NanOlogy

Aiming to improve solid tumor response without adding toxicity

Key Unmet Need in Solid Tumor Treatment

Landscape

A new era of systemic cancer therapies (e.g., immunoncology, TKIs, PARPIs, etc.) are rapidly becoming SOC across the solid tumor disease spectrum

Key Issue

These newer therapies tend to be less effective in solid tumors

Reasons

- Complex TME
- Bioavailability
- Resistance
- Toxicity

Consequence

5000+ clinical trials combining newer therapies with other systemic agents to increase response

Problems

- Stacked systemic toxicities
- Limited contribution to product lifecycle

An unmet medical need exists to improve solid tumor treatment while tackling the problems associated with systemic combinatorial therapy

NanOlogy Approach

Patented *Purcision*™ drug platform engineered for intratumoral delivery to improve solid tumor response without adding toxicity

✓ Opportunity

- Improvements in technology now allow local access to solid tumors throughout the body
- Growing recognition of the importance of treating the primary tumor throughout the disease spectrum
- Systemic combination therapies limited by toxicity

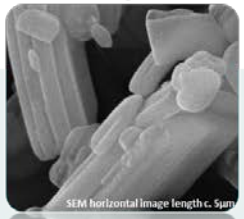
✓ Solution

- Proprietary Purcision technology platform engineers patented large surface area microparticles (LSAMs) of pure drug optimized for intratumoral delivery
  - High drug load
  - Optimal particle size for tumor retention
  - Increased surface area for therapeutic drug release
  - Established in a wide range of classic and new oncology drugs
  - Clinical evidence supporting technology

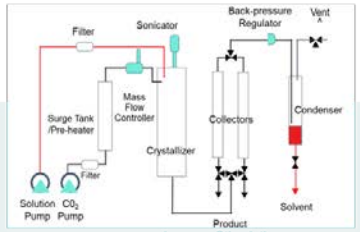
Purcision™ Technology

Proprietary super critical precipitation (SCP) technology platform enabling large surface area microparticles (LSAMs)

API Crystals

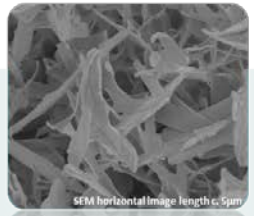


- ✓ Large and bulky crystals
- ✓ Large distribution around mean particle size
- ✓ Poor uniformity of suspensions
- ✓ Poor drug release due to small surface area
- ✓ Limited to dissolution in solvent as a solution for IV delivery



- ✓ API crystals dissolved in organic solvent and injected into precipitation chamber
- ✓ Sonicated into small uniform droplets via sonic probe
- ✓ Solvent stripped away from droplets via supercritical fluid carbon dioxide
- ✓ Stable microparticles of pure drug precipitated and collected on harvesting filters
- ✓ GMP commercial scale
- ✓ **SCP platform technology established for multiple drugs (taxanes, TKIs, PARPIs, cisplatin)**

LSAMs



- ✓ Narrow mean particle size distribution
- ✓ Excellent suspension uniformity
- ✓ Microparticles each containing > 1 billion drug molecules suspended in saline-based fluid for local delivery
- ✓ Disproportionately large surface area to particle size ratio allows for:
  - ✓ Particle entrapment
  - ✓ Prolonged therapeutic drug release

Particle attributes for optimal local delivery to disease target

High Drug Load

- Volume of open space in the tumor is small
- SCP Technology forms particles of **100% pure drug without any excipients** for intratumoral delivery
- Other technologies require excipients significantly reducing drug load – often to < 30% (LIDDS, Leon Nanodrugs, OncoGel) – and potential for efficacy

Right Particle Size

- SCP Technology forms particles **large enough to become entrapped** in the tumor
- The longer drug remains in the tumor releasing drug at high concentration, the **longer the direct tumor kill**
- Smaller particles formed by other technologies simply diffuse out of the tumor or are quickly metabolized or phagocytized

