First-in-class orally bioavailable checkpoint inhibitors targeting single and multiple immune inhibitory pathways

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Abstract

Immune checkpoint inhibitors have changed the landscape of cancer therapy with the general acceptance that they will be the mainstay of future therapies. This is evident from a large number of ongoing clinical trials evaluating checkpoint inhibitors as a single agent or in combination with other therapeutic modalities. While these antibody-based therapies show impressive clinical activity, they suffer from the shortcomings including the failure to show responses in a majority of patients, immune-related adverse events (irAEs) due to the breaking of immune self-tolerance and need to administer by intravenous injection. The recent reports on severe demyelinating polyradiculoneuropathy leading to death observed in two patients with the anti-PD-1 immunotherapy also point to the need for short-acting agents for the better management of irAEs. Towards addressing these shortcomings, we are developing small molecule agents targeting one or more immune checkpoint pathways to increase the response rate and dosing by oral route with relatively shorter pharmacokinetic exposure.

We at Aurigene have devised a strategy to identify agents targeting single or multiple immune checkpoint proteins by taking advantage of the sequence/structural similarities among immune checkpoint ligands and receptors. In this strategy, high affinity shortest pharmacophore derived from the extracellular domain of checkpoint proteins are first identified and transformed into therapeutic agents with optimized drug-like properties. Our strategy has resulted in the identification of agents targeting PD-L1 alone, VISTA alone, PD-L1 and VISTA, and PD-L1 and TIM-3. The first compound from this approach AUPM-170/CA-170, a first-in-class dual antagonist targeting PD-L1 and VISTA, is undergoing clinical trials.

Herein we report the pharmacological evaluation of another novel small molecule antagonist dually antagonizing PD-L1 and TIM-3 pathways. Potent functional activity comparable to that obtained with an anti-PD-1 or anti-TIM-3 antibody in rescuing T cell proliferation and effector functions was observed with the lead compound, PM-327. PM-327 showed selectivity against other immune checkpoint proteins as well as in a broad panel of receptors and enzymes. In preclinical models of melanoma, breast and colon cancers, PM-327 showed significant efficacy in inhibition of tumor growth upon oral dosing with excellent tolerability.

These findings support further development of PM-327 in the clinic.

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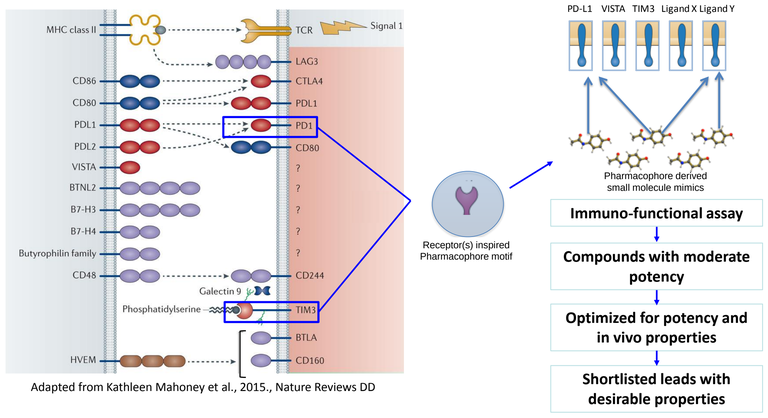
Introduction

Lack of clinical response in ~70% patients with the approved anti-PD-1/PD-L1 antibodies is likely due to the presence of other immune suppression mechanisms such as TIM3, which is supported by increased TIM3 expression in anti-PD1 antibody non-responding patient population. Preclinical studies have established that co-blockade of PD-1 and TIM3 restores dysfunctional CD8 T cells leading to markedly improved efficacy.

