Enhancing the immune response in locally advanced pancreatic cancer (LAPC) with intratumoral endoscopic ultrasound-guided fine needle injection of large surface area microparticle paclitaxel (LSAM-PTX)

NanOlogy

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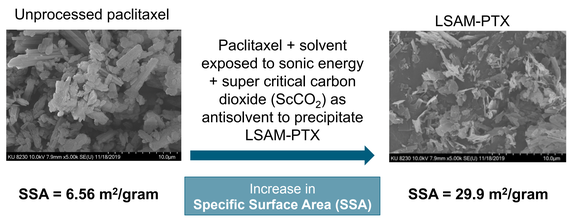
Background

LAPC has a complex tumor microenvironment (TME) resistant to immune effector cell infiltration and drug bioavailability, limiting the effectiveness of current systemic therapies. LSAM-PTX was developed for intratumoral (IT) injection of solid tumors to provide a therapeutic-level paclitaxel depot with a prolonged residence time.

Large Surface Area Microparticle Paclitaxel (LSAM-PTX) Production Technology



We previously reported[1] enhanced tumor kill in LAPC subjects receiving two monthly IT LSAM-PTX injections and anti-tumor immunomodulation in the TME. Multiplex immunofluorescence (mIF) performed on pre-treatment biopsy tissue and post-LSAM-PTX resection showed increases in densities of effector T cells and NK cells and decreases in myeloid derived suppressor cells (MDSC). To further evaluate immunomodulation following IT LSAM-PTX therapy, blood samples were obtained for immunophenotyping via flow cytometry in subjects receiving four monthly IT LSAM-PTX injections (NCT03077685).

Methodology

A total of 14 subjects on prior or concurrent SOC therapy were administered four monthly LSAM-PTX injections. Participants' mean age was 74 years, and 50% were male; subjects identified primarily as White (100%) and not Hispanic/Latino (78.6%). The average time from diagnosis to initiating four monthly IT LSAM-PTX injections was 229 days (range 39 – 614).

Blood samples were collected prior to LSAM-PTX treatment initiation and at Weeks 4, 8, and 12 prior to LSAM-PTX injection, and at Week 24.

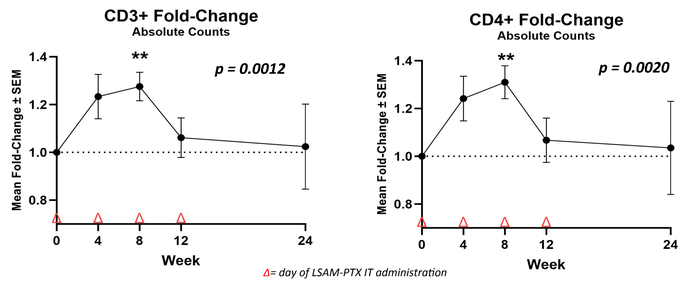
Flow cytometric analysis was performed at NeoGenomics (Aliso Viejo, CA) using three panels to evaluate absolute counts and percentages of up to 45 immunophenotypes.

Comparisons to baseline data on Day 1 were made at each later timepoint using one-way ANOVA with mixed-effects analysis for repeated measures with p-values reported from Dunnett's multiple comparison test (Prism v. 10.0.2 (GraphPad Software, Boston, MA)).

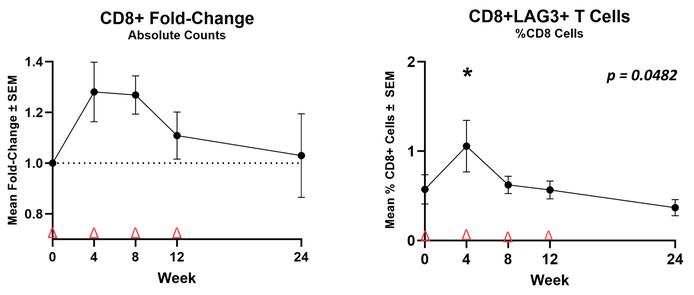
[1] Sharma NR, Lo SK, Hendifar A, et al. Response of Locally Advanced Pancreatic Cancer to Intratumoral Injection of LSAM-PTX: Initial Report of Safety and Clinical Outcome. Pancreas. 2023. In press.