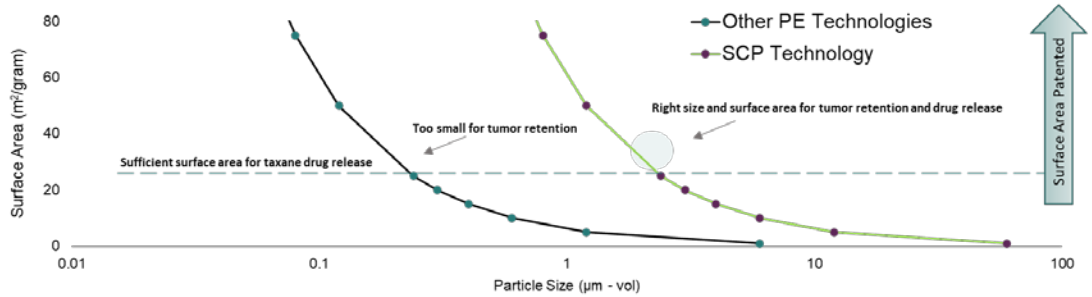
Large Surface Area

- Tumor-directed delivery requires particles with a surface area sufficient for therapeutic molecular drug release
- LSAMs are a drug depot with a **large surface area for prolonged therapeutic drug release**
- Other technologies increase surface area by decreasing particle size to the extent that particles cannot be retained in the tumor over time

Uniqueness of SCP technology versus all other particle engineering technologies

- The SCP technology is different from all other particle engineering (PE) technologies (spray drying, milling, CESS, RESS)
- The SCP technology has a unique ability to engineer **large particles with surface area of a much smaller particle**
- This uniquely **disproportionate surface area to particle size ratio** is optimal for tumor-directed delivery
- The larger size allows for **retention** in the tumor and large surface area for molecular drug **release**
- Taxane **particles with surface area ≥ 18 m^2/g** are protected by a **composition of matter patent** valid until June 2036

Extensive global IP portfolio with over 100 issued patents through 2038 on key patents including composition of matter, formulations, use, technology



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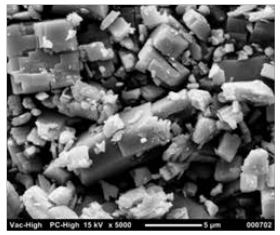
Purcision™ Technology

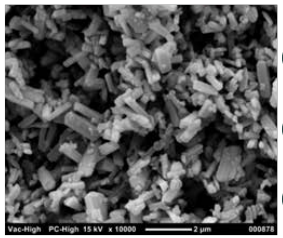
Feasibility established in a wide range of oncology molecules

Unprocessed Taxane

D_{V50} (µm)	4
SSA (mg^2/g)	6.8
Density (g/cm^3)	0.22



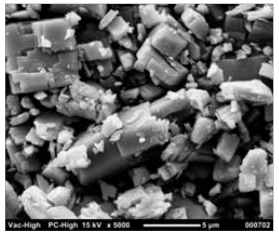
LSAM-Taxane[1]



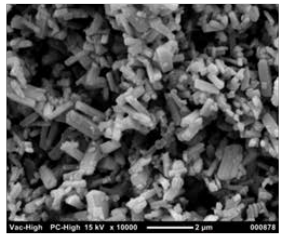
D_{V50} (µm)	5
SSA (mg^2/g)	30.0
Density (g/cm^3)	0.08

Unprocessed Platin

D_{V50} (µm)	11
SSA (mg^2/g)	2.4
Density (g/cm^3)	1.0



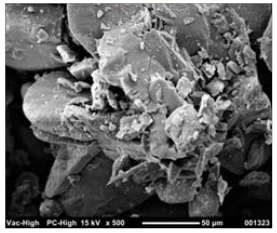
LSAM-Platin[2]



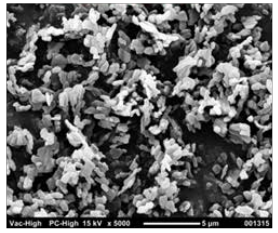
D_{V50} (µm)	2
SSA (mg^2/g)	4.4
Density (g/cm^3)	0.4

