Aurigene Oncology
Conquering Cancer

Novel Oral Small Molecule Inhibitor of Wnt/β-catenin pathway for Cancer Immunotherapy

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People's Festival of Innovations-2023, New Delhi
November 28th to December 2nd, 2023

DDR1 Suppresses Anti-tumor Immunity in Cancer

- Discoidin domain receptor 1 (DDR1) is a tyrosine kinase receptor overexpressed in various malignancies
- DDR1 is activated upon binding to collagen in the extracellular matrix, and plays a role in tumor promotion, immune exclusion, and therapeutic resistance
- Collagen stimulated DDR1 phosphorylates BCR which disrupts BCR/β-catenin interaction, resulting in increased β-catenin nuclear activity
- DDR1 is involved in low infiltration of CD4+ and CD8+ T cells and reduction of IFN-γ secretion through inhibiting IL-18 synthesis and release
- DDR1 leads to enhanced expression of PD-L1 through JNK/C-Jun signaling pathway
- DDR1 is also involved in immune exclusion by altering extracellular matrix in tumor immune microenvironment
- Significant correlation is seen between DDR1 level and Treg and T cell exhaustion markers like CCR8, PD-1, CTLA-4 and TIM3, in gastric cancer

Jeitany *et.al,* EMBO Molecular Medicine, 2018
Duan *et.al*, Cancer Science, 2022
Wang *et.al*, Frontiers in Immunology, 2022

Role of SIK2 in Cancer Cell Signaling

- SIK2 is overexpressed in several cancer cell lines and boosts cancer cell tolerance to different stresses, such as deprivation of nutrients and Taxol chemotherapy
- SIK2 is a centrosome kinase involved in centrosome splitting through PI3K activation and thereby regulates cancer cell proliferation, metastasis, and sensitivity to chemotherapy
- SIK2 phosphorylates Class IIa-HDACs and controls their nuclear-cytoplasm shuttling
- SIK2 inhibition enhances PARP inhibitor activity synergistically in ovarian and triple negative breast cancer
- SIK2 maintains breast cancer stemness by phosphorylating LRP6 and activates Wnt/β-catenin signaling
- SIK2-activated Wnt/β-catenin signaling leads to IDH1 induction, causing metabolic reprogramming in breast cancer cells

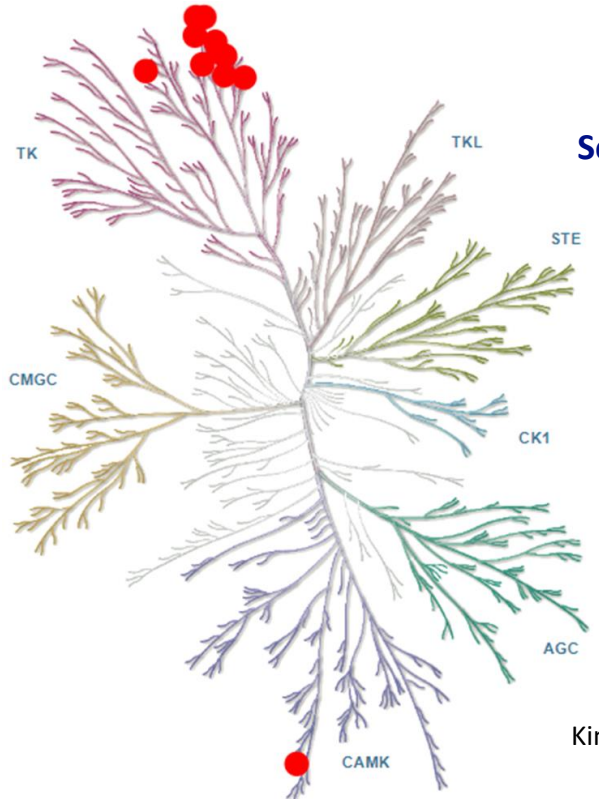
Du WQ *et al,* Expert Opin Ther Targets (2016) 20:477–85
Lu *et.al*, JCI, 2022
Rong *et.al,* Oncogene, 2022

AUR109 is a potent inhibitor of DDR1 and SIK2

- AUR109 is a potent inhibitor of DDR1 and SIK2 with additional activities against RET, FGFRs, VEGFRs and PDGFRa. In addition, AUR109 activates immune cells.
- AUR109 was initially discovered at Aurigene as an FGFR inhibitor. Phase 1 clinical trial with AUR109 has shown 9% response rate in heavily pre-treated patients with multiple tumor types

Biochemical Potency

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



Selective in a panel of 317 kinases

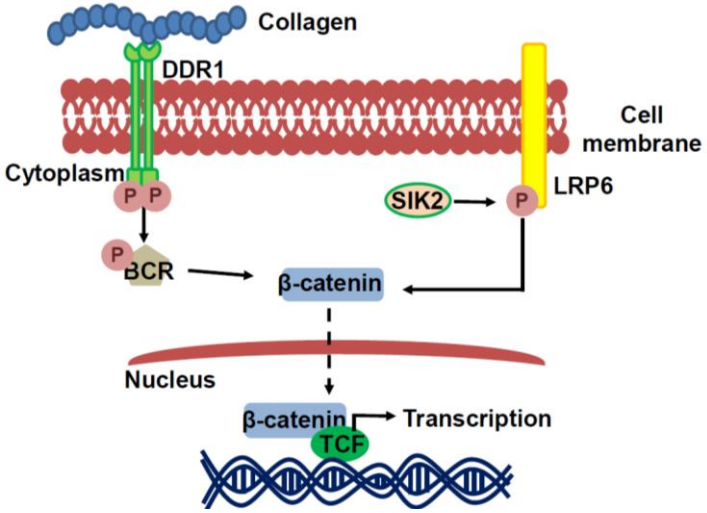
Kinases with >90% inhibition at 1 µM shown

