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Initial Results from a Phase 1/2 Trial of Large Surface Area Microparticle Docetaxel for High-Risk Non-Muscle Invasive Bladder Cancer

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Introduction and Objective

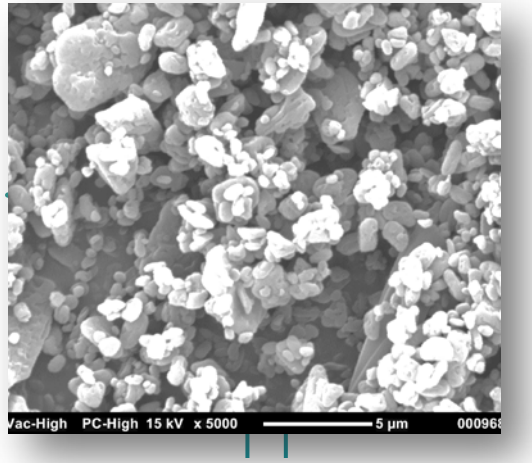
1. Large Surface Area Microparticle Docetaxel (LSAM-DTX)
   a) Pure drug microparticles formed by a supercritical precipitation technology
   b) Formulated for sustained local drug release following delivery of high concentration of drug into tumors

2. Clinical Trial (NCT03636256)
   a) Phase 1/2 trial of LSAM-DTX in patients with high-risk non-muscle invasive bladder cancer
   b) 19 subjects
   c) LSAM-DTX in saline suspension administered via direct intramural injection into resection bed post TURBT and multiple intravesical instillations
   d) Investigated LSAM-DTX safety as primary endpoint; preliminary efficacy and immune effects as secondary endpoints

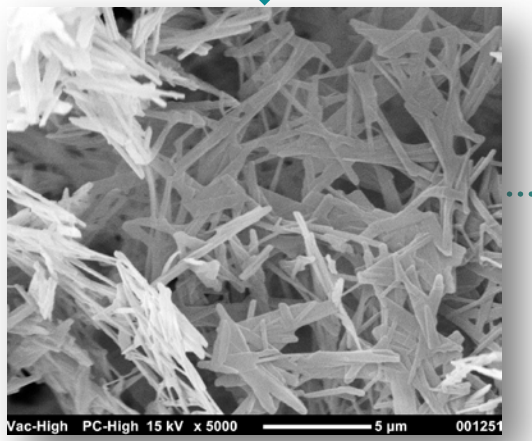
Large Surface Area Microparticle Docetaxel (LSAM-DTX)

Formed by Supercritical Precipitation (SCP)

- SCP technology uses sonication and supercritical CO_2 to transform taxane APIs into LSAMs
- LSAM-DTX (NanoDoce®) is suspended in saline prior to use for direct intramural injection into bladder wall and for intravesical instillation



Top image: unprocessed docetaxel API
Bottom image: SCP-processed LSAM-DTX



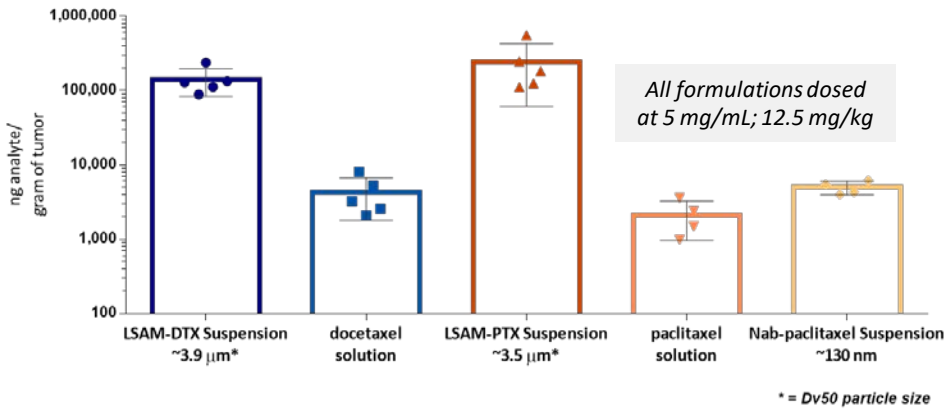
- Maintains mean particle size of c. 3.5 microns (vol) allowing entrapment within the tumor
- Large surface area (>25m^2/g) allows for continuous drug release for > 4 weeks[1] after intratumoral delivery
- Systemic clearance from tumor site is gradual at subtoxic levels[1,2]