Unprocessed TKI

D_{V50} (µm)	98
SSA (mg^2/g)	0.9
Density (g/cm^3)	0.7



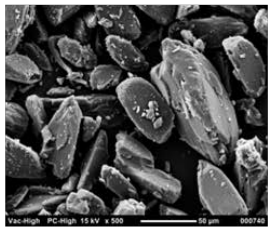
LSAM-TKI[3]



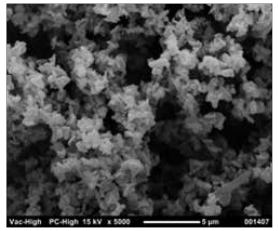
D_{V50} (µm)	2
SSA (mg^2/g)	10.0
Density (g/cm^3)	0.1

Unprocessed PARPI

D_{V50} (µm)	103
SSA (mg^2/g)	0.7
Density (g/cm^3)	0.6



LSAM-PARPI[4]



D_{V50} (µm)	5
SSA (mg^2/g)	12.0
Density (g/cm^3)	0.1

- ✓ **Particle size is maintained for tumor retention**
- ✓ **Minimal static charge allows physical stability without coating agents or other excipients**
- ✓ **Narrow particle size distribution meets regulatory requirements and allows consistent drug release from batch to batch**

- ✓ **Surface area increase for continuous high levels of local drug release**
- ✓ **Increase is determined by water solubility**
- ✓ **Inversely proportional to solubility**

- ✓ **Bulk density is decreased for homogeneity in suspension prior to use**
- ✓ **Meets regulatory requirements for suspension**

Process parameters locked and validated once optimized during process development

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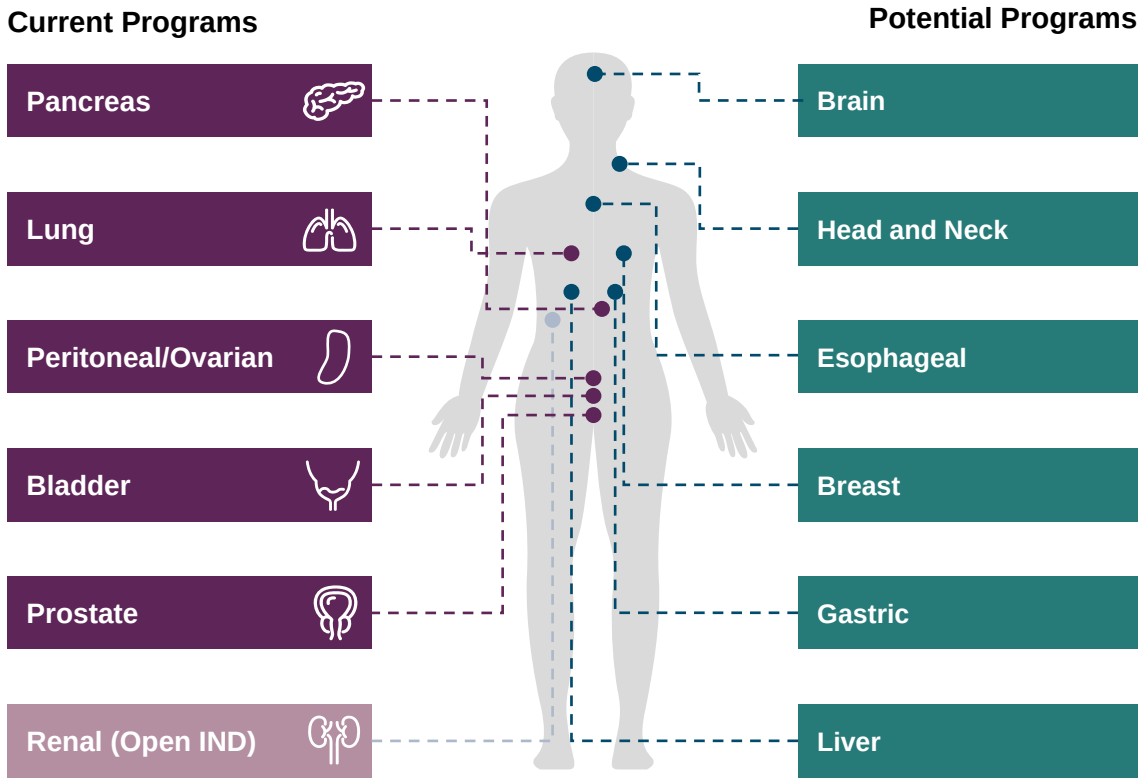
1. STV-011421-1 (docetaxel example shown)
2. CT-2021-01-C; SC2104 (cisplatin example shown)
3. CT-2020-03-A; CT-2021-06-B (sorafenib example shown)
4. CT-2021-03-A; CT-2021-06-B (niraparib example shown)