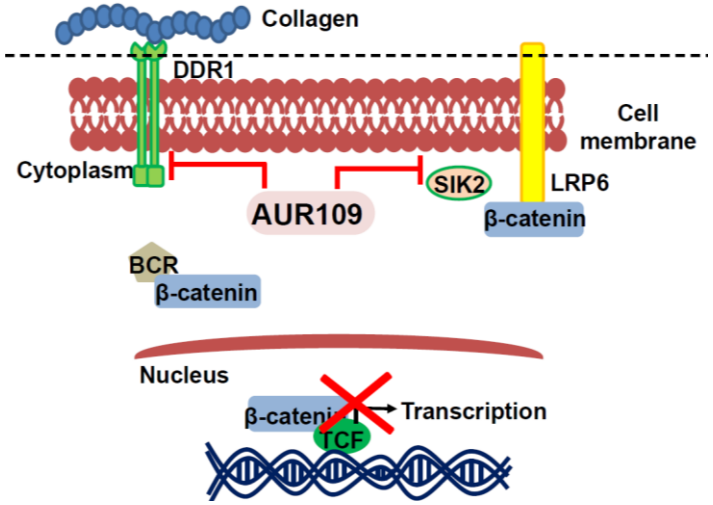
Competitive Landscape – DDR1 and SIK2 inhibitors

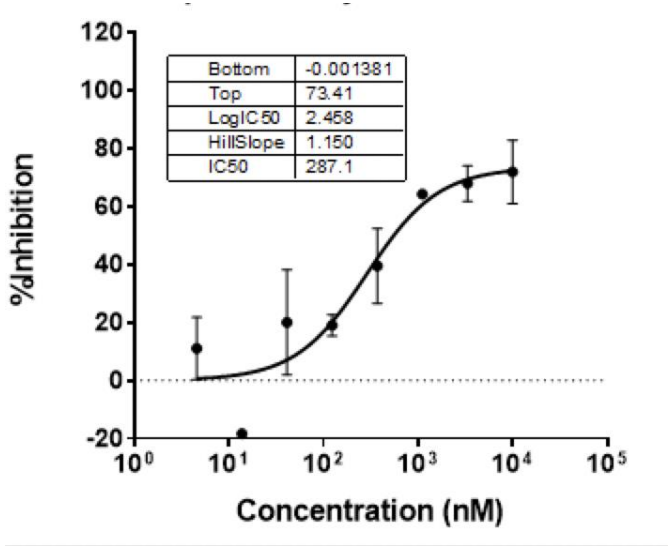
Company	Product & type	Stage	Comments
Green3Bio, Inc.	GRN-300 (ARN 3261) SIK2 inhibitor	Phase 1	• Being evaluated for Recurrent Ovarian, Primary Peritoneal, and Fallopian Tube Cancers.
DDR1 inhibitor - Angion Biomedica Corp	ANG3070 DDR1 inhibitor	Phase 1	• Targets PDGFRα and PDGFRβ, DDR1 and DDR2 , is in Phase 1 clinical trial, being evaluated for Idiopathic Pulmonary Fibrosis (IPF).
Parthenon Therapeutics	PRTH-101 DDR1 inhibitor	Preclinical	• Phase 1 expected to begin in 2023

AUR109 has potential for being a first in class inhibitor of DDR1 and SIK2

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



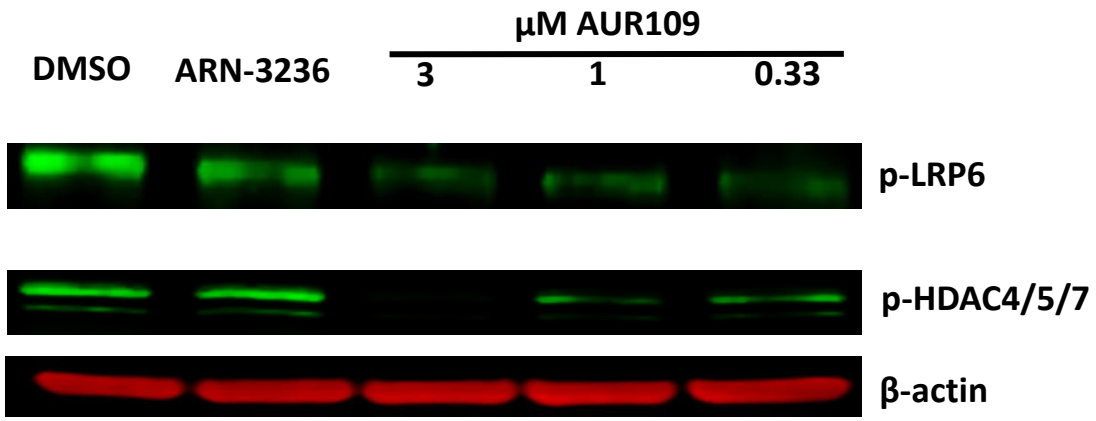




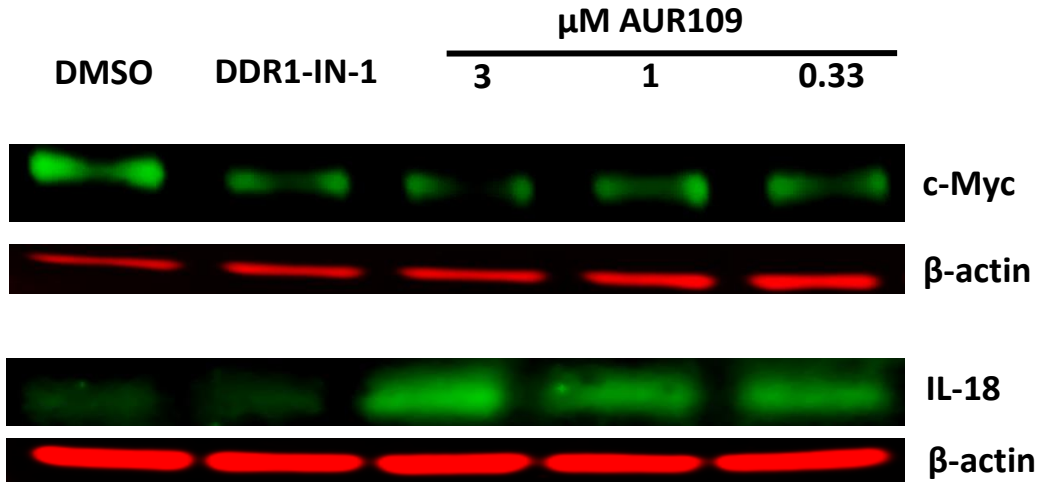
- DDR1 and SIK2 modulate Wnt/β-catenin signaling through phosphorylation of BCR and LRP6, respectively
- DDR1/SIK2-Wnt/β-catenin nodal axis regulates tumor-immune cell interactions including the immunogenicity of cancer cells and the ability of immune cells to elicit effective tumor-targeting immune responses.
- AUR109 exhibits dose dependent inhibition of β-catenin reporter activity in HCT116 cells