1. Maulhardt H. et. al. Cancers 2019 (11), 577-594
2. Verco S. et. al. Drug Delivery and Translational Research (2020)

Preclinical Evaluations of Intratumoral (IT) LSAM-DTX

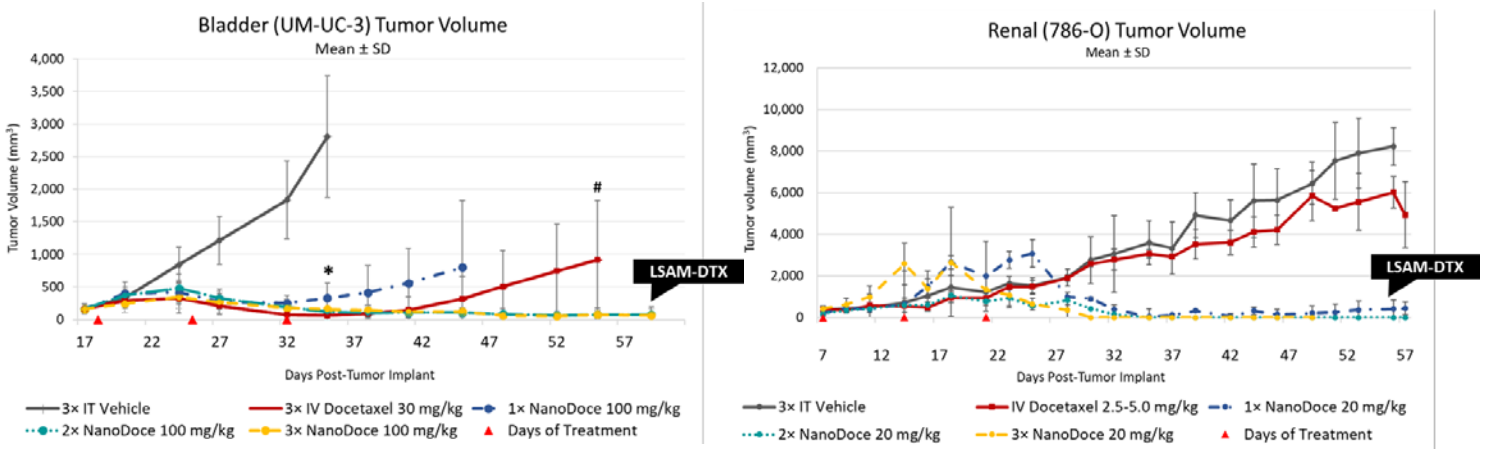
Increased Tumor Retention and Efficacy

Increased LSAM Drug Retained in Tumor Tissue 5 Days after IT Administration[1]



- Five days after IT injection of equivalent doses of drugs, tumors injected with LSAM-DTX, or LSAM-paclitaxel, retained > 40-fold more drug compared to tumors injected with docetaxel, paclitaxel, or nab-paclitaxel for injection

Tumor Response of IT LSAM-DTX vs. Intravenous (IV) Docetaxel in Urologic Tumor Xenografts[2]



(UM-UC-3 human urothelial carcinoma cells (ATCC-CRL-1749™)) implanted in 6–7-week-old female Hsd:Athymic Nude-*Foxn1*^{nu} mice.
*= $p < 0.0001$ vs. 3x IT Vehicle for all treatment groups; # = $p < 0.01$ for 3x IV Docetaxel 30 mg/kg vs. 2x & 3x NanoDoce® 100 mg/kg groups.

(786-O clear cell renal carcinomas (ATCC-CRL-1932™)) implanted in 6–8-week-old female Sprague-Dawley Rag2/Il2rg null (SRG™) rats.