NanOlogy Highlights

- Purcision technology platform validated for wide range of oncology drugs
- LSAM-PTX (paclitaxel) and LSAM-DTX (docetaxel) in clinical development
- 8 INDs across multiple indications and routes of local administration
- 7 clinical trials / 6 solid tumors / 175 subjects
- Excellent safety
- Encouraging tumor and immune response data
- IND-enabling studies underway for LSAM-cisplatin
- Feasibility studies completed on LSAM-TKIs and LSAM-PARPIs



NanOlogy Development Assets & Pipeline

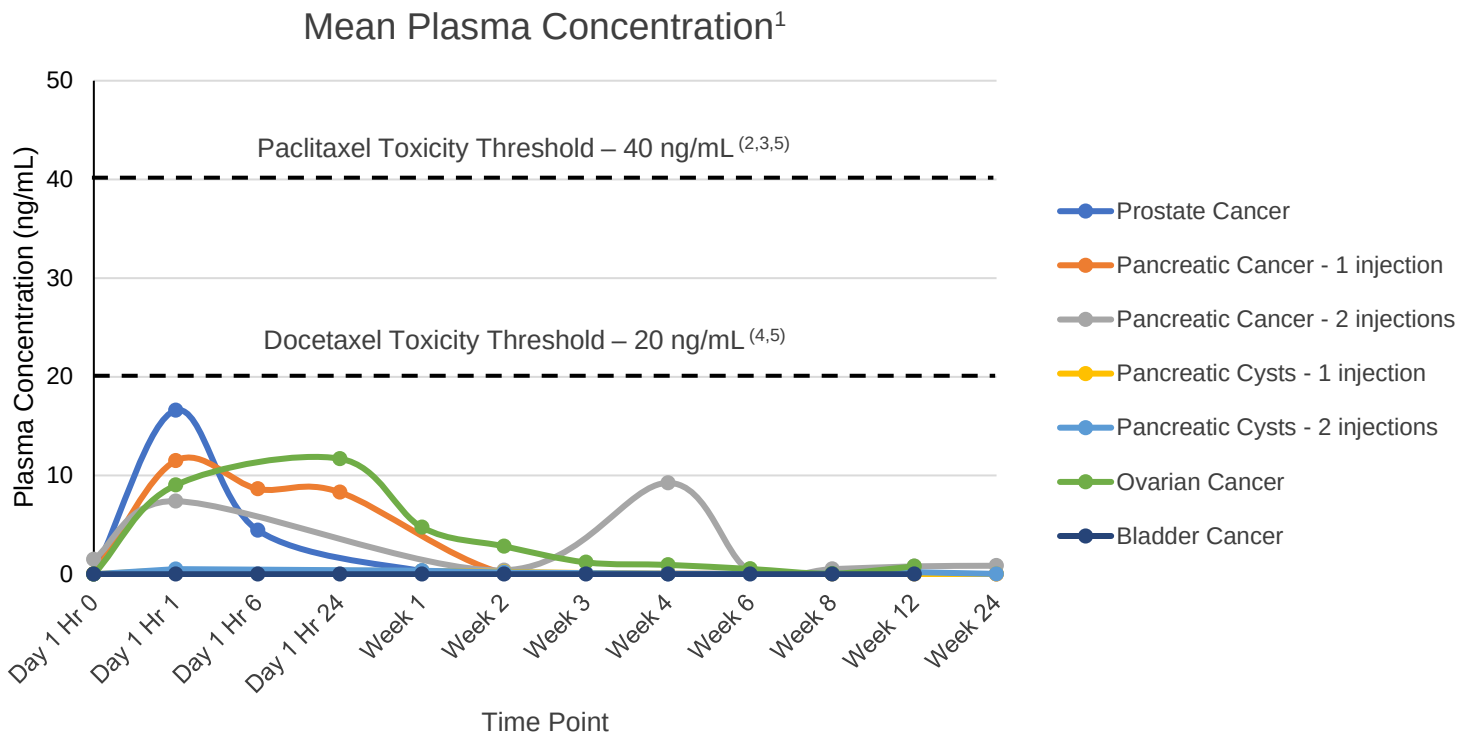
Product	Therapeutic Area	Delivery	Feasibility	IND	Phase 1	Phase 2	Phase 3
LSAM-PTX for Sterile Suspension	Lung Cancer	Intratumoral					
	Locally Advanced Pancreatic Adenocarcinoma	Intratumoral					
	Prostate Cancer	Intratumoral					
	Peritoneal Malignancies / Ovarian Cancer	Intraperitoneal					
	Mucinous Cystic Pancreatic Neoplasms	Intracystic					
LSAM-DTX for Sterile Suspension	Non-Muscle Invasive Bladder Cancer	Resection Bed Injection & Intravesical Instillations					
	Muscle Invasive Bladder Cancer	Resection Bed Injection & Intravesical Instillations					
	Renal Cell Carcinoma	Intratumoral					
	Prostate Cancer	Intratumoral					
LSAM-Cisplatin for Sterile Suspension	Diffuse Intrinsic Pontine Glioma	Intratumoral					
	Solid Tumors	Intratumoral					
LSAM-PTX for Inhalation	Non-Small Cell Lung Cancer	Nebulized Inhalation					
Submicron Particle Paclitaxel for Topical Application	Cutaneous Metastases of Breast Cancer	Topical					
LSAM-PARPs for Sterile Suspension	Solid Tumors	Intratumoral					
LSAM-TKIs for Sterile Suspension	Solid Tumors	Intratumoral					

