12.2 months (3).

Phase 2 trial: These encouraging results advocate for a randomized open multicentre phase 2 trial (THERGAP-2) comparing the therapeutic effect of the association of “CYL-02 plus gemcitabine” (Arm A) versus “gemcitabine alone” (Arm B) in patients with locally advanced, non-metastatic/unresectable/untreated PDAC patients (Promoter CHU of Toulouse, Sponsors PHRC-K Inca and InvivoGen - Monitoring CIC Biotherapy - NCT02806687). We plan to include 100 patients (50 patients in each Arm). The primary objectives are to compare the effect of each modality of treatment on the progression free survival. The secondary objectives are to compare the effects on overall survival, antitumor response, Quality of Life and biomarker indentification.

Conclusion: Six French centers are now open for inclusions since March 2017 with a good feasibility. First results are expected late 2018 after final follow-up of half of included patients. This unique phase-2 trial is the first to assess the efficacy of Gemcitabine chemosensitization following a gene therapy (4).

References: