CB-1158 Inhibits the Immuno-Oncology Target Arginase and Causes an Immune Mediated Anti-Tumor Response

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Abstract

The addition of CB-1158 to systemic treatments caused a significant increase in tumor volume reduction compared to treatment with systemic therapy alone. CB-1158 also led to a significant increase in T cell infiltration and CD8+ T cell count in tumors, suggesting a role for CB-1158 in enhancing anti-tumor immunity. In preclinical models, CB-1158 was found to inhibit arginase activity and cause an increase in arginine levels in tumors. These findings suggest that CB-1158 may have therapeutic potential in combination with other immunotherapies.

Introduction

Arginase is an enzyme that catalyzes the conversion of L-arginine to L-ornithine and urea. It is highly expressed in tumors, and its inhibition has been shown to increase the activity of cytotoxic T cells and enhance anti-tumor immunity. CB-1158 is an orally bioavailable small molecule that potently inhibits arginase activity in vitro and in vivo.

Materials and Methods

Animal Models: Balb/c mice were implanted with Lewis Lung Carcinoma (LLC) or 4T1 tumors. Animals were randomized to treatment with CB-1158 or vehicle and tumor growth was monitored over time. Immunohistochemistry and flow cytometry were used to assess T cell infiltration and CD8+ T cell count in tumors.

Results

CB-1158 Inhibits Arginase: CB-1158 was found to significantly inhibit arginase activity in vitro. Maximum inhibition was observed at doses as low as 50 mg/kg in vivo.

CB-1158 Causes an Increase in Arginine Levels: In vivo administration of CB-1158 led to a significant increase in arginine levels in tumors, as measured by flow cytometry.

CB-1158 Causes an Increase in T Cell Infiltration: CB-1158 treatment led to a significant increase in T cell infiltration and CD8+ T cell count in tumors, as measured by immunohistochemistry.

CB-1158 Causes an Increase in Tumor Volume Reduction: CB-1158 treatment led to a significant decrease in tumor volume compared to vehicle control.

Conclusion

CB-1158 is a novel orally bioavailable small molecule that potently inhibits arginase activity and causes an increase in arginine levels in tumors. Its therapeutic potential in combination with other immunotherapies warrants further investigation.

References