Excellent Safety Profile Established in 175 Patients

	Clinical Trial	Subjects	Events		Systemic SAEs			Local SAEs		
			TEAE	SAE	Possibly Related	Probably Related	Definitely Related	Possibly Related	Probably Related	Definitely Related
LSAM-PTX	Pancreatic Cancer	54	435	54	0	0	0	6	0	0
	Pancreatic Cysts	19	99	5	0	0	0	0	1	0
	Peritoneal Malignancies	21	332	24	1	0	0	1	0	0
	Ovarian Cancer	10	208	13	0	0	0	7	0	0
	Prostate Cancer	17	76	0	0	0	0	0	0	0
	Lung Cancer	18	217	23	1	0	0	0	0	0
LSAM-DTX	Bladder Cancer (NMIBC)	19	144	1	0	0	0	0	0	0
	Bladder Cancer (MIBC)	17	74	3	0	0	0	0	0	0

Plasma Levels from Clinical Trials

Subtoxic plasma drug concentrations at all timepoints demonstrated by clinical PK analysis



Avoids the systemic toxicities associated with systemic cancer treatments:

- Neutropenia
- Thrombocytopenia
- Peripheral neuropathy
- Alopecia
- Nausea & vomiting
- Colitis & severe diarrhea
- Rash & pruritis
- Hepatotoxicity
- Dose reduction or discontinuation

1. LSAM-DTX in bladder cancer only; all others LSAM-PTX
2. Clin Cancer Res 1999;5:767-774
3. S07-GM-01-2017
4. British Journal of Cancer (2007) 97, 290 – 296
5. LLOQ paclitaxel = 25 pg/mL; LLOQ docetaxel = 10 ng/mL

Promising Clinical Results (Over 40 Publications)

Early phase trial of intracystic injection of large surface area microparticle paclitaxel for treatment of mucinous pancreatic cysts

OPEN ACCESS

Link

Authors
Mohamed Othman[1], Kalpesh Patel[1], Somashekar G. Krishna[2], Antonio Mendoza-Ladd[3], Shelagh Verco[4], Wasif Abidi[1], James Verco[4], Alison Wendt[4], Gere diZerega[4,5]
Cancer Chemother Pharmacol
DOI 10.1007/s00280-015-2737-4