SIK2 and DDR1 Inhibition by AUR109 leads to Modulation of Downstream Markers

BT549 cells (TNBC, *BRCA* WT) treated with AUR109 for 24 hours followed by detection of p-LRP6 and p-HDAC4/5/7



HCT-116 cells stimulated by collagen for 18h, followed by removal of collagen and AUR109 treatment for 24h

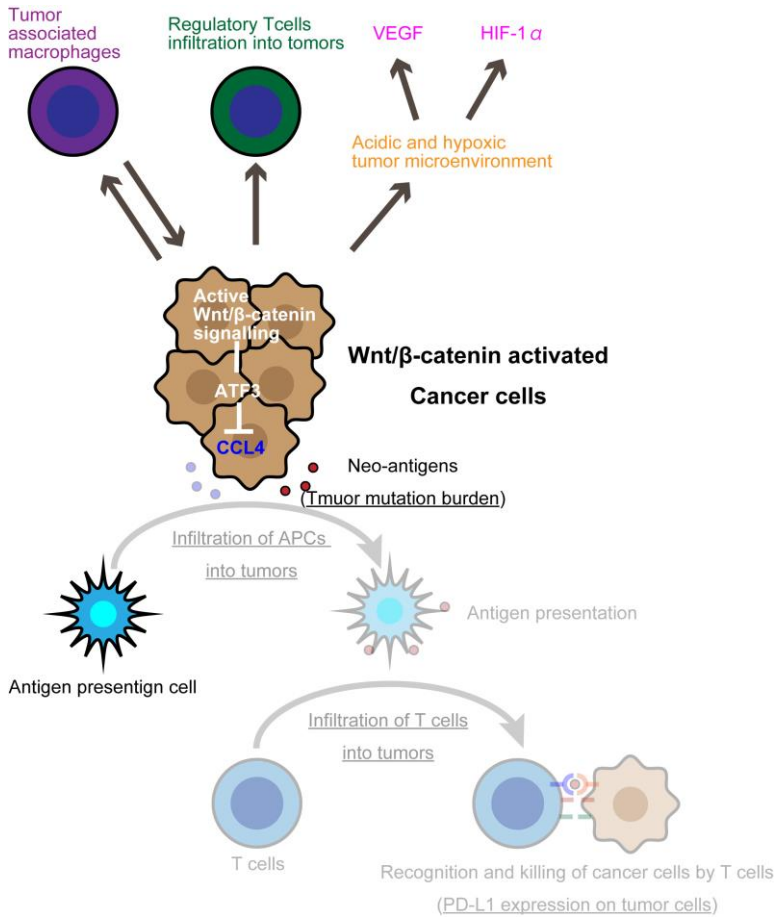


AUR109 treatment led to modulation of relevant downstream markers, demonstrating the effect on Wnt/β-catenin signaling

ARN-3236 (SIK2 inhibitor) and DDR1-IN-1 (DDR1 inhibitor) used as controls

Impact of Wnt/β-catenin signaling on Immune Exclusion and Fibrosis

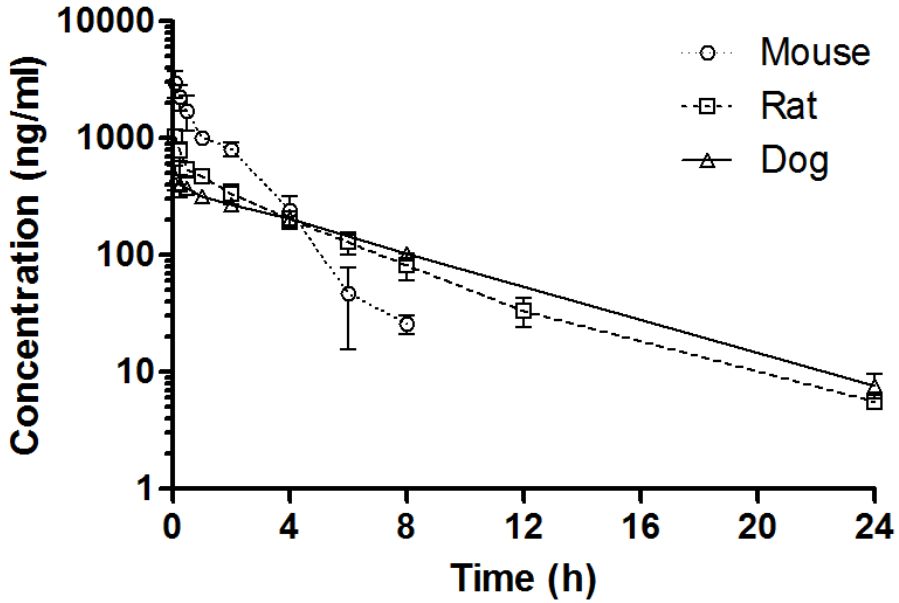
- Wnt/β-catenin signaling is implicated in fibrogenesis in a variety of tissues
- Activation of tumor-intrinsic WNT/β-catenin signaling is enriched in non-T-cell-inflamed tumors
- Wnt/β-catenin pathway is a potential mechanism of immune escape and resistance to immune checkpoint inhibitors
- AUR109 as an inhibitor of this pathway can potentially restore immune cell infiltration and augment immunotherapy