- Bladder and renal tumor volume reduction following IT LSAM-DTX was superior to IV docetaxel and superiority was maintained after completion of IT LSAM-DTX dosing
- Systemic toxicity was generally less in IT LSAM-DTX groups

1. Adapted from Verco, S., Maulhardt, H., Baltezor, M. et al. Drug Del Transl Res. (2020)
2. Adapted from Maulhardt. H. et. al. Cancers 2019 (11), 577-594

Phase 1/2 Trial of LSAM-DTX for hrNMIBC (NCT03636256)

Key Inclusion/Exclusion Criteria

- Inclusion
  - Age ≥18 years with pathological or cytological diagnosis of high-risk NMIBC:
    - HG T1; Any recurrent, HG Ta; HG Ta > 3cm (or multifocal); Any CIS; Any BCG failure in HG patient; Any variant histology; Any LVI, to include any HG prostatic urethral involvement[1]
  - Urothelial carcinoma confirmed by biopsy, urine cytology, CT scan, or other institution-approved diagnostic methodology
  - ECOG 0-2 at study entry
  - Life expectancy of at least 6 months
  - Adequate marrow, liver, and renal function
  - All visible tumors removed during TURBT

- Exclusion
  - Metastatic disease
  - Previous (within 12 months) or concurrent history of non-bladder malignancy except for non-melanoma skin cancer;
  - Intravesical therapy within 4 weeks prior to consent
  - Resection surface area greater than 8 cm^2
  - Upper tract and urethral disease within 18 months
  - Known hypersensitivity to any of the study drug components or reconstitution components
  - Participation in the treatment phase of another clinical trial within 3 months prior to consent

1. As defined in AUA/SUO Guidelines (Chang et al, J Urol 2016; 196:1021)

Phase 1/2 Trial of LSAM-DTX for hrNMIBC

Treatment Timelines

- Treatment Timelines
  - 3+3 dose-escalating design of direct intramural injection (IMI) of 4 concentrations of LSAM-DTX in suspension (3-15 mg) cystoscopically into and around the resection bed after TURBT followed by intravesical instillations (IVT) LSAM-DTX (50-75mg in 25 ml)

Procedure	Screening	Treatment		Induction						Maintenance			EOT (End of Treatment)	Survival Follow-up
		Day 1	Day 15	Day 1 Week 1 (≥ 4 W)	Day 8 Week 2	Day 15 Week 3	Day 21 Week 4	Day 28 Week 4	Day 35 Week 6	Day 85 Week 13	Day 92 Week 14	Day 99 Week 15	Day 180	Months 9 & 12
LSAM-DTX Intramural Injection (IMI)		X												
LSAM-DTX Intravesical Instillation (IVT)		X		X	X	X	X	X	X	X	X	X		

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Phase 1/2 Trial of LSAM-DTX for hrNMIBC

Patient Demographics, Safety, Pharmacokinetics

Demographics (n=19)	
Age	
Median	72
Range	56-82
Sex	
Male	14
Female	5
Race	
Black/African-American	1
White	18
Stage	
Ta	7
CIS	8
T1	3
T1 w/ CIS	1
Prior BCG Use	12

LSAM-DTX Safety	
Events	
TEAE	203
SAE	1 (kidney stone)
Systemic SAEs	
Possibly Related	0
Probably Related	0
Definitely Related	0
Local SAEs	
Possibly Related	0
Probably Related	0
Definitely Related	0

LSAM-DTX PK

- Plasma docetaxel concentration was nondetectable in all subjects at all timepoints in the NMIBC study arm (n=19)
- In a MIBC study arm (not presented here), docetaxel concentration was nondetectable in all subjects at all timepoints except 2 subjects (11.6ng/mL at hour 4 and 10.3ng/mL at hour 1 respectively) (n=18)
- LLOQ=10ng/mL

