Intratumoral NanoDoce administration provided high docetaxel levels in xenograft tumor tissues following 3 cycles (Figure 2). Tumor levels were evaluated by H&E and immunohistochemistry (H&E and immunohistochemistry (IHC) (Pan-Cytokeratin AE-1/AE-3, CD11b, CD16, and CD68) was evaluated (Figures 4 and 6).

RESULTS: Tumor volume reductions with 2 and 3 doses of NanoDoce were significantly greater than (renal and bladder) or similar (prostate) to IV docetaxel and significantly greater than vehicle (p<0.05). Histology confirmed tumor findings; significant tumor regression with increased immune-cell infiltrate observed in IT NanoDoce treatments compared to controls. High tissue levels of docetaxel were detected in NanoDoce-treated animals. IHC showed (peritumour-infiltrating immune cells in NanoDoce-treated animals while vehicle and IV docetaxel had limited to no infiltration.

Figure 1. Submicron Particle Production Technology

- Large active pharmaceutical ingredient (API) crystals cannot be suspended and must be dissolved for IV delivery
- Small amount of systematically delivered dose reaches the tumor site in a short period of time
- Each submicron particle contains 2-3 billion molecules of particle
- Particles suspended and locally delivered to tumor site are entrapped at disease site long for durations
- Increased particle surface area allows for sustained therapeutic API release

Figure 2. Docetaxel Tumor Residence Time

- Compared to IV docetaxel, concentrations (µg docetaxel/gram tumor) were much greater in renal and bladder tumors following IT NanoDoce-treatment
- Docetaxel in tumor tissues was detected up to 50 days after IT administration of NanoDoce

Table 1. Study Designs

<table>
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<th>Study</th>
<th>Renal</th>
<th>Bladder</th>
<th>Prostate</th>
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Summary and Conclusions

- Local injections of submicron particle docetaxel (NanoDoc®) resulted in tumor reduction in three different models of uro-oncologic cancers and produced a unique disruption of the tumor microenvironment
- Treatment with multiple cycles of IV docetaxel resulted in minimal renal tumor volume reduction or unsustainable bladder tumor volume reduction
- Intratumoral NanoDoc® administration provided high docetaxel levels within the tumor; orders of magnitude greater than IV administration
- Histologically, intratumoral injections of NanoDoc® demonstrated high levels of tumor regression and increased local immune cell infiltrates compared to IV docetaxel treatment
- IT injection of NanoDoc® may kill tumor cells through direct and indirect means
- NanoDoc® directly inhibits tumor cell mitosis
- In reducing tumor burden, NanoDoc® indirectly promotes immune-cell mediated tumor clearance
- Clinical testing of submicron particle taxanes in uro-oncologic cancers is underway