Biomedicines 2023, 11(1), 190

Summary of Intra-venous PK Parameters

Species	Dose	C_0	CL	V_{ss}	$t_{1/2}$	$AUC_{0-\infty}$
Units	mg/kg	ng/ml	L/h/kg	L/kg	h	h*ng/mL
Mouse	1	3340	0.236	0.38	1.2	4230
Rat	1	1170	0.393	1.6	3.6	2600
Dog	1	500	0.374	2.0	4.3	2690



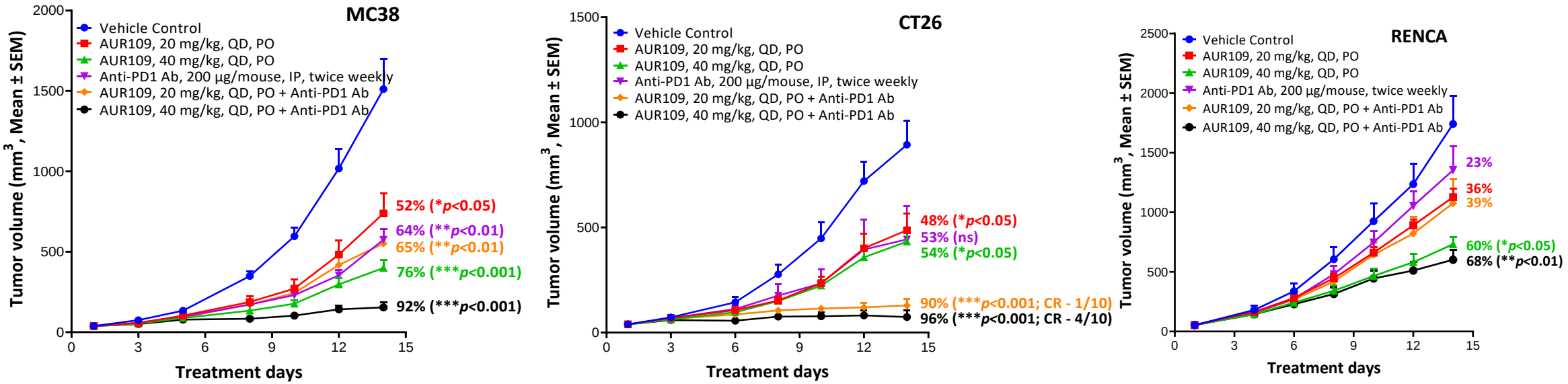
AUR109 shows very low clearance, low to moderate volume of distribution and moderate half-life

Summary of Oral PK Parameters

Species	Parameter	Units	Dose (mg/kg)					
		Units	**10**	**20**				
			Male	**Male**				
Mouse	**C_{max}**	ng/ml	3040	9050				
(n=3)	**t_{max}**	h	2	6				
	AUC_{0-24h}	h*ng/ml	23900	109000				
			10		**30**		**50**	
			Male	**Female**	**Male**	**Female**	**Male**	**Female**
Rat	**C_{max}**	ng/ml	2430	2510	7480	9290	11700	15300
(n = 3)	**t_{max}**	h	2	4	4	4	4	6
	AUC_{0-24h}	h*ng/ml	21200	19000	71500	82900	134000	191000
			5		**15**		**30**	
			Male	**Female**	**Male**	**Female**	**Male**	**Female**
Dog, young	**C_{max}**	ng/ml	818	1140	3830	3910	4910	5690
(n = 3-5)	**t_{max}(range)**	h	2-4	2-4	2-6	2-4	2-4	2-4
	AUC_{0-24h}	h*ng/ml	7400	10400	47900	44800	59700	65500

AUR109 showed dose proportional increase in systemic exposure across tested species

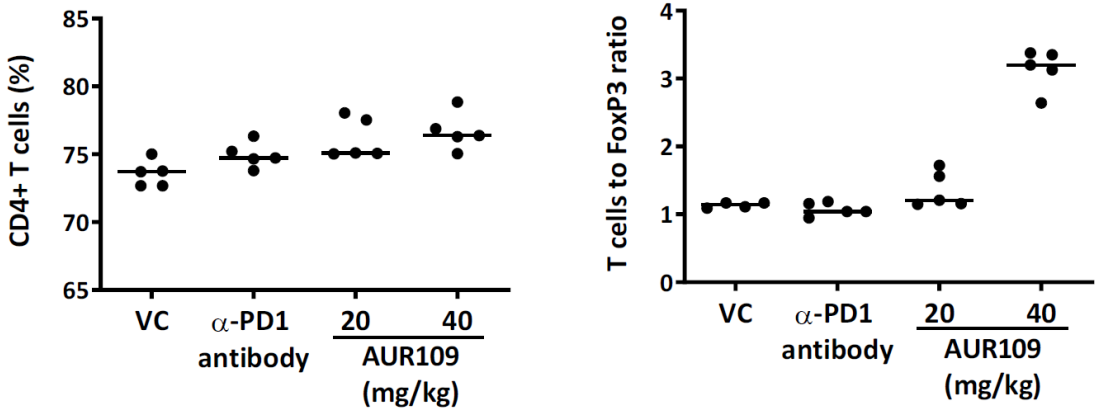
AUR109 is Efficacious in Multiple Syngeneic Tumor Models



