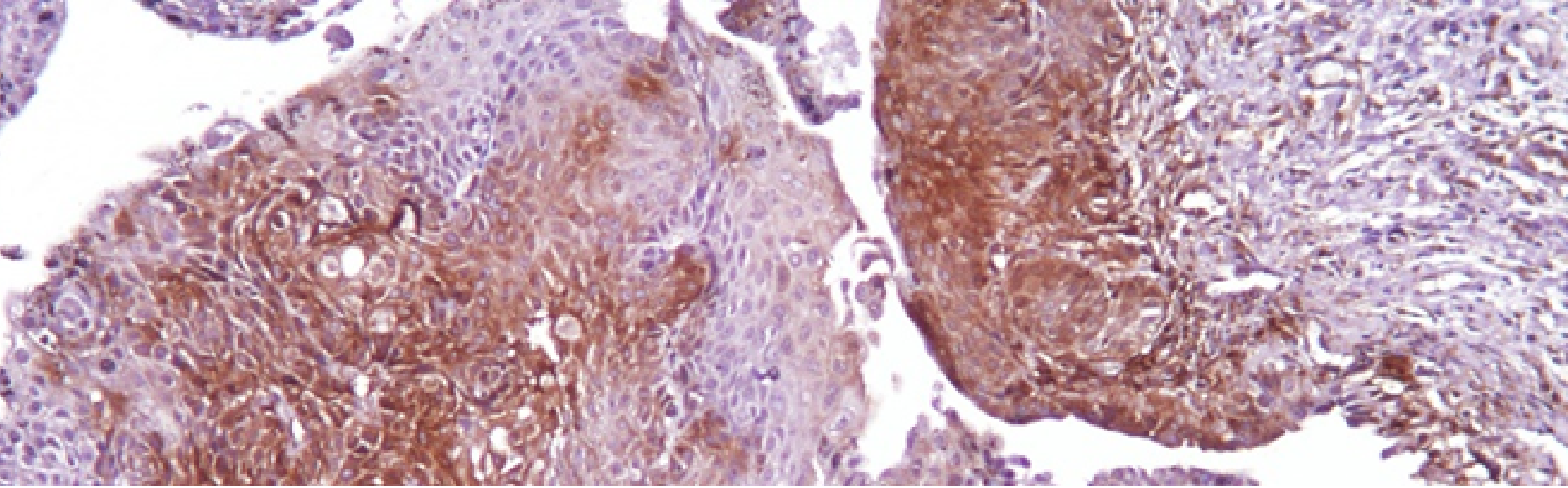

THE UNIVERSITY OF TEXAS
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Novel combination therapy using lentiviral interferon and immune checkpoint blockade for treatment of bladder cancer in a murine model

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Novel combination therapy using lentiviral interferon and immune checkpoint blockade for treatment of bladder cancer in a murine model

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Introduction

Non-muscle invasive bladder cancer (NMIBC) makes up 70% of newly diagnosed bladder cancer cases

The first-line treatment for NMIBC is transurethral resection of bladder tumor followed by Bacillus-Calmette Guerin (BCG) immunotherapy

Recurrence or progression of disease after BCG treatment occurs in up to 70% and 10-20% of patients, respectively[1]

Bladder sparing intravesical therapies for patients with BCG unresponsive disease are limited and their development represents an unmet need in urologic oncology

[1]Kaufman et al, Lancet (2009)

Interferon α and NMIBC

- **Interferon (IFN)** is a pleiotropic cytokine with antiangiogenic and cytotoxic properties
- IFNα increases programmed cell death ligand-1 (PD-L1) and protein **(PD-1) expression** on tumor and immune cell subsets[1]
- IFN monotherapy for treatment of NMIBC has shown efficacy but is not durable[2]
- **BCG combination therapy with IFN** in BCG unresponsive patients yields minimal benefit[3]
- The above limitations are likely due to **inadequate drug exposure** to the urothelium

[1]Garcia-Diaz A et al. Cell Rep (2017)
[2]Torti FM et al. J Clin Onc (1988)
[3]Joudi FN et al. Urol Oncol (2006)