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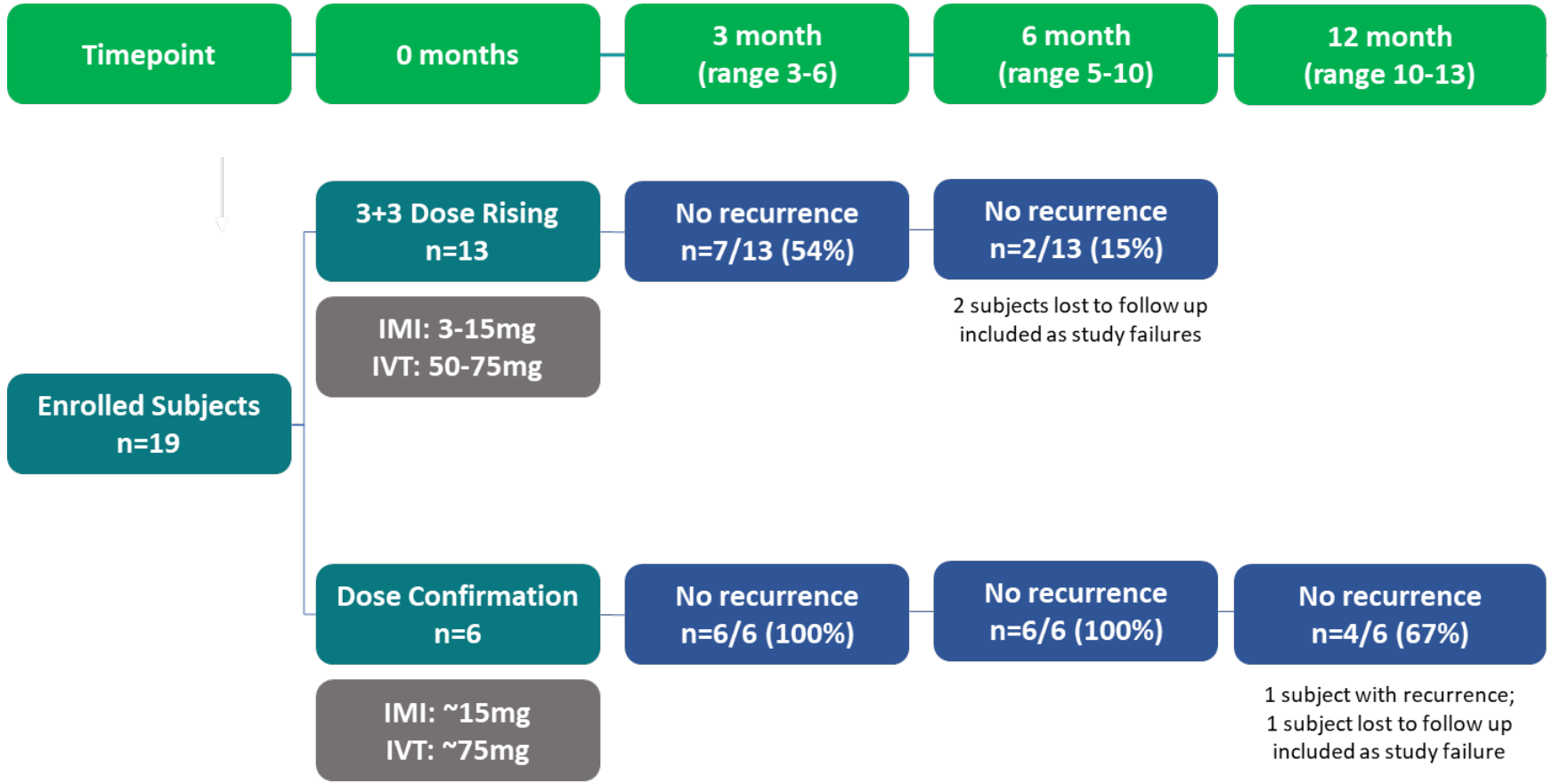
Phase 1/2 Trial of LSAM-DTX for hrNMIBC

Preliminary Efficacy

Preliminary Data	LSAM-DTX All Doses
3-Month Complete Response (CR)	13/19 (68%)
6-Month Durability (CR)[1]	8/13 (62%)
12-Month Durability (CR)[1]	4/13 (31%)

