Oral Administration of AZD4547 as Treatment for Cutaneous Squamous Cell Carcinoma in Organ Transplant Patients

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INTRODUCTION

Cutaneous Squamous cell carcinoma (cSCC) is a keratinocyte-derived invasive carcinoma of the skin. On average, more than a million new cSCC cases are diagnosed each year in the United States, representing a significant public health problem. Ultraviolet (UV) radiation-induced immunosuppression is considered one of the most important environmental risk factors for the development of cSCC[1]. This concept is further supported by the observation that chronically immunosuppressed patients such as organ transplant patients (OTP) remaining on lifelong immunosuppressive regimens to prevent allograft rejection are at significantly high risk of developing cSCC compared to the general population[2]. Cemiplimab is the only FDA-approved systemic immune checkpoint therapy specifically indicated for patients with advanced cSCC in non-immune compromised patients[3]. However, the safety and efficacy of immune checkpoint inhibitor therapy in solid organ transplant recipients are largely unknown, as these patients are routinely excluded from clinical trials because of their risk for severe and irreversible allograft rejection. Initial management of high-risk cSCC in OTP recipients usually involves minimization of immunosuppression, aggressive surgical therapy, and possible adjuvant radiation therapy after incomplete resection or if extensive lymph node or perineural involvement is present[2]. Systemic treatments for metastatic or unresectable advanced cSCC have traditionally involved more toxic treatments with less durable response rates, such as chemotherapy and epidermal growth factor receptor (EGFR) targeted therapy[2].

Thus, there is a need for agents that can target both tumor cell-intrinsic as well as extrinsic properties to effectively treat advanced cSCC in immunocompromised patients without affecting systemic immune response. AZD4547 is an orally bioavailable FGFR inhibitor with significant effects, suggesting a potential role in modulating tumor cell effect mechanisms in cSCC in OTP patients[2].

Scientific Premise of the Current Project

1. Topical administration of AZD4547 was associated with a significant decrease in UVB-induced epidermal hyperplasia and squamous cell carcinoma with a concomitant reduction in epidermal PDL1, macrophage, and mast cell infiltration.
2. We propose to characterize further the effect of AZD4547 on the UVB-induced pro and anti-tumorigenic immune cell population. Additionally, the effect of systemic AZD4547 on immune cell phenotype will also be investigated.
3. **Using a syngeneic cSCC allograft tumor model, the impact of AZD4547 on tumor growth and immune cell infiltration will be determined.**

HYPOTHESIS

- Fibroblast Growth Factor Blockade Suppresses cSCC Tumor Growth by Enhancing T-cell-Mediated Tumor Immunity.

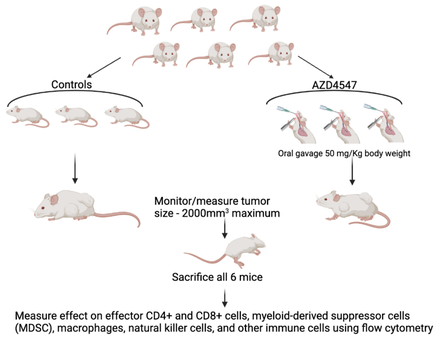
OBJECTIVES

- Determine the effect of oral administration of AZD4547 on tumor growth in a mouse syngeneic xenograft model
- Elucidate the effect of AZD4547 on tumor-immune cell infiltrate

MATERIALS & METHODS

Pharmacological method: Oral administration of AZD4547

- Injection of syngeneic cells using a 21G needle on the left and right flank in FVB female mice
- Administered either Vehicle or AZD4547 *via* oral gavage three times per week
- Tumor size was monitored twice a week until the end of the study
- Tumors and spleens were harvested and subjected to immune phenotyping using FACS analysis



RESULTS

AZD4547 Inhibits cSCC Tumor Growth

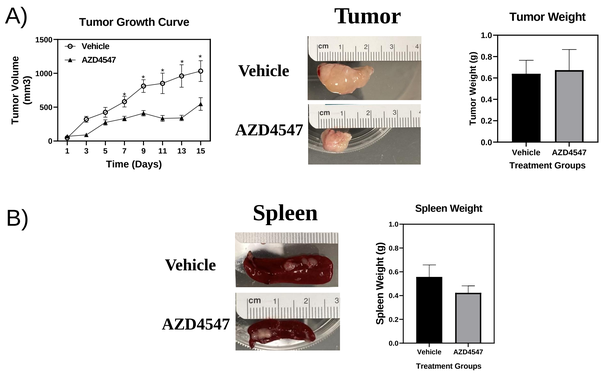


Figure 1: 5X10^6 cells were injected into the flank of FVB mice. Mice were randomized into either vehicle or AZD4547 group. (A) Tumor size was measured twice a week until the end of the study. Tumor and spleen (B) were also weighed. Data represents mean±SEM n=3 and n>5 in for CD8+ T cells in spleen and tumor cells respectively

Immune Phenotyping Using FACS Analysis

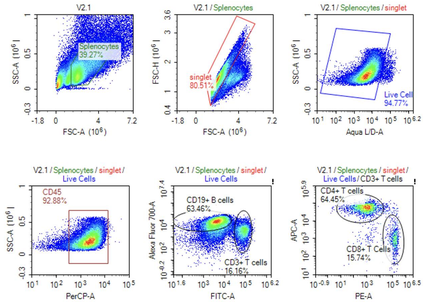


Figure 2: Tumor samples were collected and subjected to single cell suspension preparation. Cells were immunostained with antibodies for lymphoid panel including Cytotoxic and Regulatory T cells and subjected to FACS analysis.

AZD4547 enhances T cell-mediated cSCC Tumor immunity

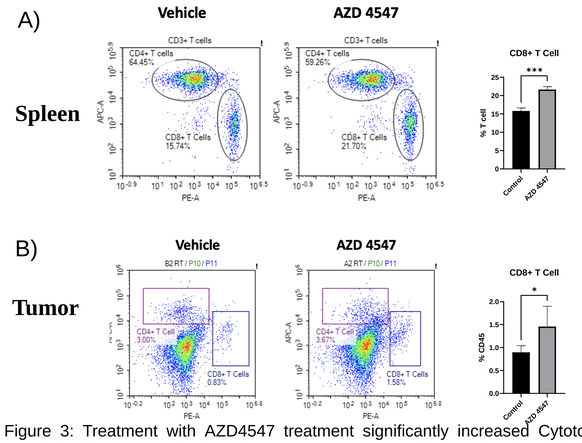


Figure 3: Treatment with AZD4547 treatment significantly increased Cytotoxic T cell population in tumor and spleen. Data represents mean±SEM n=3 and n>5 in for CD8+ T cells in (A) spleen and (B) tumor cells respectively. * Denotes significance compared to control.

CONCLUSIONS & FUTURE DIRECTIONS

- AZD4547 administered through oral gavage inhibits the growth of syngeneic cSCC tumor cells *in vivo* and promotes tumor T cell infiltration and attenuates T regulatory cell infiltration.
- AZD4547 is a promising future therapeutic treatment option for organ transplant patients with aggressive cutaneous squamous cell carcinoma.

ACKNOWLEDGEMENTS

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