Gene therapy in NMIBC

Gene therapy is the delivery of nucleic acid into a host cell to treat disease

rAd-IFNα/Syn3 (Adstiladrin; nadofaragene firadenovec) is a replication-deficient recombinant adenovirus gene transfer vector that delivers the human IFNα2b gene[1]

In a recent single-arm, open-label Phase 3 trial, intravesical adstiladrin resulted in a 53.4% complete response at 3 months in patients with BCG-unresponsive carcinoma in situ[2]

[1]Duplisea J et al. W J Urol (2019)
[2]Dinney CP et al. Urol Oncol Suppl (2019)

Gene therapy in NMIBC

Lentivirus (LV) is another potential vector for intravesical delivery of IFNα that can integrate into the host genome and enhance efficiency of drug delivery

Previous work by our group has successfully transduced LV-IFNα viral vectors into mouse bladder cancer cell lines

[1]Mokappati et al. unpublished data

Immune checkpoint blockade in NMIBC

In animal studies poly(I:C), an IFN surrogate, used in combination with **anti-PD-1 monoclonal antibody** therapy prolongs animal survival[1]

Recently, **pembrolizumab** (anti-PD1 monoclonal antibody), was approved by the FDA for treatment of BCG unresponsive NMIBC[2]

[1]Plote D et al. Oncoimmunology (2019)
[2]Balar AV et al. JCO Suppl (2019)

Study Rationale

1. Intravesical delivery of IFNα using an adenoviral gene therapy has shown efficacy for the treatment of BCG unresponsive bladder cancer
2. IFNα therapy induces profound expression of PDL-1
3. Gene therapy using a lentiviral vector is hypothesized to enhance the efficiency of drug delivery

Hypothesis and Study Aim

A combination of IFNα gene therapy with PD-1 blockade should result in enhanced efficacy over either therapy alone

The **objective** of this study is to describe the treatment efficacy of combination therapy using LV-IFNα with PD-1 blockade in a murine bladder cancer model

Study Design

Day 0

Female mice instilled intravesically with 25K MB49 cells

Tumor uptake confirmed

Day 4

Intravesical Treatment Instillation

Vehicle
LV-IFN
Anti-PD-1
LV-IFN + anti-PD-1

Imaging data, histology bladder weight and FACS RNA DNA Protein

2x weekly intraperitoneal anti-PD1 injection

Mice sacrificed for tissue collection

Results

Figure 1: LV-IFNα upregulates PDL1

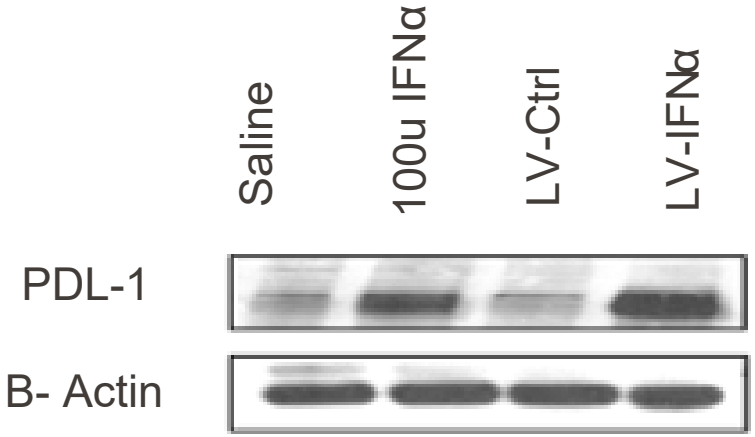


Figure 1: Western blot confirmed the upregulation of PDL1 in MB49 cell lines treated with IFNα [recombinant (100U)] or LV-IFNα.