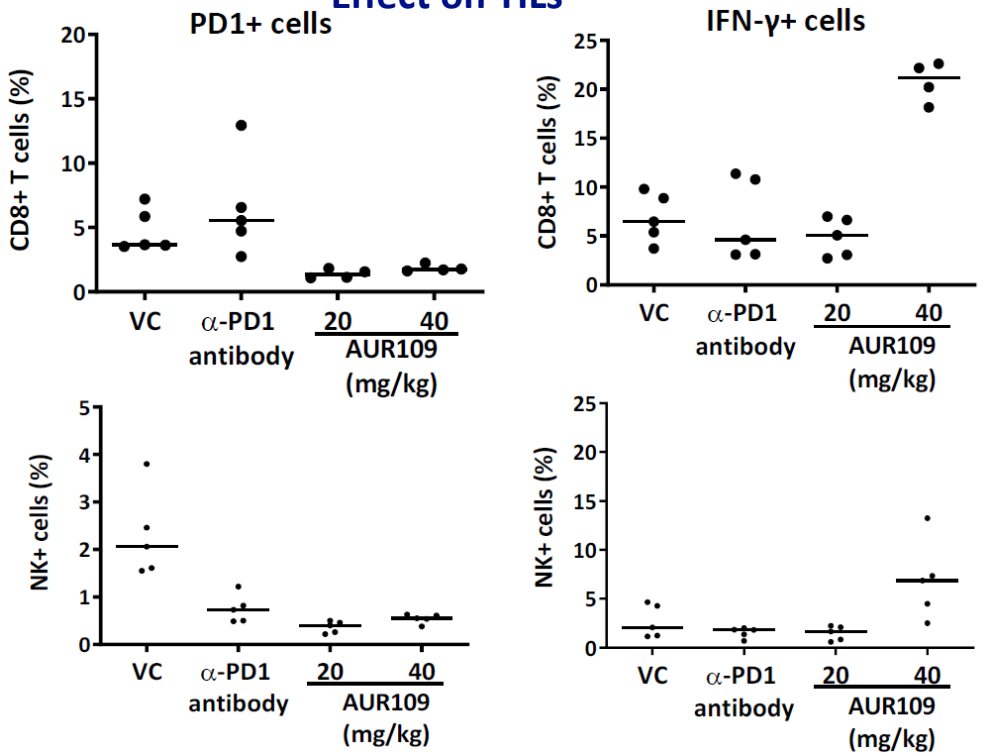
- **AUR109 is efficacious as a single agent and demonstrates synergistic activity in combination with anti-PD1**
- **Tumor growth stasis was observed when combined with anti-PD1 Ab in CT26 and MC38 syngeneic models**
- **AUR109 did not show significant *in-vitro* antiproliferative activity in CT26 and MC38 cells in in-vitro culture. Hence, efficacy seems to be driven by the release of immune suppression**

Potent Activation of Immune Cells (T and NK) in the RENCA Tumor Model

Effect on Circulating T cells

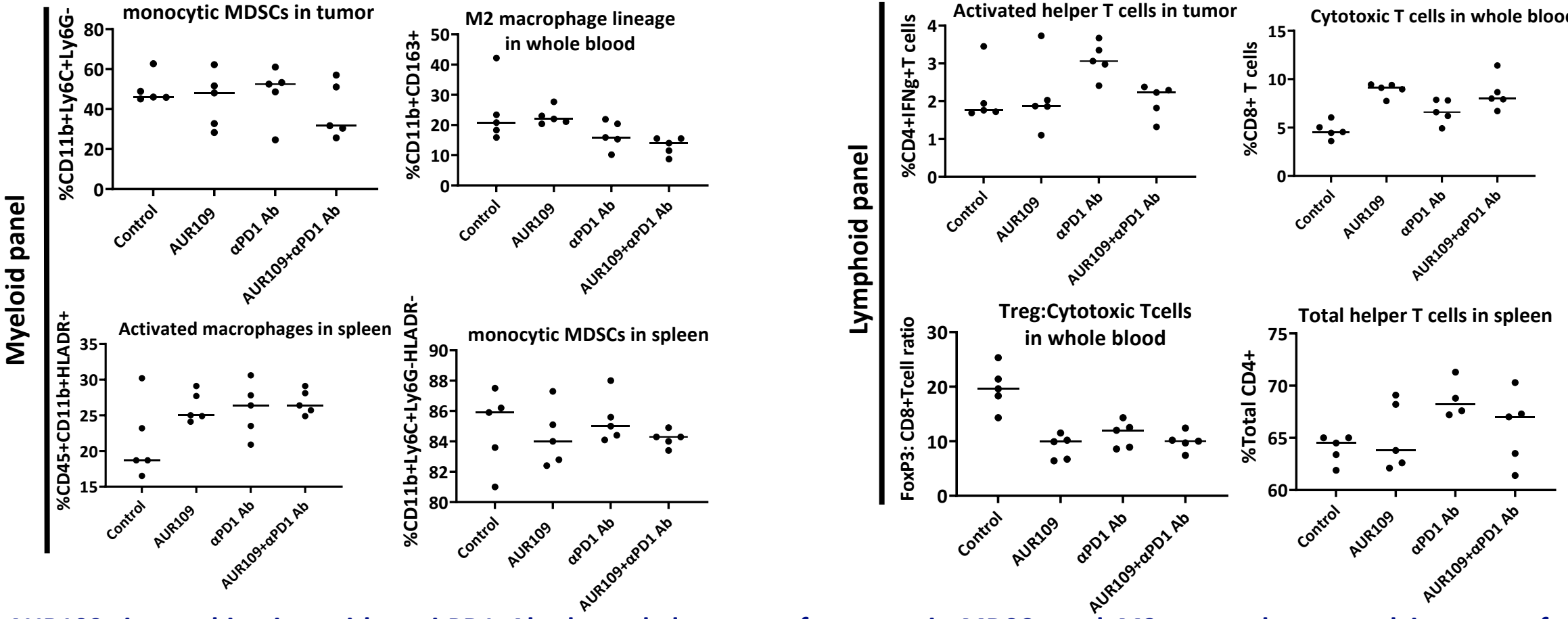


Effect on TILs



- **AUR109 treatment resulted in an increase in CD4 T cells and higher ratio of total T cells to regulatory T cells**
- **AUR109 treatment resulted in decrease in PD-1 expression with a concomitant increase in IFN-γ expression on CD8 T cells and NK cells**