CLINICAL TRIAL REPORT

Link

A phase I study of intraperitoneal nanoparticulate paclitaxel (Nanotax®) in patients with peritoneal malignancies

Stephen K. Williamson[1] · Gary A. Johnson[1] · Holly A. Maulhardt[2] · Kathleen M. Moore[3] · D. S. McMeekin[3] · Thomas K. Schulz[4] · Gregory A. Reed[5] · Katherine F. Roby[1] · Christine B. Mackay[5] · Holly J. Smith[6] · Scott J. Weir[1] · Jo A. Wick[1] · Maurie Markman[7,8] · Gere S. diZerega[2,9] · Michael J. Baltezor[10,11] · Jahna Espinosa[11] · Charles J. Decedue[11]

Drug Delivery and Translational Research
https://doi.org/10.1007/s13346-020-00868-4

REVIEW ARTICLE

Link

Local administration of submicron particle paclitaxel to solid carcinomas induces direct cytotoxicity and immune-mediated tumoricidal effects without local or systemic toxicity: preclinical and clinical studies

Shelagh Verco[1] · Holly Maulhardt[1] · Michael Baltezor[2] · Emily Williams[1] · Marc Iacobucci[3,4] · Alison Wendt[1] · James Verco[1] · Alyson Marin[1] · Sam Campbell[2,3] · Paul Dorman[3,4] · Gere diZerega[1,3]

Drug Delivery and Translational Research
https://doi.org/10.1007/s13346-022-01226-2

REVIEW ARTICLE

Link

Local administration of large surface area microparticle docetaxel to solid carcinomas induces direct cytotoxicity and immune-mediated tumoricidal effects: preclinical and clinical studies

Holly Maulhardt[1] · Shelagh Verco[1] · Michael Baltezor[2] · Alyson Marin[1] · Gere diZerega[1,3]
Drug Deliv Transl Res. 2023; 13(2): 503–519.
Published online 2022 Sep 4. doi: 10.1007/s13346-022-01226-2

Breast Cancer Research and Treatment (2022) 194:57–64
https://doi.org/10.1007/s10549-022-06584-6

CLINICAL TRIAL

Link

Phase 1/2 study of topical submicron particle paclitaxel for cutaneous metastases of breast cancer

Mario E. Lacouture[1,5] · Shari B. Goldfarb[1] · Alina Markova[1] · Sant P. Chawla[2] · Karan Dewnani[3] · Marc Iacobucci[3] · Julie E. Lang[4]

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American Urological Association

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Link

Open Access | Journal of Urology | Adult Urology | 16 May 2022

Phase 1/2 Trial Results of a Large Surface Area Microparticle Docetaxel for the Treatment of High-Risk Nonmuscle-Invasive Bladder Cancer

Max Kates, Ahmed M. Mansour, Donald L. Lamm, Neal Shore, Holly Maulhardt, Alison Wendt, James Verco, Alyson Marin, Karan Dewnani, Shelagh Verco, and Gere S. diZerega
View All Author Information

Gynecologic Oncology Reports 34 (2020) 100627

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Link

Short communication

Phase II study of intraperitoneal submicron particle paclitaxel (SPP) plus IV carboplatin and paclitaxel in patients with epithelial ovarian cancersurgery

Sally Mullany[a], David Scott Miller[b], Katina Robison[c], Kimberly Levinson[d], Yi-Chun Lee[e], S. Diane Yamada[f], Joan Walker[g], Maurie Markman[h], Alyson Marin[i], Peter Mast[i], Gere diZerega[i,j,*]

Medical Oncology (2021) 38:106
https://doi.org/10.1007/s12032-021-01555-1

ORIGINAL PAPER

Link

Submicron particle docetaxel intratumoral injection in combination with anti-mCTLA-4 into 4T1-Luc orthotopic implants reduces primary tumor and metastatic pulmonary lesions

Holly Maulhardt[1] · Alyson Marin[1] · Holly Hesseltine[1] · Gere diZerega[1,2]