Figure 2: PD-L1 immunohistochemistry demonstrating increased expression in LV-IFNα treated tumors (B) compared to controls (A)

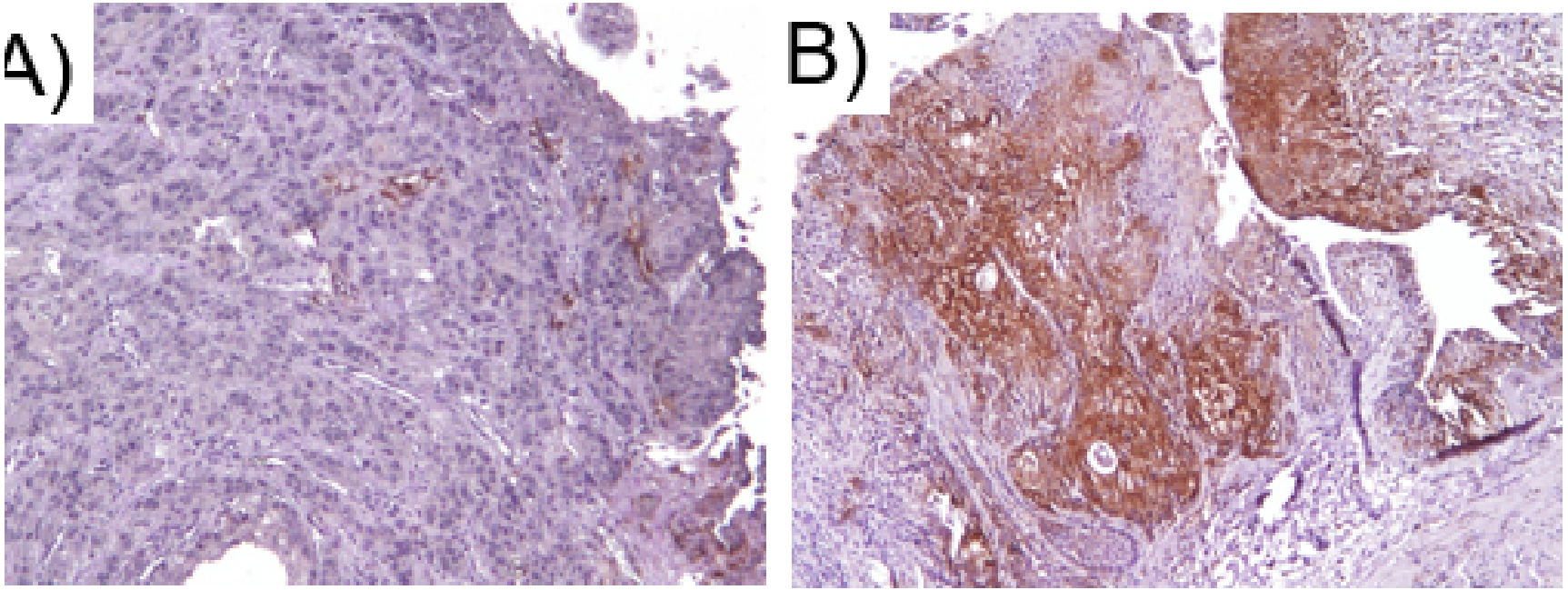


Figure 3: Bioluminescence decreased amongst the treatment groups with maximal therapeutic effect reached at 18 days post treatment administration

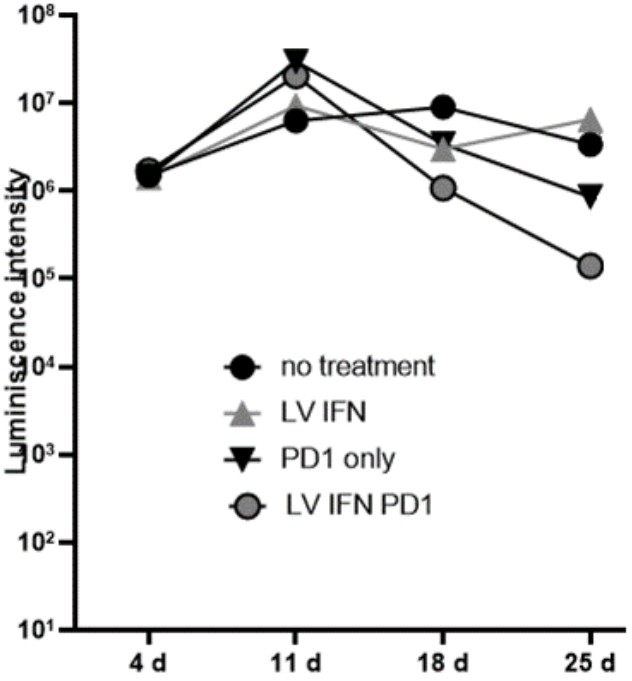


Figure 4: Mouse bladder weights demonstrating that the LV-IFN + anti-PD1 combination group had the lowest bladder tumor burden