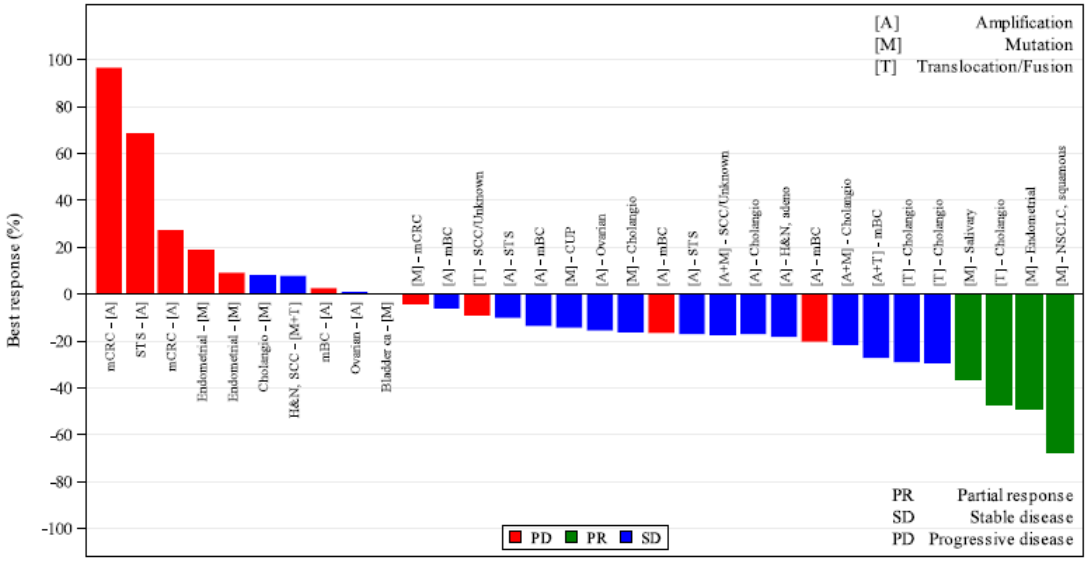
AUR109 Enhances Anti-tumor Immunity: CT26 tumor model



- AUR109, in combination with anti-PD1 Ab showed decrease of monocytic MDSCs and M2 macrophages, and increase of activated monocytes
- AUR109 enhances anti-PD1 Ab effect via an increase in cytotoxic T cells, total helper T cells, activated CD4 cells, with a concomitant decrease in regulatory T cells

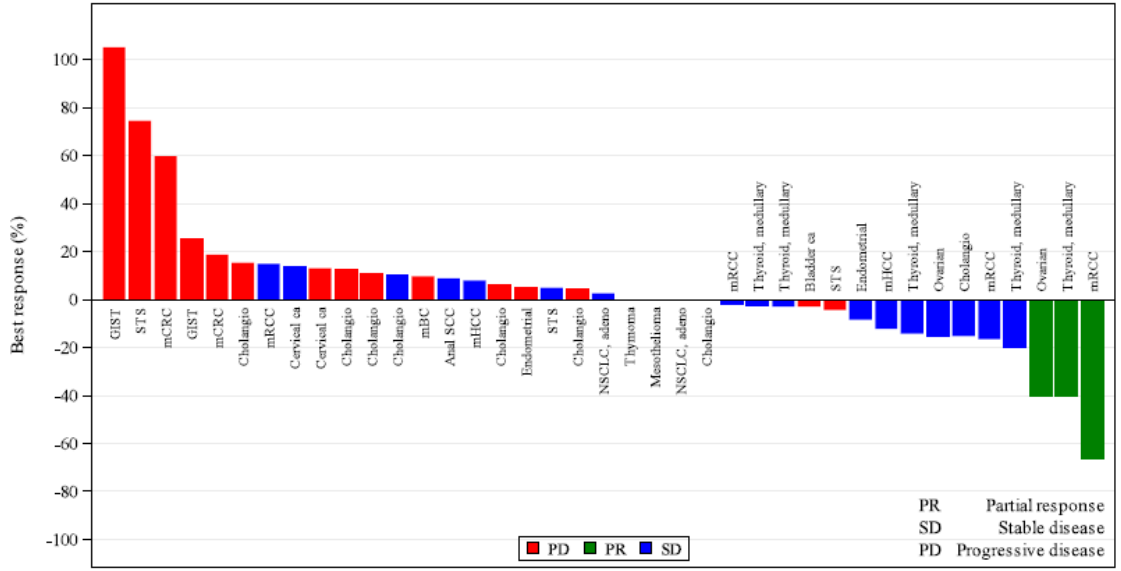
Results from Phase-1 Clinical Trial

Efficacy in Patients with FGFR Aberration



CUP = Unknown primary tumour; H&N, SCC = Head and neck, squamous cell carcinoma; mBC = breast cancer; mCRC = colorectal carcinoma; NSCLC = non-small cell lung cancer; SCC/unknown = squamous cell carcinoma of unknown origin; SCLC = Squamous cell lung cancer; STS = soft tissue sarcoma. 4 patients with low exposure (dose: 100-200 mg) and 1 with unscheduled scan without comparison scan (600 mg) are not included. Other unscheduled visits are included.

Efficacy in Patients without FGFR Aberration



Anal SCC = Anal squamous cell carcinoma; mRCC = renal carcinoma; NSCLC = non-small cell lung cancer; SCC/unknown = squamous cell carcinoma of unknown origin; SCLC = Squamous cell lung cancer; STS = soft tissue sarcoma. 4 patients with low exposure (dose: 100-200 mg) and 1 with unscheduled scan without comparison scan (600 mg) are not included.

