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Sensitization of PD-1/L1 Refractory Lung Tumors in an Immunocompetent Mouse Model with AdAPT-001

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Abstract

The reputation of checkpoint inhibitors as potential game changers in oncology is well-deserved as the the 14/14 complete responses recently reported with the PD-1 inhibitor, dostarlimab, in mismatch repair (MMR) deficient locally advanced rectal cancer demonstrates but comes with an important caveat: in most cases and in most cancers non-responders greatly outnumber responders. This begs the question of how to mimic the unprecedented result with dostarlimab in MMR-proficient and otherwise checkpoint inhibitor non-responsive cancers. Several strategies to sensitize tumors to checkpoint inhibitors are under active investigation. These include combinations with other checkpoint inhibitors, chemotherapy, angiogenesis inhibitors, targeted agents, DNA damage repair inhibitors, epigenetic modifiers, and TGF-β inhibitors. This short communication presents data on AdAPT-001, a Type 5 oncolytic adenovirus, currently in a Phase 1/2 clinical trial called BETA PRIME (NCT04673942), which encodes for a transforming growth factor-beta (TGF-β) trap, as an anti-PD-L1 sensitizer.

Introduction

By now, the unprecedented results from a neoadjuvant study with the PD-1 inhibitor, dostarlimab, in 14 patients with mismatch repair (MMR)-deficient stage II or III rectal adenocarcinoma that were spared from standard of care surgery- and chemoradiation-related morbidity and dysfunction [1] have been widely discussed and celebrated. That said, only 5-10% of rectal adenocarcinomas are MMR deficient [2], and, more generally, most cancer patients, >70%, are non-responsive to checkpoint inhibitors (CIs) [3], which raises the broader clinical question about how to improve outcomes in the CI-resistant population writ large.

Potential strategies to confer susceptibility to checkpoint inhibitor-resistant tumors include combination with other CIs, chemotherapy, angiogenesis inhibitors, targeted agents, DNA damage repair inhibitors, epigenetic modifiers, and TGF-β inhibitors [4]. Regarding the latter, several TGF-β inhibitors are in development; among them is AdAPT-001, a Type 5 oncolytic adenovirus, currently in a Phase 1/2 clinical trial called BETA PRIME (NCT04673942), which encodes for a transforming growth factor-beta (TGF-β) trap that is the focus of this short communication. The AdAPT-001 TGF-β trap is a chimeric soluble type-II receptor fused with the Fc region of human immunoglobulin, which "traps" or antagonizes the activity of TGF-β [5]. In *in vitro* studies the chimeric receptor from AdAPT-001 is as selective for the isoforms TGF-β1 and TGF-β3 as the native receptor. Moreover, it is a potent TGF-β1-antiproliferative and TGF-β1-extracellular matrix transcriptional inhibitor with broad potential based on AdAPT-001's activity in multiple cancer cell lines, including A549 (lung), HCT116 (colorectal), Panc02 (pancreatic), MeWo (melanoma), Hep3b (hepatocellular), MCF7 (breast), and SCC-9 (head/neck). Even in normal fibroblasts where viral replication was nearly abolished, biologically active levels of the trap were generated.

A highly pleiotropic cytokine, TGF-β suppresses immunosurveillance as well as contributes to angiogenesis, fibrosis, cell proliferation, migratory invasion, and metastatic spread [6,7]. Because of this pleiotropicity, TGF-β inhibitors are potential "Swiss Army Knives" for the treatment of cancer, as illustrated in Figure 1 [8].

Accordingly, then, on the premise that TGF-β overexpression is a root cause of T-cell dysfunction and resistance to checkpoint inhibitor activity, the antitumor efficacy of the mouse version of AdAPT-001 (mTGFβR-IgG) in a KRAS mutated, anti-PD-L1-resistant murine lung cancer called ADS-12 was investigated.

Materials and Methods

Mice

129S1/SvImJ mice, approximately 6-8 weeks old, were acquired from Jackson Laboratory. The study was reviewed and approved by an Institutional Animal Care and Use Committee.

Test article

The test article was a modified adenovirus mAdAPT-001 (also known as Ad-TAV-mTGFbR-IgG). The virus is a targeted and TGF-beta ligand trap expressing type 5 oncolytic adenovirus designed to selectively replicate in

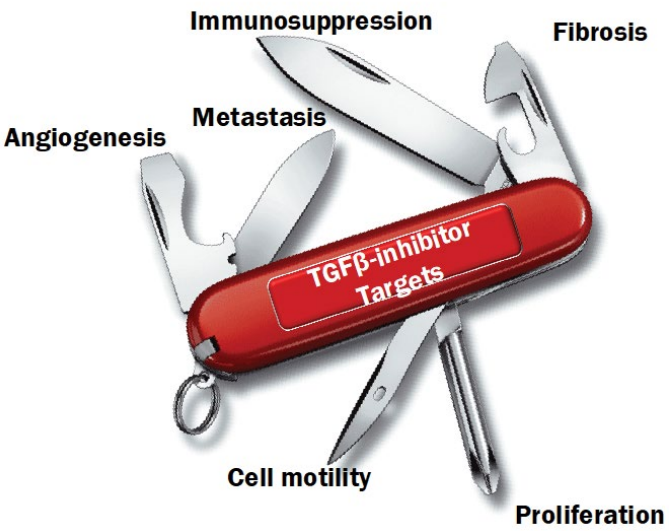

Figure 1. Potential TGF-β inhibitor targets.

