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

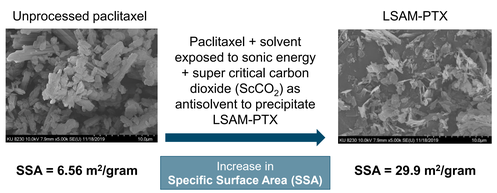
Hiren J. Mehta[1], Abhishek Biswas[2], Sarah Wang[2], Jason Akulian[3], A. Christine Argento[4], Shelagh Verco[5], Holly Maulhardt[5], Kim Ferguson[5], Alyson Marin[5], Alison Wendt[5], Karan Dewnani[6], Gere diZerega[5,6]

[1] University of Florida Health, [2] Parkview Health, [3] University of North Carolina School of Medicine, [4] Johns Hopkins Medicine, [5] US Biotest, [6] NanOlogy

Background

Large Surface Area Microparticle Paclitaxel (LSAM-PTX) was developed for intratumoral (IT) injection to provide a paclitaxel depot at therapeutic levels in the tumor with prolonged IT residence time while limiting systemic exposure. IT LSAM-PTX clinical trials include prostate, pancreas, ovarian/peritoneal, and lung cancers.

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



Methodology

Subjects with non-resectable stage 3/4 lung cancer received up to three monthly IT injections of LSAM-PTX 15mg/mL based on total tumor volume, in combination with standard of care, including systemic chemotherapy, immunotherapy, and/or radiotherapy (NCT04314895). Subjects were followed for 6-months for safety and up to 1 year for preliminary efficacy. CT scans were scheduled prior to each LSAM-PTX injection and at 12, 18, 24, 38 and 52-weeks to determine change in target tumor longest diameter and volume. Blood and tissue were collected for pharmacokinetic analysis and blood for flow cytometry.

Demographics

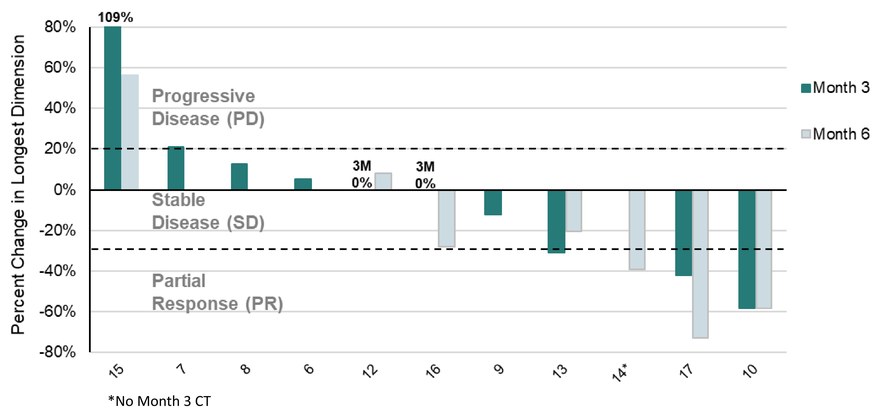
- Of the 18 subjects enrolled, 14 (78%) were male and 17 (94%) were consider white. The median age at enrollment was 67 (range: 49-84). Seventeen subjects were confirmed to have NSCLC (53% squamous, 47% adenocarcinoma). One subject had a benign lesion.
- Three, five, and ten subjects underwent one, two, and three LSAM-PTX injections, respectively.

NSCLC Subtype (n=18)					
Squamous Cell Carcinoma:	9 (50%)	Adenocarcinoma:	8 (44%)	Benign:	1 (6%)
Staging (n=18)					
IA3:	1 (6%)	III:	9 (50%)	IV:	8 (44%)

Results

- Median volume of tumor injected was 13.1cm^3 (range 1.9-483.5cm^3) and median volume of LSAM-PTX injected was 1.7ml (range 0.26-41.7ml). Disease Control Rate (CR + PR + SD per RECIST) for evaluable subjects at 3- and 6-months were 80% (8/10; 3 unevaluable) and 86% (6/7; 2 unevaluable), respectively.

Longest Dimension Change (RECIST 1.1) from 1st Injection



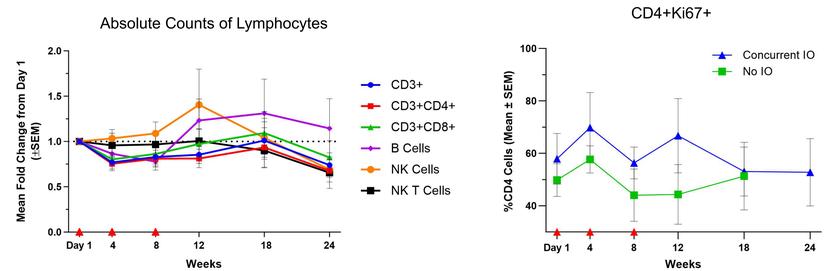
*No Month 3 CT

- Eleven subjects received concurrent therapies including systemic chemotherapy (9), immunotherapy (9), and radiotherapy (1).