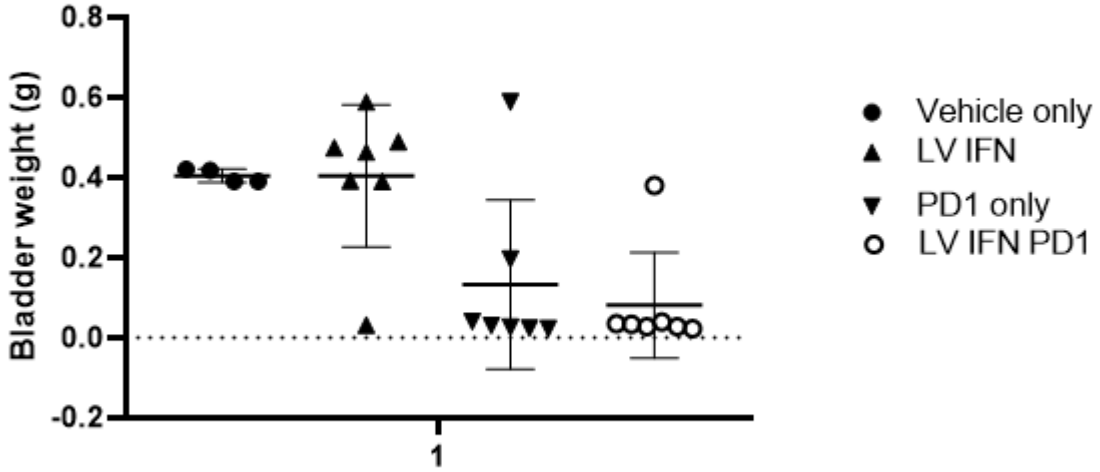


Figure 5: Efficacy of combination therapy in MB49 intravesical model showing survival benefit in mice treated with combination of LV-IFN and PD1 antibody