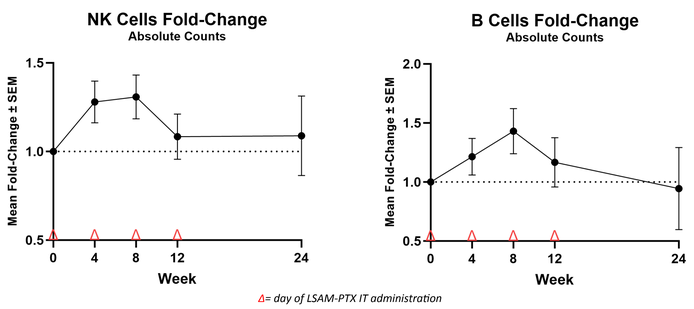
Summary of Key Findings

- Treatment with four IT injections of LSAM-PTX was associated with increases in peripheral lymphocytes during the treatment period.
- An enhancement of immune subsets associated with anti-tumor effector functions was found, including significant increases in circulating CD3+ and CD4+ cells (p=0.0012 and 0.002 respectively) which is consistent with the 4-fold increase in CD4+helper T cells detected in the TME of resected tissue.



- Increases in circulating CD8+ T cells, B cells, and NK cells were seen during the treatment period corresponding with effector T cells and NK cells increases (4.8-fold increase in density) within the TME. A significant increase in LAG3+CD8+ T cells was seen following treatment initiation (p=0.048) marking early T cell activation.





Clinical Trial Sites

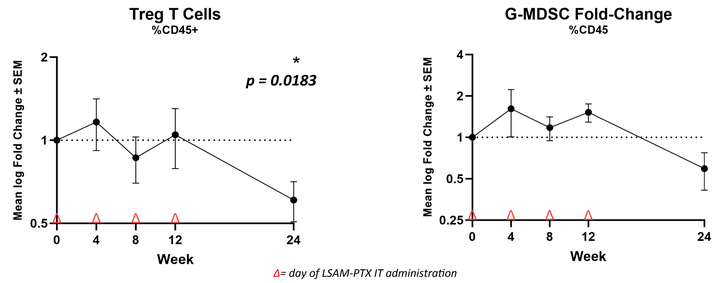
- Cedars-Sinai Medical Center, Dr. Simon K. Lo
- Baylor College of Medicine, Dr. Mohamed O. Othman
- Parkview Research Center, Dr. Neil R. Sharma
- Texas Tech Univ. Health Sciences Center El Paso, Dr. Antonio Mendoza-Ladd

- Ongoing median overall survival = 12.6 months (following initial injection on Day 1); median follow-up = 12.2 months.

Subject Number	Diagnosis to 1st LSAM-PTX Injection (Days)	OS from Day 1 (Months)	OS from Diagnosis (Months)	Chemotherapy or Radiation Concomitant with LSAM-PTX
1*	67	6.3	8.5	FOLFIRINOX, radiation
2	369	7.5	19.6	mFOLFIRINOX
3	614	7.8	27.9	None
4	506	8.7	25.3	Gemcitabine
5*	330	10.4	21.2	Gemcitabine
6	43	11	12.4	FOLFIRINOX, gemcitabine/nab-paclitaxel
7	39	11.4	12.7	FOLFIRINOX, gemcitabine/nab-paclitaxel
8	43	13.8	15.2	None
9*	291	14.3	23.8	FOLFIRI
10	319	15.1	25.6	Gemcitabine
11	246	16.4	24.5	None
12	70	17.1**	19.4**	FOLFIRINOX
13*	129	21.1**	25.3**	Gemcitabine/nab-paclitaxel
14	134	29.6**	34.0**	Gemcitabine/nab-paclitaxel, gemcitabine

* Subject underwent surgical resection; ** Ongoing survival.

- Six months following treatment initiation there was a significant decrease in circulating Treg cells (p=0.0183) and a decrease in peripheral immunosuppressive G-MDSC, consistent with the reduction in MDSC measured in the TME.



- Notably, systemic paclitaxel toxicities, including immunosuppression, were not reported following IT LSAM-PTX and negligible amounts of paclitaxel were found in blood samples.

Conclusions

- Immunophenotyping of blood from LAPC subjects treated with IT LSAM-PTX demonstrates immunomodulation to a phenotype associated with anti-tumor immune effects, including favorable immunosurveillance, and is consistent with changes found in the TME in resected tissues.
- Immunosuppressive cell types typically associated with poor outcomes were reduced at six months.
- Anti-tumor immunomodulation without immunosuppression suggests that IT LSAM-PTX may be amenable to combination with immunotherapy.