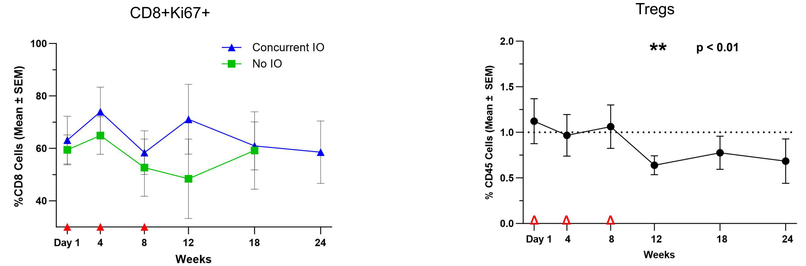
Subject Number	Concurrent Therapies with LSAM-PTX	Diagnosis to 1st LSAM-PTX Injection (Days)	OS from Diagnosis (Months)	OS from Day 1 (Months)
1		98	3.4	0.2
2	pembrolizumab/paclitaxel/carboplatin	33	2.4	1.3
3		1633	45.9	1.3
4	pembrolizumab/pemetrexed	119	6.4	2.5
5	pembrolizumab/paclitaxel/carboplatin	62	4.8	2.8
6		377	15.8	3.4
7	pembrolizumab	43	6.0	4.6
8		1020	38.5	5.0
9	docetaxel	209	12.4	5.5
10	pembrolizumab/pemetrexed/carboplatin	26	7.9	7.0
11		2377	87.4	9.3**
12	durvalumab/nab-paclitaxel	397	24.8	11.8
13	pembrolizumab	465	27.2	11.9
14	pembrolizumab/pemetrexed/carboplatin	47	13.6	12.1*
15		7	13.2	13.0*
16	radiation therapy/paclitaxel/carboplatin	336	27.0	16.0*
17	pembrolizumab/pemetrexed/carboplatin	56	22.6	20.8*

* Ongoing survival; ** Lost to follow up

- Overall Survival at 3-, 6-, and 12-months post treatment initiation was 71% (12/17), 47% (8/17), and 25% (4/16; 1 LTFU), respectively.
- LSAM-PTX was well tolerated. There were a total of 217 TEAEs, of which 22 (15 systemic, 7 local) were possibly related to LSAM-PTX (Grade 1 - 9, Grade 2 - 12, Grade 4 - 1). There were 23 SAEs across 12 subjects, of which 1 was possibly related to LSAM-PTX. Of the 217 reported adverse events, one (0.5%) Grade 4 event of pulseless electrical activity was considered possibly related to LSAM-PTX administration and no TEAEs were considered definitely related to LSAM-PTX.
- Immunophenotyping of peripheral blood found no significant changes in absolute lymphocyte concentrations, increases in proliferating (Ki67+) CD4+ and CD8+ T cells in subjects on concurrent immunotherapy, significant reductions in Tregs, and reductions in MDSCs.



Δ= day of LSAM-PTX IT administration



Δ= day of LSAM-PTX IT administration

- Following up to three IT LSAM-PTX administrations, plasma pharmacokinetic analysis found low systemic paclitaxel exposure with dose proportionate increases and no apparent systemic accumulation, which is consistent with clinical trials of IT LSAM-PTX in other solid tumors. Following IT LSAM-PTX, paclitaxel concentrations in lung tumor tissue were substantially higher than plasma paclitaxel concentrations.

Conclusion

- This early phase lung cancer trial demonstrated safety and tolerability of IT LSAM-PTX in combination with various concurrent therapies including systemic immunotherapy, and warrants a follow-on randomized controlled trial to confirm efficacy.
- Flow cytometry and safety data suggest LSAM-PTX may cause immunomodulation, including increases in immune effectors cells and decreases in Tregs and immune suppressor cells, and complement systemic therapy without significantly increasing adverse events.
- Limitations of the trial included single arm design, and heterogeneous mix of tumor subtype, medical history, and concurrent therapies.

Clinical Trial Sites

- University of Florida Health, Dr. Hiren J. Mehta
- Parkview Health, Dr. Abhishek Biswas and Dr. Sarah Wang
- University of North Carolina Health, Dr. Jason Akulian
- Johns Hopkins Medicine, Dr. A. Christine Argento