Enhancement of Anti-PD-1 Antitumor Efficacy in Syngeneic Preclinical Models by the Angiogenesis Inhibitor Lucitanib

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INTRODUCTION

- Lucitanib (BAY 73-4501) is an oral multikinase inhibitor whose targets are associated with angiogenesis and other key cancer and immunity pathways.
- Angiogenesis plays a critical role in cancer cell growth through tumor vascularization and also promotes tumor invasiveness within the tumor microenvironment.
- Therapies targeting angiogenesis and immune checkpoint pathways enhance antitumor responses by modulating the tumor cell microenvironment.
- For example, in studies that have shown that immune checkpoint inhibitors can be more effective at treating tumors that show vascular normalization. Tumor inhibition can be observed in tumors with reduced vascular density.
- Combination therapies targeting angiogenesis and immune checkpoint pathways have demonstrated synergistic activity in preclinical and clinical studies.
- For example, the combination of lenvatinib and pembrolizumab has shown enhanced activity in patients with renal cell carcinoma with metastasis.
- These data suggest that the combination of lucitanib and an immune checkpoint inhibitor may also demonstrate preclinical and clinical efficacy.
- Preclinical studies were performed to investigate the antitumor activity and the mechanism of action of lucitanib in combination with anti-PD-1 in syngeneic mouse tumor models.

METHODS

- Luciferase-based tumor xenograft models, systemic  RGB tumor xenograft models, and primary cell culture models were used to evaluate lucitanib activity in preclinical studies.
- Primary cell cultures were prepared from H22 human cell line and lucigenin-efflux assays were performed on the primary cultures using 0.5 µM lucitanib and lenvatinib on wild-type and mutated kinases.
- In vivo assessment of the antitumor activity of lucitanib, anti-PD-1, and the combination was determined in H22 HCC syngeneic tumor models.
- Tumor volume was measured by caliper, and percentage change from control was calculated.
- Immunoregulatory and antitumor responses were determined in in vitro and in vivo models.
- Statistical analysis comparisons between groups were performed using two-way ANOVA (Tukey's test) and P < 0.05 was considered significant.

RESULTS

Antitumor Activity of Lucitanib in Preclinical Models

Lucitanib demonstrated potent antitumor activity in vitro and in vivo. In vitro, lucitanib inhibited the growth of H22 and M07e human cell lines with IC50 values of 0.0053 µM and 0.0033 µM, respectively. In vivo, lucitanib significantly inhibited tumor growth in H22 syngeneic mouse models. In addition, lucitanib treatment led to a significant decrease in the expression of VEGFR2 and HIF-1α.

Combination Therapy of Lucitanib and Anti-PD-1

Lucitanib in combination with anti-PD-1 demonstrated superior antitumor activity compared to single-agent therapy. In vivo, lucitanib and anti-PD-1 treatment led to a significant decrease in tumor volume and improved survival compared to single-agent therapy. In vitro, lucitanib and anti-PD-1 treatment led to a significant decrease in the expression of VEGFR2 and HIF-1α.

CONCLUSIONS

- In vitro and preclinical studies demonstrate that lucitanib is a potent and selective inhibitor of multiple tumor kinases associated with angiogenesis, tumor vascularization, immune response, and metastasis.
- The combination of lucitanib and anti-PD-1 shows in vivo antitumor activity in multiple syngeneic mouse models.
- The mechanisms of action through antitumor effects and immunomodulatory effects on dendritic cells and T cells need further investigation.
- Lucitanib and anti-PD-1 combination has demonstrated clinical activity in combination with pembrolizumab.

REFERENCES


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Supplementary Figure 1: Lucitanib Inhibits In Vivo Cellular Phosphorylation

Supplementary Figure 2: Lucitanib Blocks VEGF Signaling In Vivo

Supplementary Figure 3: Lucitanib Exhibits Potent Kinase Inhibition Activity

Supplementary Figure 4: Lucitanib Is a Selective Angiogenesis Inhibitor

Supplementary Figure 5: Proposed Mechanism of Action