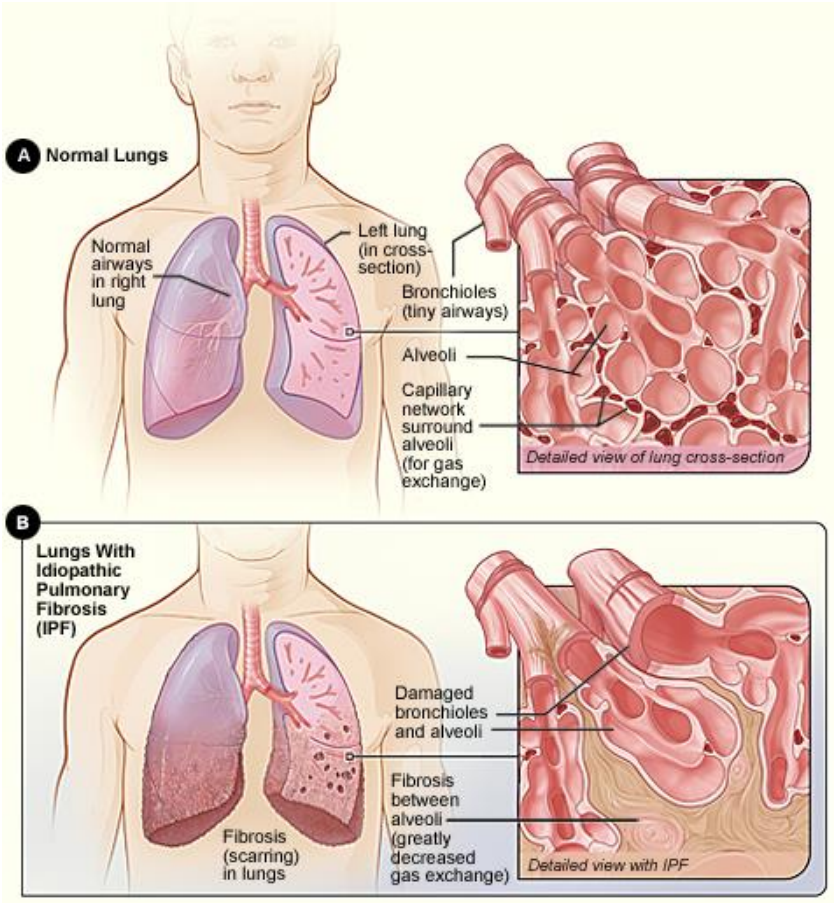
Response Rates in Phase-1 Clinical Trial

	FGFR Mutation (n = 18)	FGFR Aberration (includes mutation) (n = 32)	No FGFR Aberration (n = 44)	Total Efficacy Evaluable (n = 76)
	n(%)			
Responders (CR or PR)[1]	4 (22.2%)	4 (12.5%)	3 (6.8%)	7 (9.2%)
Duration of Response (Median, Days)	196	196	59	110
[1] All responders attained PR				

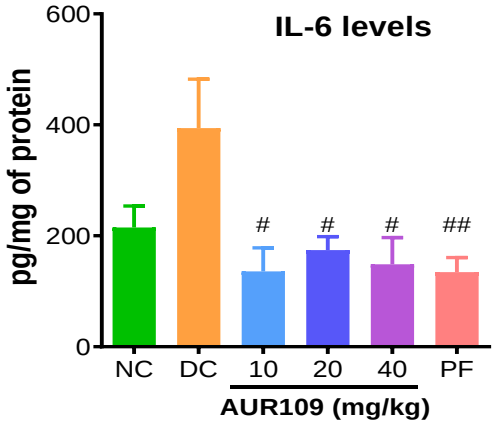
Encouraging efficacy in highly pre-treated patients in a Phase I clinical trial

Additional Opportunity for AUR109 in Idiopathic Pulmonary Fibrosis (IPF)

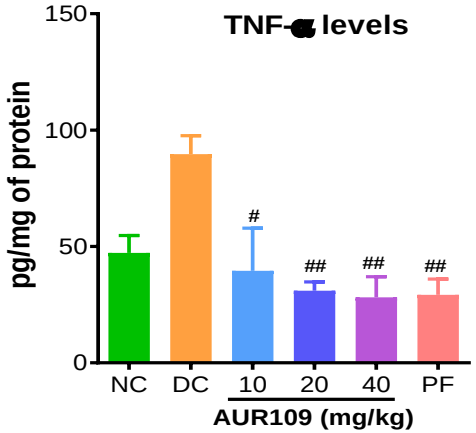
- Idiopathic pulmonary fibrosis (IPF) is a rare, progressive illness of the respiratory system
  - IPF is characterized by the thickening and stiffening of lung tissue leading to progressive and irreversible decline in lung function
  - Estimates have ranged from 2-29 people per 100,000 in the general population.
- Inhibition of DDR1 and SIK2 are targets of interest for discovery of new drugs for IPF
  - B-catenin plays an important role in IPF (Lam and Gottardi, Curr Opin Rheumatol. 2011 Nov; 23(6): 562–567).
- Two marketed agents
  - Esbriet® (pirfenidone MAP kinase inhibitor) and Ofev®(nintedanib (PDGF, FGF, VEGF inhibitor) – >$3 billion total global revenues in 2021
  - Esbriet and Ofev display modest slowing of IPF progression - Inconclusive evidence of survival benefit, no improvement on patient quality of life and significant tolerability issues