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JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY
Volume 32, Number 0, 2019
Mary Ann Liebert, Inc.
Pp. 1–12
DOI: 10.1089/jamp.2018.1517

Link

Inhaled Submicron Particle Paclitaxel (NanoPac) Induces Tumor Regression and Immune Cell Infiltration in an Orthotopic Athymic Nude Rat Model of Non-Small Cell Lung Cancer

James Verco, BS,[1] William Johnston,[1] Michael Frost, MD,[2] Michael Baltezor, PhD,[3] Philip J. Kuehl, PhD,[4] Anita Lopez, MS,[4] Andrew Gigliotti, PhD,[4] Steven A. Belinsky, PhD,[4] Ronald Wolff, PhD,[5] and Gere diZerega, MD[1,6]

ORIGINAL ARTICLE

Response of Locally Advanced Pancreatic Cancer to Intratumoral Injection of Large Surface Area Microparticle Paclitaxel

Initial Report of Safety and Clinical Outcome

Link

Sharma, Neil R. MD*; Lo, Simon K. MD†; Hendifar, Andrew MD†; Othman, Mohamed O. MD‡; Patel, Kalpesh MD‡; Mendoza-Ladd Antonio MD§; Verco, Shelagh PhD‖; Maulhardt, Holly A. BS‖; Verco, James BS‖; Wendt, Alison BS‖; Marin, Alyson MS‖; Schmidt, Christian Max MD, PhD, MBA, FACS¶; diZerega, Gere MD‖,#

Author Information

THE EFFICACY OF INTRACYSTIC INJECTION OF LARGE SURFACE AREA MICROPARTICLE PACLITAXEL (NANOPAC®) IN THE MANAGEMENT OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS: RESULTS FROM AN EXPANDED ACCESS PROTOCOL

0002236

Link

Link

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

Link

Phase 2a Intratumoral Large Surface Area Microparticle Paclitaxel in Stage 3/4 Lung Cancer

Onco Ther
https://doi.org/10.1007/s40487-024-00261-y

REVIEW

Link

Intratumoral Injection of Large Surface Area Microparticle Taxanes in Carcinomas Increases Immune Effector Cell Concentrations, Checkpoint Expression, and Synergy with Checkpoint Inhibitors: A Review of Preclinical and Clinical Studies

Gere S. diZerega · Holly A. Maulhardt · Shelagh J. Verco · Alyson M. Marin · Michael J. Baltezor · Samantha A. Mauro · Marc A. Iacobucci

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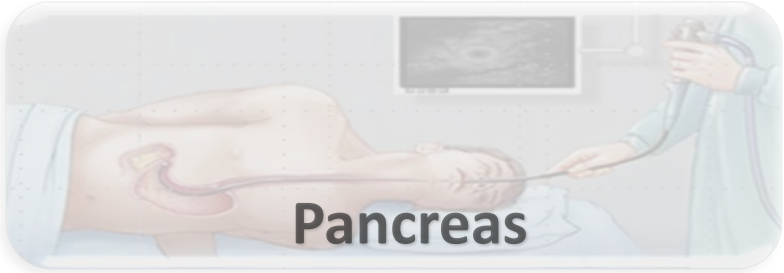
Clinical Highlights

Phase 2a dose-rising/expansion single arm trial of intratumoral LSAM-PTX in LAPC (n=54)



Clinical Data[1,2,3]

- **Safe/well tolerated; mild/mod transient abdominal pain; no reports of pancreatitis**
- **Results from 2-injection cohort:**
  - **8/22 (36%) downstaged from nonresectable to resectable**
  - **6 resected ; 5/6 R0 (83%); complete/major pathologic response in 4/6 samples**
  - **mOS: 35.2M/18.9M (resected/nonresected subjects)**
- **Evidence of tissue/peripheral immunomodulation**
- **CSR to FDA 4Q2023**

Phase 2a dose-rising/expansion single arm trial of intratumoral LSAM-PTX in lung cancer (n=18)

Clinical Data[4]