Our approach – small molecule immune checkpoint antagonists



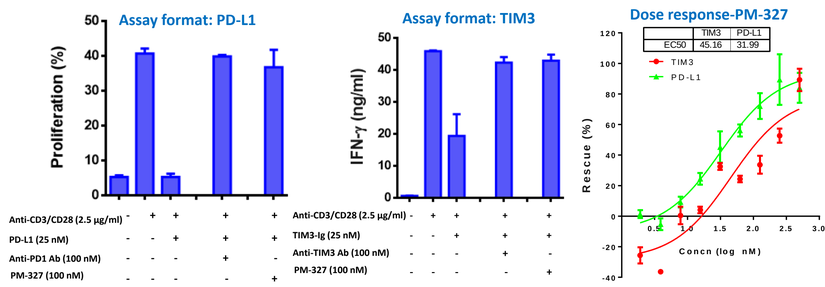
Adapted from Kathleen Mahoney et al., 2015., Nature Reviews DD

Advantages of a small molecule immune checkpoint antagonists disrupting PD-1 and TIM3 pathways include:

- Oral bioavailability for the ease of dosing
- Short-acting agents for better management of adverse events
- Simultaneous targeting of PD-1 and TIM3 checkpoint pathways to improve the response rate with an opportunity to expand patient population beyond those that respond to anti-PD1/PD-L1 therapies
- Additionally, PD-1 and TIM3 dual positive T cells are thought to be the more suppressed than PD-1 positive T cells. Targeting both of these pathways may rescue the function of these highly suppressed T cells

In vitro potency, selectivity and PK profile of PM-327, a small molecule agent

Dual antagonism of PD-L1 and TIM3 with PM-327



PM-327 exhibits equipotent antagonism against PD-L1 and TIM3 pathways

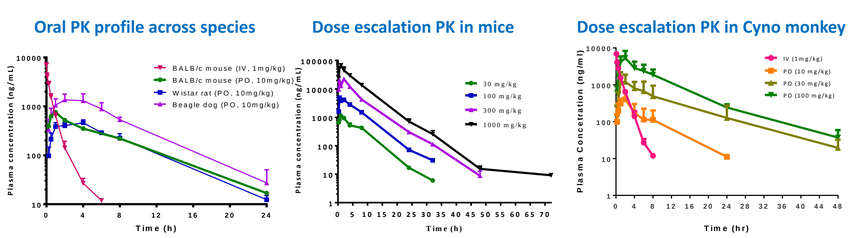
In vitro functional potency and selectivity of PM-327

Rescue from	Assay readout	EC_{50} values (nM)					
		Mouse		Monkey		Human	
		PM-327	Ref Ab	PM-327	Ref Ab	PM-327	Ref Ab
PD-L1	Proliferation	19.8	22.7	70.7	109.2	29.0	43.5
	IFN-Y secretion	32.9	18.0	42.3	54.2	99.4	32.5
PD-L2	Proliferation	15.5	10.7	77.3	29.3	53.7	37.4
	IFN-Y secretion	41.8	30.2	61.1	20.0	82.9	73.3
TIM3	IFN-Y secretion	41.6	25.2	98.0	19.9	120.7	55.5

Percent rescue Test concentration in µM							
LAG-3		CTLA-4		VISTA		B7.1/ CD28	
0.1	1	0.1	1	0.1	1	0.1	1
0	0	0	2	0	0	0	0

PM-327 is functionally potent against both PD-1/TIM3 pathways and is selective against other checkpoint pathways

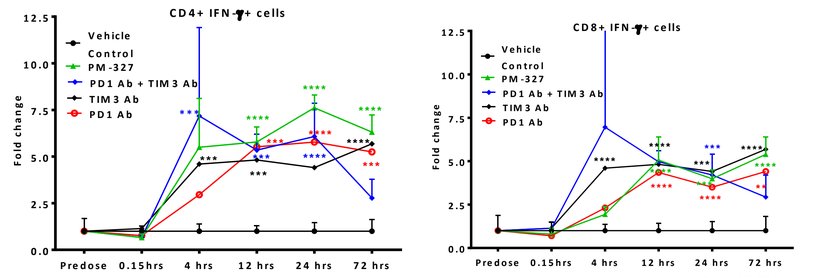
Oral pharmacokinetic profile and dose escalation PK of PM-327 mice and monkey



