Local administration of large surface area microparticle docetaxel is associated with anti-tumor immunomodulation across multiple tumor types

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INTRODUCTION

Large surface area microparticle docetaxel (LSAM-DTX) was developed for local administration to the tumor site where it acts as a depot continuously releasing drug without significant systemic toxicity or immunosuppression [1]. LSAM-DTX has been found within tumors for up to 50-days [2].

To characterize immunomodulation after local administration of LSAM-DTX, immunophenotyping was performed in 3 tumor settings:
- Before/after direct injection of LSAM-DTX at the site of transurethral resection of non-muscle invasive bladder cancer (NMIBC) + instillation in clinical trial subjects [3].
- After intratumoral (IT) LSAM-DTX in subcutaneous implanted syngeneic murine renal tumors (Renca).
- After IT LSAM-DTX + intraperitoneal (IP) anti-CTLA-4 in syngeneic orthotopic murine metastatic luciferase-enabled breast tumors (4T-1-luc) [4].

METHODS & MATERIALS

Non-muscle Invasive Bladder Cancer

Multiplex immunofluorescence from 5 NMIBC clinical trial subjects (NCT#03632626) in bladder tumors pre/post LSAM-DTX therapy [3].

CD4+ and CD8+ T cells increased in TME in subset of subjects

Blood

<table>
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<tr>
<th>Fold-change in T Cells following LSAM-DTX therapy</th>
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<td>CD4+ T Cells</td>
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<td>Pre-treatment</td>
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<td>Post-treatment</td>
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CD4+ and CD8+ T cells increased in TME in subset of subjects

Immune cell distribution in TME pre/post-LSAM-DTX in subject with complete response

Renal Cancer

In the Renca tumor model [5], flow cytometry was used to evaluate immunomodulation in blood, tumor, and spleen at early timepoints. Animals (N=5/group) were treated with IT LSAM-DTX, IV vehicle, or IV docetaxel (IV doc) on Days 1, 8, & 15 and sampled for flow cytometry on Days 1, 4, 7, 11, & 18.

T Cells

- Circulating CD4+ and CD8+ T cells increased in IT LSAM-DTX vs. IV doc following 2 weekly treatment cycles.
- CD4+ and CD8+ T cells in the TME slightly decreased in LSAM-DTX vs. IV doc following 1 cycle and recovered to similar levels at later timepoints.
- Splenic CD4+ and CD8+ T cells were similar through 2 treatment cycles.

Macrophages

- Reduced circulating and splenic M2 macrophages in LSAM-DTX vs. IV doc.
- Reduced M1 and increased M0 macrophages in TME of IT LSAM-DTX vs. IV doc.

Metastatic Breast Cancer

Flow cytometry data analyzed with outliers removed using one-way ANOVA (Kruskal-Wallis). Significance reported as *p < 0.05; **p < 0.001; ***p < 0.0001.

T Cells

- Increased circulating CD3+, CD4+, CD8+, T reg and B cells.

Natural Killer and Dendritic Cells

- Compared to untreated animals, NK, NK T and DC were increased in both bloods and the TME.

Thoracic Metastatic Burden

- LSAM-DTX/anti-CTLA-4 was associated with significantly reduced thoracic metastasis; 4/10 animals in the combination group had no evidence of metastatic burden on Day 30.

CONCLUSIONS

- Immunophenotyping in 3 diverse tumor settings found commonalities in antitumor immunomodulation following local LSAM-DTX including changes in T cells and MDSC.
- NMIBC subjects demonstrated infiltrations of CD4+ T, CD8+ T, and NK cells.
- Mice administered LSAM-DTX into renal tumor xenografts had increased circulating T cells and reduced M2-macrophage levels in the blood and spleen when compared to IT docetaxel.
- Intratumoral LSAM-DTX in a metastatic breast cancer model increased T cells in the TME and reduced thoracic metastasis when combined with systemic immunotherapy.
- Preclinical/clinical antitumor immunomodulation suggests that IT LSAM-DTX may be amenable to combination with immunotherapy and warrants further clinical research to confirm.