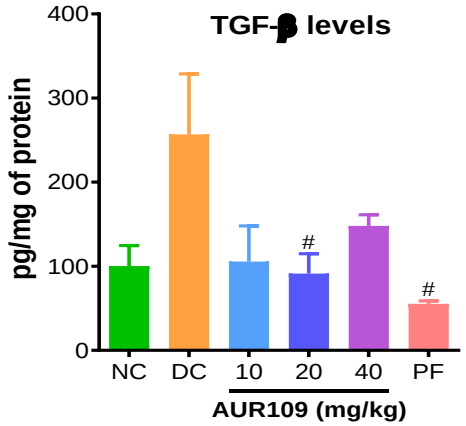


Efficacy of AUR109 in Bleomycin Induced Pulmonary Fibrosis model



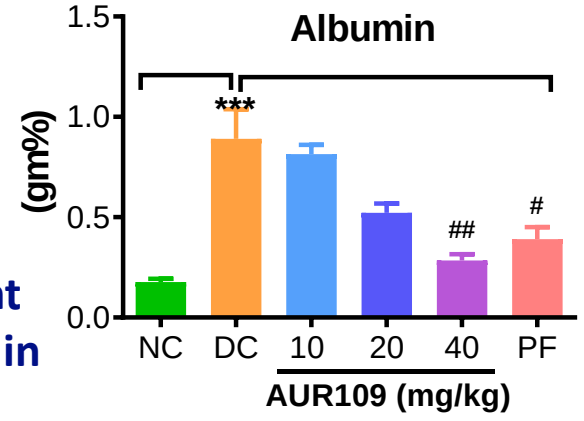
Effect on Cytokine modulation

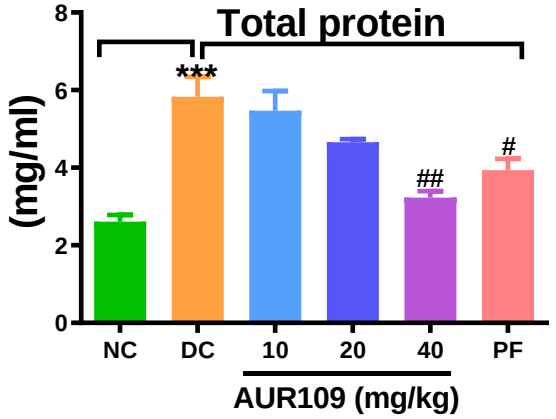




5 days after Bleomycin induction, AUR109 was dosed at 10, 20 and 40 mg/kg/day, Pirfenidone was dosed at 200 mg/kg/day (both compounds were dosed for 23 days once daily)

Effect on Albumin and total protein levels in BAL fluid





AUR109 treatment caused a dose-dependent reduction in albumin and total protein levels in the bronchoalveolar fluid

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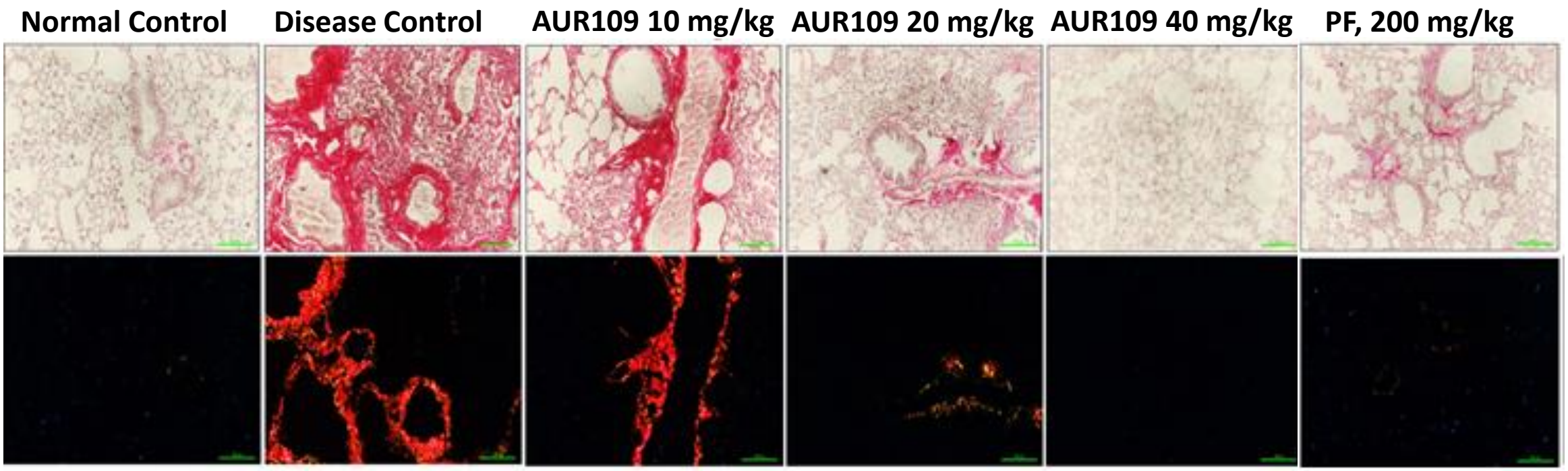
AUR109 treatment showed Significant Reduction in Fibrosis

Picrosirius red staining of lung tissues



The data supports additional clinical positioning of AUR109 in IPF, a significant opportunity

Clinical Positioning of AUR109

- A dose ranging study to evaluate the safety, PK, PD and efficacy is planned to be conducted in patients of Colorectal, Ovarian and Renal cancers
- AUR109 can be evaluated both as a single agent and in combinations with IO and other therapeutic agents
- Biomarkers downstream of DDR1 and SIK2 as well as Fibrosis specific markers to be evaluated to establish PK/PD correlation
- IND submitted to US FDA in August 2023

Summary

- AUR109 is a potent inhibitor of DDR1 and SIK2 along with other clinically validated kinases
- AUR109 exhibits dose dependent inhibition of β-catenin reporter activity
- AUR109 demonstrated tumor growth inhibition as a singe agent in multiple syngeneic tumor models. Combination with anti-PD1 antibody enhanced anti-tumor efficacy
- AUR109 treatment resulted in decrease in suppressive immune cell populations with concomitant increase in activated immune cells essential for anti-tumor immunity
- Compelling efficacy demonstrated in the pulmonary fibrosis model offers a significant opportunity for this compound both in oncology (many cancers have fibrosis, which prevents exposure of the tumor to the drug) and lung fibrosis indications
- Pre-clinical safety has been demonstrated in safety pharmacology and toxicology studies
- Clinical safety and signs of efficacy have been observed in a Phase 1 trial
- Data supports the continued clinical development of AUR109 for various solid cancers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