PM-327 exhibits excellent oral PK profile across species and dose-dependent exposure in mice and Cyno monkey

Immune PD modulation and efficacy of PM-327

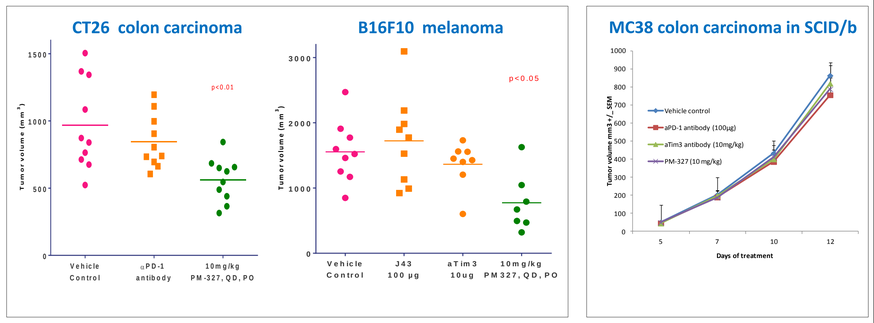
In vivo immune PD modulation in non-tumor bearing mice



**=p<0.05; ***=p<0.001

PM-327 exhibits sustained immune PD modulation in mice
PD modulation is comparable to anti-TIM3 antibody and a combination of anti-PD1 and anti-TIM3 antibodies

In vivo efficacy in multiple syngenic tumor models

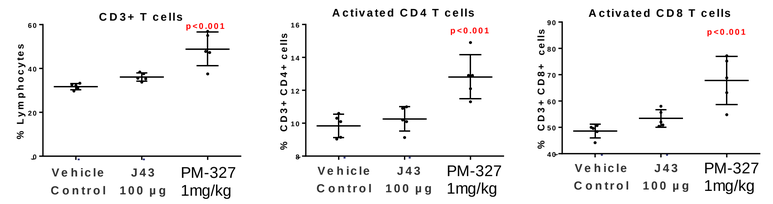


PM-327 shows significant efficacy in multiple syngenic tumor models

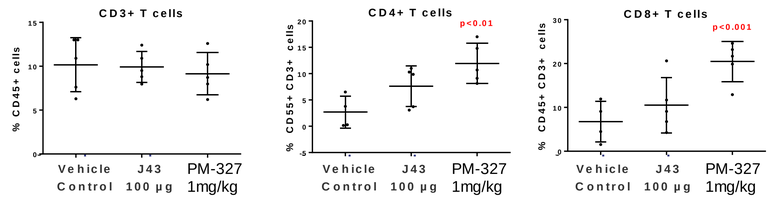
No efficacy in immunodeficient model

PD modulation in CT26 tumor bearing mice

Cell surface markers in the whole blood



Cell surface markers in tumors



PM-327 shows desirable PD modulation upon repeated administration in CT26 model

Safety profile and therapeutic window

Assay	Results
CEREP receptor, ion channel and enzyme panel	No significant inhibition at the tested concentration of 10 µM
hERG, AMES and micronucleus test	Clean profile
14 day non-GLP tox in mouse	Well tolerated with the expected NOAEL >1000mg/kg
Rat cardiovascular safety studies	No changes in mean arterial pressure, heart rate and cardiac contractility up to a maximum tested plasma concentration of 15µg/ml

Excellent safety profile with a therapeutic window of >100 fold

Summary

We have identified an orally bio-available PD-L1/TIM3 dual antagonist

- The lead candidate targeting PD-L1 and TIM-3 pathways exhibits desirable potency, DMPK properties including oral bioavailability, shows anti-tumor efficacy in multiple syngeneic tumor models, promotes tumor infiltrating T cell activation and exhibits a desirable safety profile

Flexible oral administration and antagonism of PD-L and TIM3 checkpoint pathways may provide for improved or expanded clinical benefit in cancer patients