- **Safe/well tolerated; no confirmed drug-related SAEs**
- **OS at 3,6,12M: 71% (12/17), 47% (8/17), and 25% (4/16)**
- **DCR evaluable subjects at 3,6M: 80% (8/10) and 86% (6/7)**
- **Evidence of peripheral immunomodulation**
- **CSR to FDA 1Q2024**

Phase 1/2 dose-rising/expansion single arm trial of IMI/IVT LSAM-DTX in hrNMIBC (n=19) and MIBC (n=17)

Clinical Data[5]

- **Safe/well tolerated; no confirmed drug-related SAEs**
- **Results from the hrNMIBC arm**
  - **CR 4M 15/19 (79%) (all doses)**
  - **CR > 7M 7/9 (78%) (high dose cohort)**
- **Evidence of tissue immunomodulation**
- **CSR to FDA in 2022**

1. Sharma et. al. *Pancreas* Mar 2023
2. Hendifar et. al. *AACR pancreatic cancer conf* Sep 2023
3. Gopakumar et. al. *AACR pancreatic cancer conf* Sep 2023
4. Mehta et. al. *NACLC* poster presentation Dec 2023
5. Kates et. al. Journal of Urology May 2022

Other Clinical Trials

	Indication	Subjects	Trial Phase	Dose	Dose Range	Clinical Data
LSAM-PTX	Pancreatic Cysts (MCN/IPMN) NCT03188991	19	Phase 2a	**EUS-FNI** • 1 intracystic injection • 2 intracystic injections (0,3M)	Equal to volume aspirated from cyst 6, 10, and 15mg/mL	• Safe/well tolerated • Cyst volume reduction in 14/19 (74%) subjects • Evidence of epithelial lining necrosis (-DNA or endomicroscopy) • PK analysis of cyst fluid at 3M > 250ng/mL (ULOQ) paclitaxel
	Peritoneal Malignancies NCT00666991	21	Phase 1	**Intraperitoneal** • 1 to 6 intraperitoneal infusions	50 – 275mg/m^2	• Safe/well tolerated • 6/21 (29%) subjects (salvage patients) survived > 1 year • Peritoneal fluid concentrations 450-2900 times greater than peak plasma drug concentrations/plasma concentration subtoxic at all timepoints
	Ovarian Cancer NCT03029585	10	Phase 2	**Intraperitoneal** • 1 intraperitoneal instillation at end of debulking surgery	100 – 200mg/m^2	• Safe/well tolerated • PFS 60% ≥ 6M • ORR 50% (CR 20%; PR 30%) • OS 70% > 1 year
	Prostate Cancer NCT03077659	16	Phase 1	**TRUS-guided-FNI** • 1 intralobular injection • 28 days before prostatectomy	20% lobe volume (up to 5 mL) 6, 10, and 15mg/mL	• Safe/well tolerated; no reports of prostatitis • Mean tumor volume reduction 46% • Mean PSA-density decrease 35%

Clinical Immunomodulation in Pancreas, Bladder, Lung

- MultiOmyx™ multiplex immunofluorescence analysis of tumor tissue in pancreas[1]/bladder[2] trials pre/post LSAM investigational drug injection
  - Increases in cytotoxic T cells
  - Increases in NK cells
  - Decreases in MDSCs
  - Increased density of PD-L1
- Flow cytometry analysis of blood in pancreas[3]/lung[4] trials pre/post LSAM investigational drug injection
  - Increases in cytotoxic T cells
  - Increases in NK cells
  - Decreases in MDSCs
- Preclinical synergy shown with LSAM investigational drug + immune checkpoint inhibitors in metastatic breast cancer[5] and melanoma[6] models

Supports further clinical research to improve response of solid tumors to systemic immunoncology agents without adding to toxicity

1. Sharma et. al. *Pancreas* Mar 2023
2. Kates et. al. *Journal of Urology* May 2022
3. Hendifar et. al. *AACR pancreatic cancer conf* Oct 2023
4. Mehta et. al. *NACLC* poster presentation Dec 2023
5. Maulhardt et. al. *Medical Oncology* 2021
6. Maulhardt et. Al. International Journal of Nanomedicine 2024