1. Subjects with CR at 3 months



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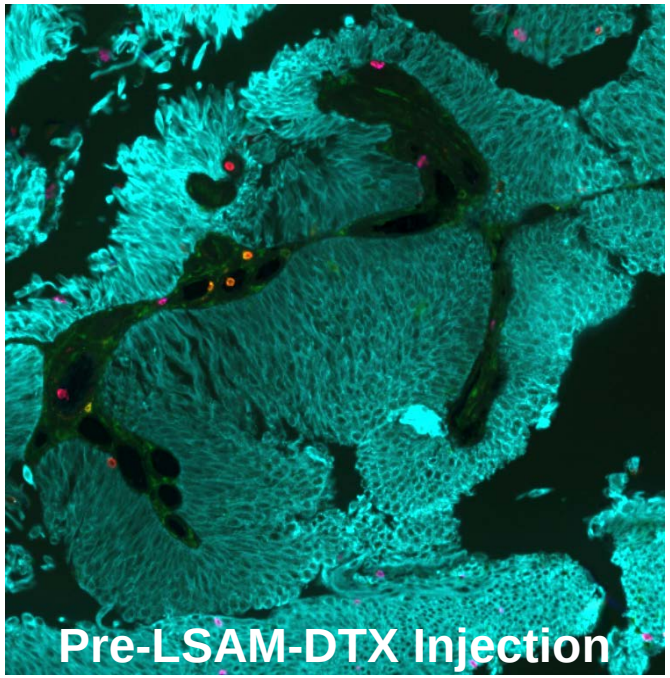
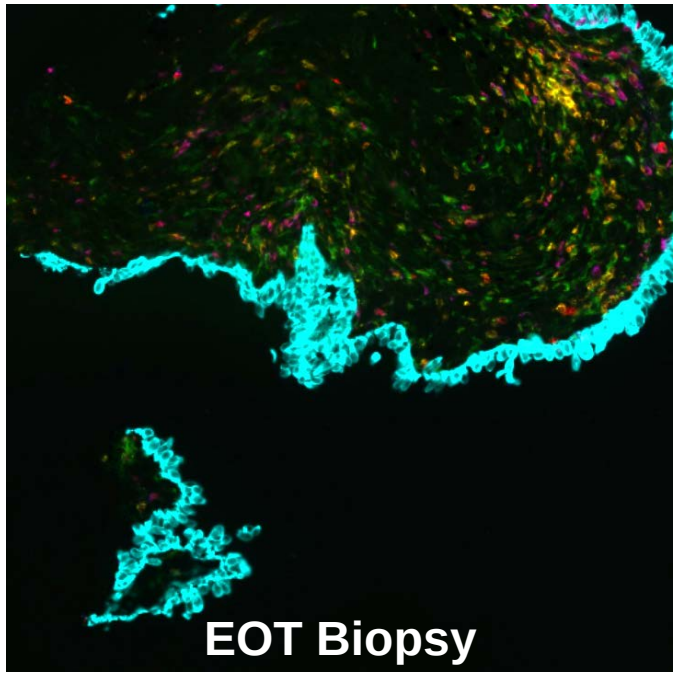
Immunomodulation Following LSAM-DTX Treatment

- Multiplex immunofluorescence (mIF) in pre-LSAM-DTX and EOT biopsies
  - Suitable tissue biopsies obtained from 5 subjects
  - Tumor microenvironment (TME) regions of interest identified by pathologist
  - 9 rounds of multiplex staining of 17 biomarkers; 16 co-expressions quantitated





Results

Increased density of immune effector cells in TME at EOT versus pre-LSAM-DTX treatment

Light Blue = PanCK; Yellow = CD4+ Helper T cells, Magenta = CD8+ Cytotoxic T Cells

Example ROI selected based on similar cell density; magnification= 0.2X

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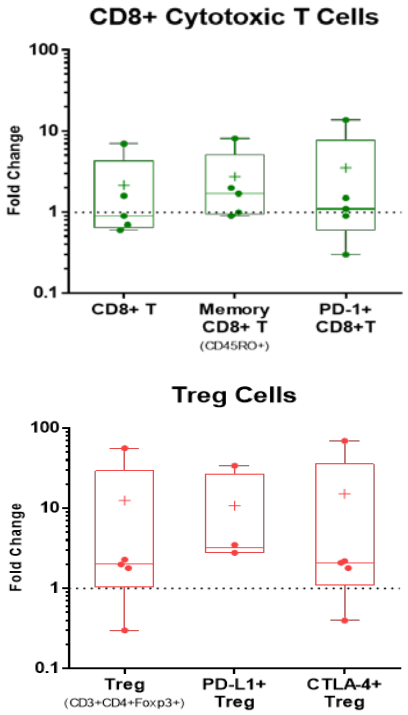
Immunomodulation Following LSAM-DTX Treatment

