The A2AR antagonist AZD4635 prevents adenosine-mediated immunosuppression of CD103+ dendritic cells

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Introduction

Adenosine signaling is a normal physiologic process preventing autoimmunity, that is co-opted by tumors as an immune escape mechanism. AZD4635 (HTL-1071) is a selective oral A2AR antagonist, currently in clinical trials as a single agent and in combination with durvalumab (anti-PD-L1 Ab) in patients with solid malignancies. The role of antigen presentation by dendritic cells (DC), in particular CD103+ DCs, is critical to drive anti-tumor immunity, and is impaired under conditions of high extracellular adenosine. Previously we demonstrated enhanced T cell function contributing to tumor efficacy in the syngeneic model MC38 with AZD4635 alone and in combination with anti-PD-L1. Using mouse OVA models, we now demonstrate that AZD4635 monotherapy, and when combined with anti-PD-L1, could significantly prevent adenosine (NECA)-mediated immunosuppression in mouse CD103+ cross-presenting DC, leading to improved OVA-specific T cell function, and contributing to tumor efficacy. AZD4635 also blocked NECA-induced immunosuppression in the human HLA-A2+ Melan-A model system, resulting in antigen-specific priming of naïve CD8+ T cells. Thus, we demonstrate that AZD4635’s MOA includes restoration of DC function, augmenting the elicitation of antigen-specific T cell responses.

Methods

OVA Antigen Presentation in vitro: AZD4635 (3µM) was tested for effects in reversing DC immunosuppression induced by 5-N-ethylcarboxamidoadenosine (NECA), a stable adenosine analog, in mouse CD103+ DC cultures [1]. Antigen presentation of bound Kb-SIINFEKL complexes was measured by flow cytometry with antibody clone #25-D1.16.

Human Melan-A Tumor Antigen-specific Assays: AZD4635 (3 µM) was tested in vitro in reversing NECA (5 µM)-induced DC dysfunction of Mo-DC to prime Melan-A antigen-specific (ELAGIGILTV) T cells from autologous naïve HLA-A2+ CD8+ T cells [2].

Ex-vivo CD103+ DC Antigen Presentation: CD103+ DC were flow sorted from TDLN of mice bearing MC38-OVA tumors from AZD4635 tumor efficacy studies. Sorted cells were co-cultured with OT-I CD8+ T cells with proliferation measured 4 days later.

In vivo Tumor Efficacy Studies: Treatments of MC38-OVA tumor-bearing mice started once tumors reached ~100mm3. Mice (n=10) were treated for 14 days: Vehicle, AZD4635 50 mg/kg (oral) anti-PD-L1 10 mg/kg IP 2x/wk.

Results

AZD4635 Reduces Adenosine-mediated Suppression of Antigen Presentation

AZD4635 Improves Antigen T cell Responses by Correcting Adenosine Defects in DC

AZD4635 Enhances CD103+ DC Cross-priming and combines with anti-PD-L1 Contributing to Tumor Efficacy

AZD4635 Reverses Tolerogenic Human DCS and Promotes T cell Priming to Tumor-associated Antigens in vitro

Conclusions

- Adenosine receptor signaling antagonism by AZD4635 improved differentiation and antigen presentation by DCs, including CD103+ cross-presenting/crosspriming DCs, leading to better priming, expansion and function of antigen-specific T cells.
- AZD4635’s MOA includes restoration of DC function, supporting its anti-tumor activity.

References