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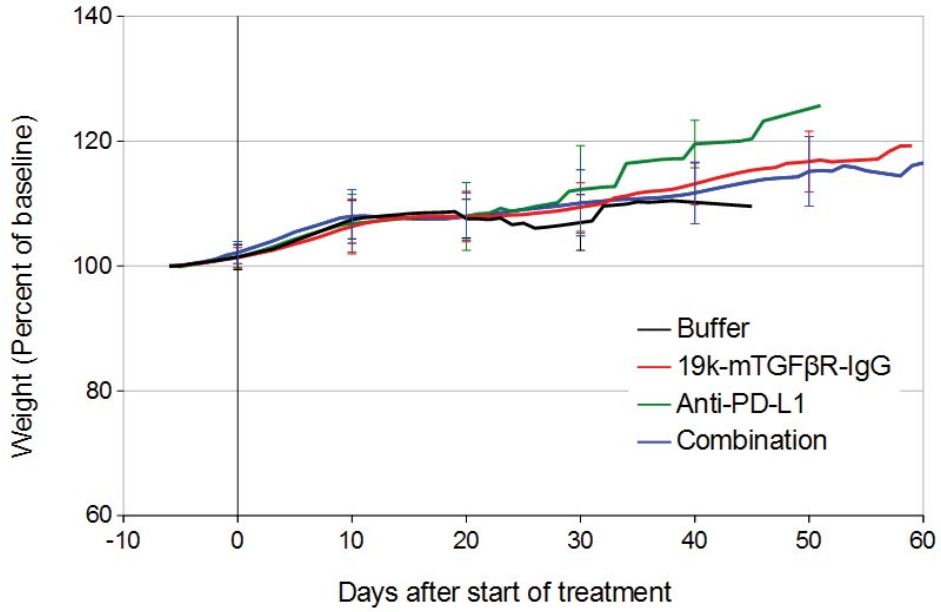

Figure 2. Weight of mice in studies of AdAPT-001 combination therapy with anti-PD-L1 antibody 129/S4 mice with ADS-12 tumors were treated with intratumoral buffer or AdAPT-001 on days 0, 4, and 8 or anti-PD-L1 antibody on days 1, 5, 9, and 13 or the combination. Mean ± standard deviation of weight normalized to pre-treatment baseline is plotted for each group. n=10 mice in each group.