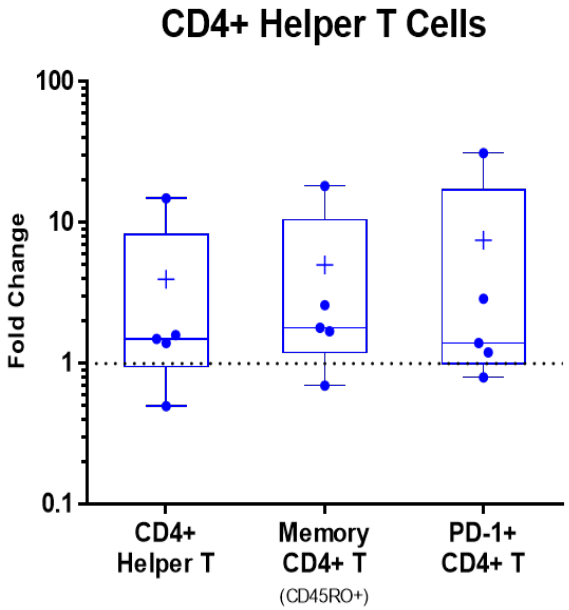
Changes in Immune Cell Densities in TME

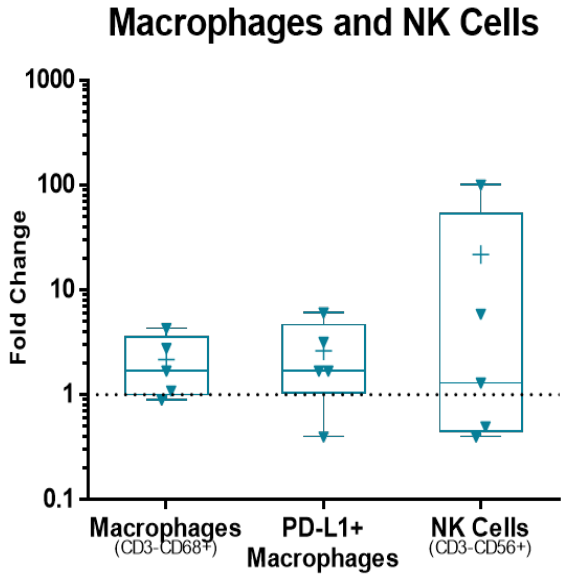
- Across 5 NMIBC subjects:
  - Increased density of T Cells Pre to Post LSAM-DTX treatment
  - All subjects show increased density of macrophages (including PD-L1+)
  - 3/5 subjects show increase in NK Cell density
  - Variable changes in densities of Myeloid and MDSC cells

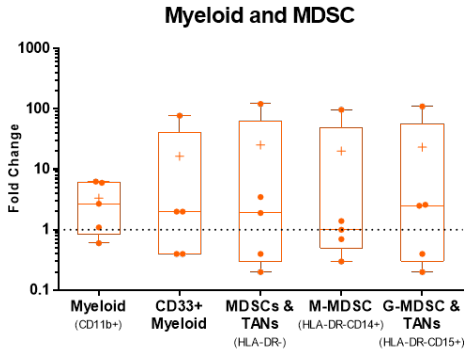
Pre to Post LSAM-DTX Treatment

Change in Cell Density (Cells/mm²); Line = Median; + = Mean









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Summary

1. Safety
   - No drug-related treatment-emergent adverse events recorded
   - PK analysis demonstrated negligible systemic exposure throughout the study
2. Efficacy
   - At 3-month timepoint (all doses): CR = 13/19 (68%)
   - 6-month durability (all doses): CR = 8/13 (62%)
   - 12-month durability (all doses): CR = 4/13 (31%)
   - Maximum dose cohort: 3-month/6-month CR = 6/6 (100%); 12-month CR = 4/6 (67%)
3. Immune effect
   - Preliminary evidence of favorable immune effects
4. Conclusion
   - Data support further clinical research of LSAM-DTX to:
     - Optimize dose and confirm efficacy in high-risk NMIBC
     - Evaluate if the immune effect of LSAM-DTX can increase the overall response rate when used in combination with immune checkpoint inhibitors or other immunoncology agents

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