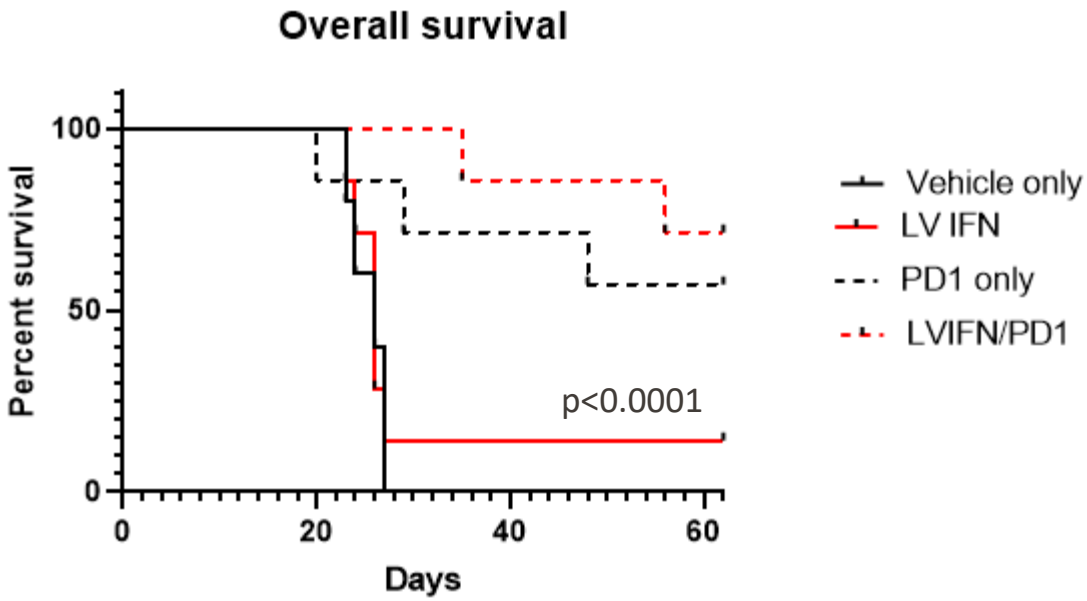
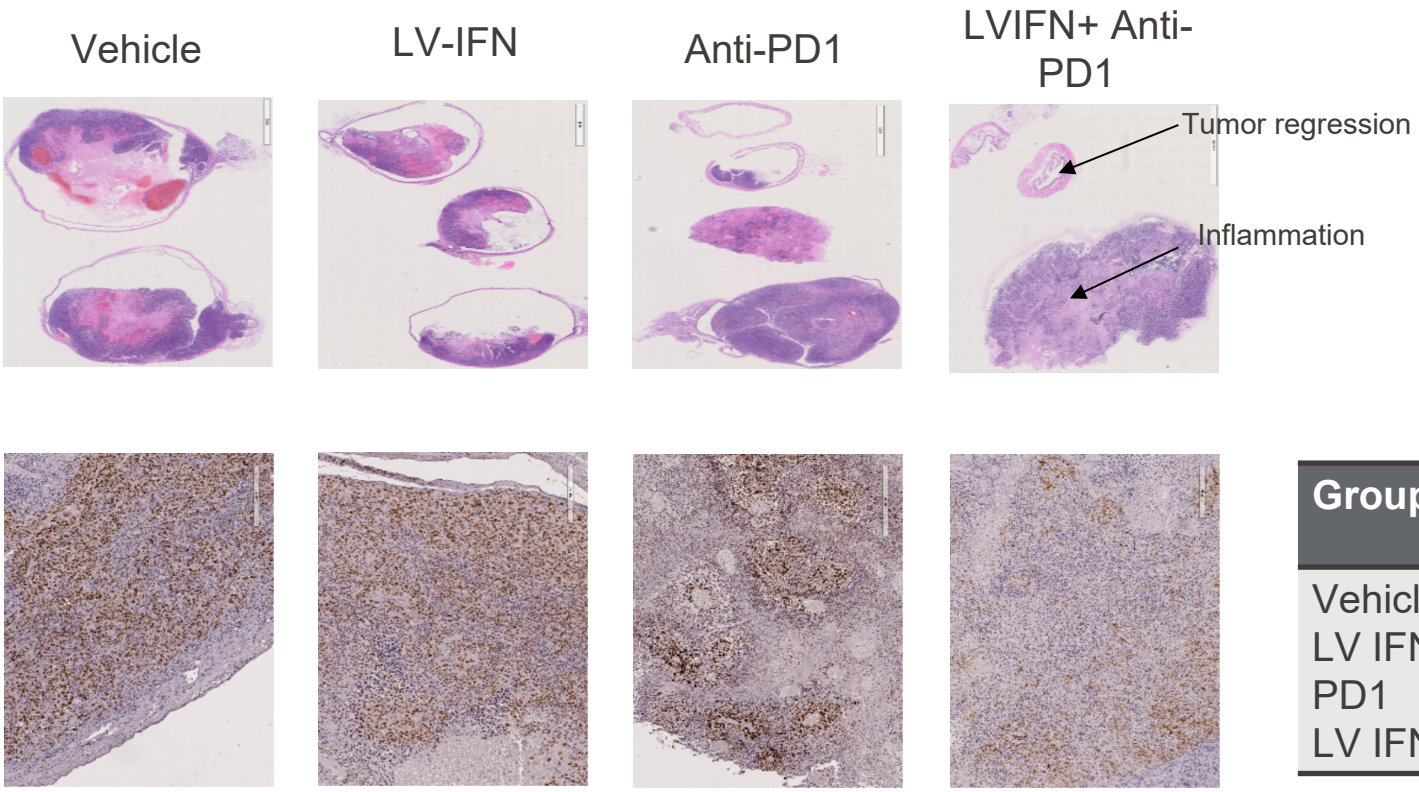


Figure 6: Histological analysis and Ki-67 staining



Group	% Bladder tumor free
Vehicle	0
LV IFN	14
PD1	71
LV IFN/PD1	86

Conclusions:

- Combination therapy with LV-IFNα and anti-PD1 antibody successfully eradicates bladder tumor burden in an intravesical murine model
- Combination therapy is more effective than either therapy alone
- These findings represent a potentially novel therapeutic strategy for bladder cancer and pave way for future exploration in the clinical setting

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