Generation of profound anti-tumor immunity by AUR109, a spectrum-selective kinase inhibitor, either as a single agent or in combination with immune checkpoint inhibitors

Girish Daginakatte, Saravanan Thiyagarajan, Kiran Aithal B, Rashmi Nair, Abhijeet Pawar, Gopinath CH, Mamon Dey, Payel Das, Charamanna K B, Mohamad Fairus, Pratheev Alagappan, Reshma Reghu, Monalisha Mandal, Simran Akbar Mujawar, Padmanabhan M, Shekar Chelur, Kishore Narayanan, Kavitha Nellore, Susanta Samajdar, and Murali Ramachandra*

Aurigene Oncology Limited, Bangalore, India

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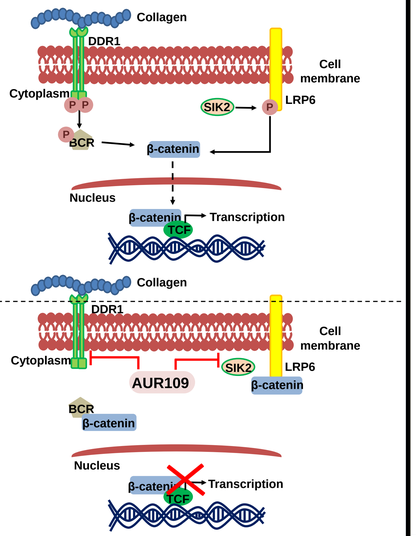
- AUR109 is an orally bioavailable clinical stage spectrum kinase inhibitor that inhibits the activity of oncogenic pathway-related kinases including DDR1, SIK2, and related RTKs
- DDR1 and SIK2 modulate Wnt/β-catenin signalling through phosphorylation of BCR and LRP6, respectively. β-catenin reporter assay was used to understand the impact of AUR109 on Wnt/β-catenin signalling
- WNT/β-catenin signalling affects cancer immunosurveillance across many cancers. It modulates tumor-immune cell interactions including the immunogenicity of cancer cells and the ability of immune cells (NK cells, Treg cells, MDSCs and CTLs) to elicit effective tumor-targeting immune responses
- Here, we have analysed effect of AUR109 inhibition of WNT/β-catenin pathway on immune cells as a single agent and in combination with immune checkpoint inhibitors

AUR109 modulates Wnt/β-catenin signaling through DDR1 and SIK2

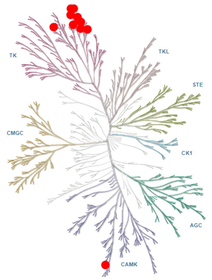


Profile of AUR109

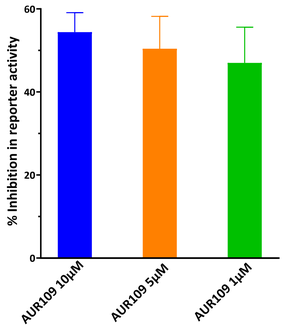
Kinases	AUR109 IC_{50} (nM)
DDR1	6
SIK2	23
RET	8
FGFR1-4	11-35
VEGFR1-3	5-26
PDGFRα	35

Selectivity in a panel of 317 kinases

Kinases with >90% inhibition at 1 µM shown

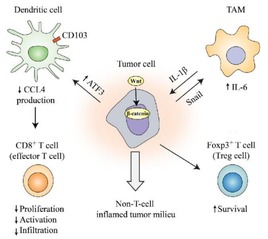


AUR109 regulates β-catenin transactivation



AUR109 exhibits dose dependent inhibition of β-catenin reporter activity in HCT116 cells

Impact of Wnt/beta-catenin pathway in modulation of anticancer immune response



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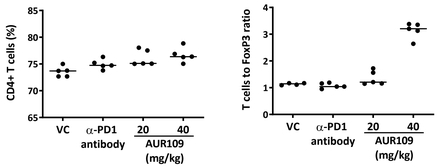
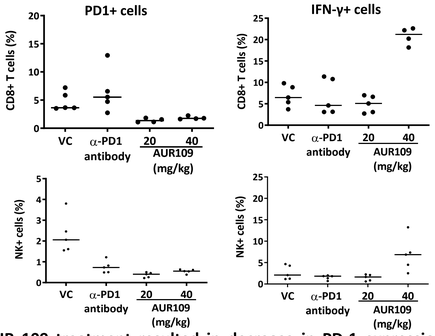
Immunophenotyping in RENCA tumor model