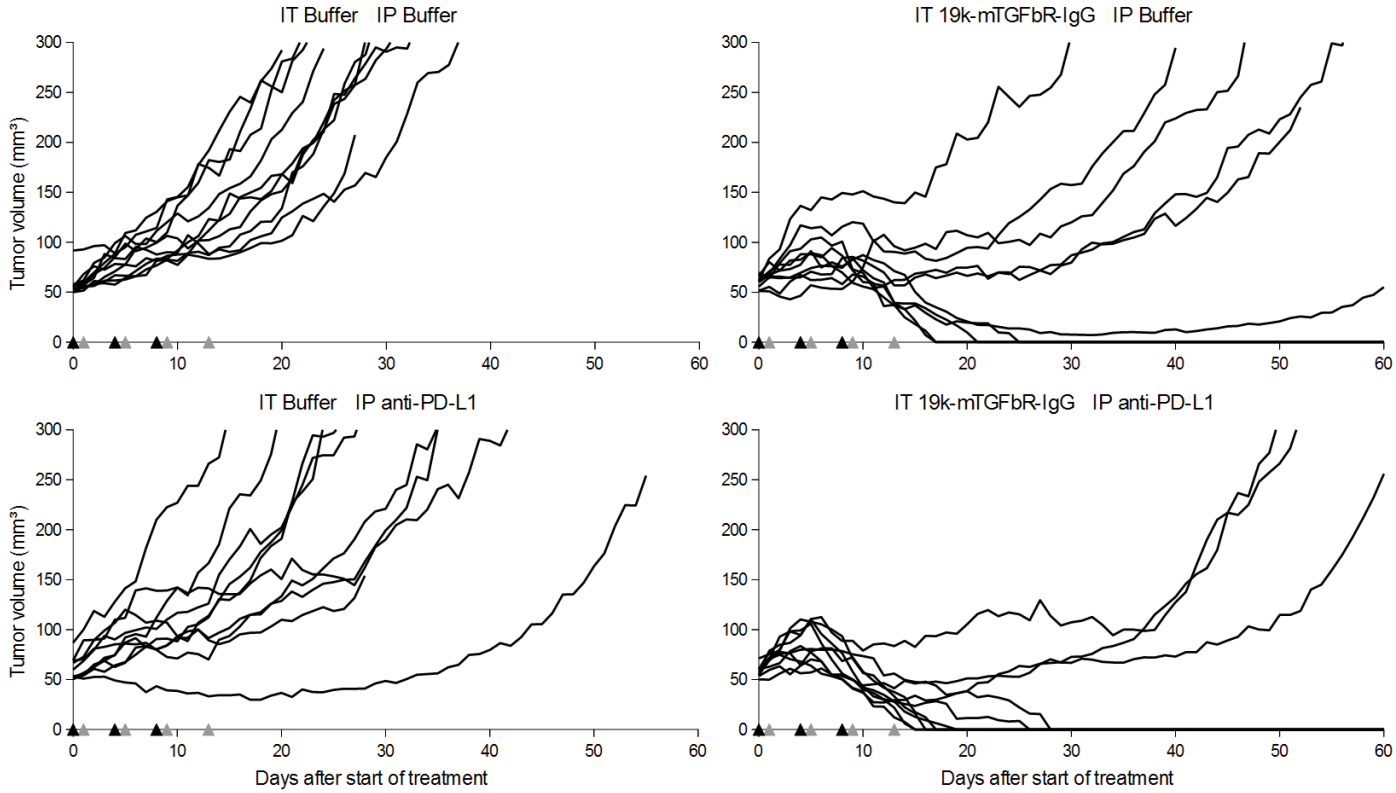

Figure 3. Tumor volumes of ADAPT-001 + anti-PD-L1 antibody combination therapy. Intratumoral doses of buffer or AdAPT-001 are indicated by black arrowheads, intraperitoneal doses of buffer or anti-PD-L1 antibody are indicated by grey arrowheads. Each line represents the tumor volume of one mouse. n=10 mice per group.

and destroy cancer cells through viral oncolysis and tumor-specific immunity. ADAPT-001 was formulated in 20 mM Tris, 25 mM NaCl, 2.5% glycerol pH 8.

Control

The Control Article was the Vehicle of AdAPT-001: a solution of 20 mM Tris, 25 mM NaCl and 2.5% glycerol pH 8.

Tumor

ADS-12 cell line, a novel murine K-ras mutant driven lung adenocarcinoma, was provided by EpicentRx. Tumors were induced subcutaneously by injection of 1E6 cells in 50 µL in the right flank.

Experimental design

In this experiment, forty 129/S4 mice 6-8 weeks old of either gender were injected subcutaneously with one million ADS-12 cells in the right flank. When tumors reached between 50-100 mm^3, 10 mice each were randomized into one of 4 groups. These groups were treated with intratumoral injections of either

- Buffer given intratumorally (IT) and intraperitoneally (IP)
- The mouse version of AdAPT-001 at 10^9 plaque forming units (PFU)/dose on days 0, 4, and 8 given IT and IP buffer
- anti-PD-L1 antibody 10F.9G2 diluted in PBS on days 1, 5, 9, and 13 and IT buffer
- IT AdAPT-001 + IP anti-PDL1.

Statistics

Data were analyzed by a one-way ANOVA for comparison of multiple groups using GraphPad Prism 5. $P < 0.05$ was considered statistically significant.

Results

All mice tolerated the treatments well. Animals were sacrificed due to tumor progression (with size >1.5 cm or ulceration) in accordance with the termination criteria set by the animal protocol or survived to the end of the study. Mice treated with AdAPT-001 gained weight at the same rate as control mice, as shown in Figure 2.

As shown in Figure 3, no discernible activity was observed from anti-PD-L1 antibody alone. Treatment with AdAPT-001 alone in these larger tumors led to complete responses in 4/10 mice, and combination therapy led to complete responses in 7/10 mice. Tumor volume was smaller in the combination therapy group compared to AdAPT-001 alone ten days after starting treatment ($p<0.01$).

Conclusion

In summary, as treatment resistance to CIs defines the largest unmet need in oncology worldwide, it is of paramount importance to overcome this resistance and to improve clinical outcomes with new therapeutic strategies. AdAPT-001 is a tumor-specific oncolytic immunotherapy with the potential to sensitize anti-PD-1/PD-L1-resistant cancer cells and to inhibit tumor growth, metastasis, and recurrence. Data from the ongoing Phase 1/2 BETA PRIME clinical trial is awaited to corroborate these results.

Conflicts of Interest

None.

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