Effect of AUR109 on T cells in circulation



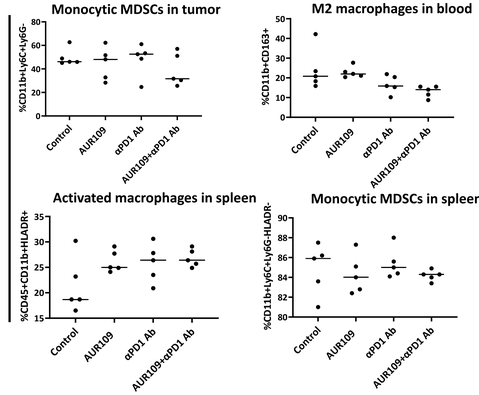
AUR109 treatment resulted in an increase in CD4 T cells and higher ratio of total T cells to regulatory T cells

Effect of AUR109 on TILs

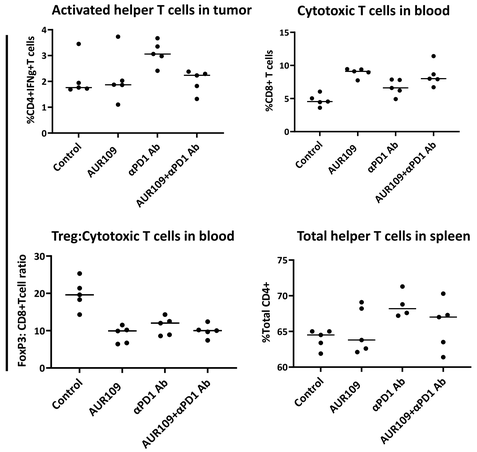


AUR 109 treatment resulted in decrease in PD-1 expression with a concomitant increase in IFN-γ expression on CD8 T cells and NK cells

Immunophenotyping in CT26 tumor model

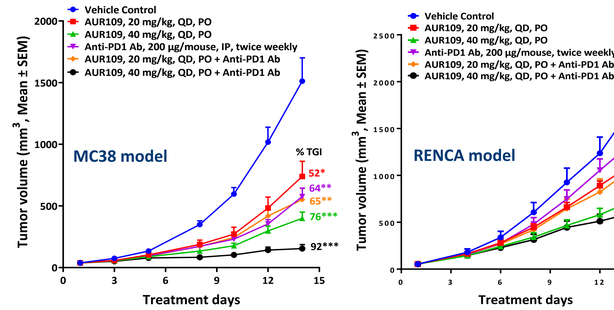


AUR109 (40 mg/kg, QD), in combination with anti-PD1 Ab (200 µg/animal, Q3W) showed decrease in monocytic MDSCs and M2 macrophages, and increase in activated monocytes

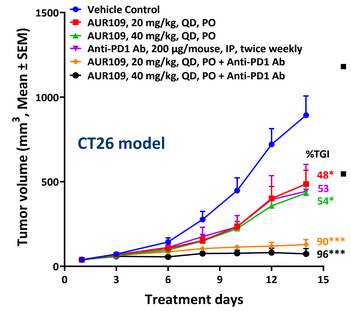


AUR109 (40 mg/kg, QD) enhances anti-PD1 Ab (200 µg/animal, Q3W) effect via an increase in cytotoxic T cells, total helper T cells, activated CD4 cells, with a concomitant decrease in regulatory T cells

In vivo efficacy in syngeneic mouse models



Statistics: One-way ANOVA - *:p<0.05; **:p<0.01; ***:p<0.001



- Tumor growth stasis was observed when AUR109 was combined with anti-mouse PD1 Ab in CT26 and MC38 syngeneic models
- AUR109 did not show significant *in vitro* antiproliferative activity in CT26 and MC38 cells

Summary

- AUR109 with a potent activity against DDR1 and SIK2 inhibits β-catenin reporter activity
- AUR109 treatment resulted in decrease in suppressive immune cell populations with concomitant increase in activated immune cells essential for anti-tumor immunity
- AUR109 demonstrated dose dependent tumor growth inhibition as a singe agent in multiple syngeneic tumor models. Combination with anti-PD1 antibody enhanced anti-tumor efficacy
- The data presented here support the continued clinical development of AUR109 for various solid cancers including gastric, ovarian and bladder cancers

Contact: murali_r@aurigene.com; Phone: +91-8071025444